Reviews

Unilateral Amblyopia Affects Two Eyes: Fellow Eye Deficits in Amblyopia

Kimberly Meier[1] and Deborah Giaschi

[1]Department of Psychology, University of British Columbia, Vancouver, British Columbia, Canada
[2]Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence: Kimberly Meier, Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, B.C., Canada, V6T 1Z4;
kmeier@psych.ubc.ca.

Submitted: October 21, 2016
Accepted: February 21, 2017

Citation: Meier K, Giaschi D. Unilateral amblyopia affects two eyes: fellow eye deficits in amblyopia. *Invest Ophthalmol Vis Sci*. 2017;58:XXX–XXX. DOI: 10.1167/iovs.16-20964

Unilateral amblyopia is a visual disorder that arises after selective disruption of visual input to one eye during critical periods of development. In the clinic, amblyopia is understood as poor visual acuity in an eye that was deprived of pattern vision early in life. By its nature, however, amblyopia has an adverse effect on the development of a binocular visual system and the interactions between signals from two eyes. Visual functions aside from visual acuity are impacted, and many studies have indicated compromised sensitivity in the fellow eye even though it demonstrates normal visual acuity. While these fellow eye deficits have been noted, no overarching theory has been proposed to describe why and under what conditions the fellow eye is impacted by amblyopia. Here, we consider four explanations that may account for decreased fellow eye sensitivity: the fellow eye is adversely impacted by treatment for amblyopia; the maturation of the fellow eye is delayed by amblyopia; fellow eye sensitivity is impacted for visual functions that rely on binocular cortex; and fellow eye deficits reflect an adaptive mechanism that works to equalize the sensitivity of the two eyes. To evaluate these ideas, we describe five visual functions that are commonly reported to be deficient in the amblyopic eye, hyperacuity, contrast sensitivity, spatial integration, global motion, and motion-defined form, and unify the current evidence for fellow eye deficits. Further research targeted at exploring fellow eye deficits in amblyopia will provide us with a broader understanding of normal visual development and how amblyopia impacts the developing visual system.

Keywords: amblyopia, binocular vision, contrast sensitivity, motion perception, spatial integration, visual development

Amblyopia ("lazy eye") is a visual developmental disorder that arises after selective disruption of visual input to one eye early in life. The two most common causes of amblyopia are anisometropia, which is an unequal refraction between the two eyes, and/or strabismus, which is a misalignment in fixation of one eye.[1–7] Amblyopia can also be caused by more extreme deprivation as in developmental cataracts (cloudy lens) or ptosis (a drooping eyelid). Clinically, amblyopia is identified by assessing visual acuity with an optotype (letter or symbol) chart. Amblyopia is diagnosed if a child has at least a two-line difference in visual acuity between the eyes, even when the amblyogenic factors have been removed (i.e., through the appropriate lens prescription for anisometropia, corrective surgery to align the eyes in strabismus, or cataract extraction).[8] An amblyopic eye is an otherwise healthy eye, and the effects of amblyopia are widely assumed to be cortical in origin, arising from the imbalance of input to the developing visual system. Amblyopia typically arises between the ages of 6 months to 8 years.[8,9] If an adult develops anisometropia, strabismus, or unilateral cataract, amblyopia does not occur. Thus, amblyopia is a consequence of the abnormal progression of visual development during sensitive periods, and cannot impact a mature visual system.

Treatments for amblyopia take advantage of the plasticity of the brain.[10] Occlusion therapy, the gold standard of treatment for over a century,[11] consists of covering the nonamblyopic eye with the aim of forcing a child to rely only on visual input from the amblyopic eye. This treatment can successfully improve visual acuity in the amblyopic eye in 60% to 75% of cases,[12,13] and has also been used as a preventative measure. While occlusion therapy does work in older children between the ages of 7 and 18 years,[14–18] and in some cases adults,[19,20] it may have a quicker effect[21] and a higher success rate[22–24] in children younger than 7 years, indicating that intervention during sensitive periods of development can lead to a more successful reversal of the effects of early disordered visual input. However, more recent treatments for amblyopia are being developed that showcase the potential for plasticity in the adult brain.[25] One of these is perceptual learning,[26] in which patients train on difficult visual tasks (usually discrimination or detection tasks) using the amblyopic eye. While the effects of perceptual learning can often be restricted to the specific stimulus set being trained on,[27] some transfer of improvement is apparent, with adults showing an improvement in amblyopic eye visual acuity following training.[28]

Although amblyopia is clinically treated as a monocular disorder of reduced visual acuity in the affected eye, decades of research indicates our clinical understanding of amblyopia is incomplete. First, amblyopia is not a monocular disorder. In other words, it does not arise simply from the disuse of one eye. While amblyopia is traditionally diagnosed and treated as a monocular condition, researchers are now considering amblyopia to be importantly tied to abnormal development of the binocular visual system early in life. The mechanism for

Investigative Ophthalmology & Visual Science

amblyopia may lie in the interactions between the two eyes, such that the nonamblyopic eye suppresses input from the amblyopic eye.[29–31] Recent research on an alternative therapy for amblyopia, dichoptic training, suggests suppression can be mitigated by reducing the signal provided to the nonamblyopic eye (typically in the form of reducing image contrast) so that the input to the amblyopic eye is not suppressed and can be integrated.[32] Thus, a more complete understanding of amblyopia involves knowing how the binocular visual system changes or adapts as a result of early visual disruption, and how the binocular system can be targeted for successful treatment outcomes (see Refs. 33, 34 for reviews).

Second, amblyopia is not simply a disorder of reduced visual acuity. As will be discussed below, an amblyopic eye can show deficits on a range of other spatial vision tasks, including contrast sensitivity, hyperacuity, and spatial integration. It can also show deficits on a range of tasks that involve motion perception, like global motion discrimination, and motion-defined form perception. Vision deficits often persist even after the acuity deficit has been successfully alleviated with occlusion therapy (e.g., contrast sensitivity,[35,36] motion-defined form perception,[37,38] Glass pattern detection,[39] multiple object tracking,[40,41] and stereopsis[42]). Understanding the nature of deficits that can result from early visual disruption, beyond acuity, will provide a better picture of the effects of disruption on the developing visual system (see Refs. 33, 43, 44 for reviews).

Finally, amblyopia does not impact vision in one eye only. Because amblyopia affects the development of binocular vision, this has consequences for the development of the visual pathways associated with the nonamblyopic eye. While visual acuity is clinically normal in this eye, baseline visual acuity is worse compared with control eyes.[45] Moreover, other aspects of spatial vision and motion perception have shown to be deficient. The purpose of this review is to bring together the evidence for perceptual deficits involving the nonamblyopic eye, and consider what they can tell us about normal visual development, and how amblyopia impacts a developing visual system. We will use the term fellow eye to refer to the nonamblyopic eye, but this eye has various names in the literature, including the normal eye, fellow fixing eye, normal fixing eye, dominant eye, good eye, sound eye, nondeprived eye, contralateral eye, amblyopic-mated eye, or even control eye.

Possible Mechanisms for Fellow Eye Deficits in Amblyopia

Historically, the fellow eye in amblyopia was assumed to be normal, because abnormal visual experience occurs monocularly and the visual acuity of the fellow eye is within the normal range. This has led researchers to assess participants with amblyopia on a variety of psychophysical tasks using each eye separately, then comparing results obtained using the amblyopic eye with those obtained using the fellow eye. While interocular differences in sensitivity are important, as will be discussed below, this strategy is not optimal for revealing deficits: first, it does not tell us whether the fellow eye is deficient in some aspects of vision, because the fellow eye is not being compared with a control. Second, if there are indeed deficits in the fellow eye, it may underestimate the magnitude of the amblyopic deficit, particularly for observers with greater fellow eye deficits. Thus, a complete description of amblyopic deficits can only be obtained by comparing thresholds with a control group of children or adults with typical visual development.

Some researchers have probed performance of the fellow eye under the assumption that the fellow eye should perform better than controls.[46] Animal models of visual deprivation have shown that ocular dominance columns of monocularly-reared macaques[47–49] and cats[50–52] can become imbalanced, with more area devoted to, or greater responsiveness for, input from the fellow eye. This led researchers to hypothesize that this change may be accompanied by a viewing advantage for the fellow eye relative to controls. However, as will be discussed, this has not been shown to be the case; no visual function has been identified where performance using the fellow eye is consistently superior to control performance. This may be, in part, because the full monocular deprivation used in early experimental animal models may not capture the variety of ways that amblyopia can occur from natural causes in humans, particularly with less severe forms of deprivation such as strabismus or anisometropia (see Ref. 53 for a discussion), or because of structural and functional differences between human and nonhuman cortex (see Ref. 54 for a discussion). As will be reviewed below, fellow eye performance has found to be similar to, or worse than, controls.

Although researchers have been aware of fellow eye deficits in the amblyopic visual system for a while,[55] no cohesive theory has been put forth to explain why these deficits arise. Outlined below are four ideas that have been touched upon in various studies that have described fellow eye deficits in amblyopia but largely remain to be formalized. While these theories may generate slightly different predictions, they are not necessarily mutually exclusive.

Deficits in the Fellow Eye are Caused by Occlusion Therapy

It is possible that the fellow eye is normal with the onset of amblyopia, but the visual deprivation of the fellow eye associated with occlusion therapy leads to deficits in that eye (see Fig. 1A). Indeed, cases of reverse amblyopia (wherein the fellow eye develops reduced visual acuity relative to the amblyopic eye during occlusion therapy) have been reported.[56–61] These cases of reduced visual acuity in the fellow eye are uncommon and typically reversible, but few have investigated the effect of occlusion therapy on other aspects of vision, such as motion perception or Vernier acuity. It is possible that reduced visual acuity in the fellow eye is a rare and extreme consequence of occlusion, and that children are more likely to develop deficits for subtler functions in the fellow eye that have thus far gone unnoticed because they are not clinically assessed. If this were the case, fellow eye deficits should not be apparent before amblyopia treatment, and should have a delayed onset relative to deficits in the amblyopic eye. More severe deficits may be predicted for children who have undergone longer durations of occlusion therapy, regardless of their visual acuity outcomes following treatment.

Amblyopia Slows the Maturation of Visual Functions in the Fellow Eye

It is possible that the onset of amblyopia, which occurs after birth but before 8 years of age,[8,9] impacts development in such a way that slows the maturation of the fellow eye (Fig. 1B). Because some visual functions continue to develop and refine into the school-aged years, the onset of amblyopia during critical periods of visual development may disrupt normal development of these late-maturing functions while leaving intact those that have already matured,[62] at least for low-level functions.[44] Because amblyopia interferes with binocular development, the maturation of visual functions associated

Investigative Ophthalmology & Visual Science

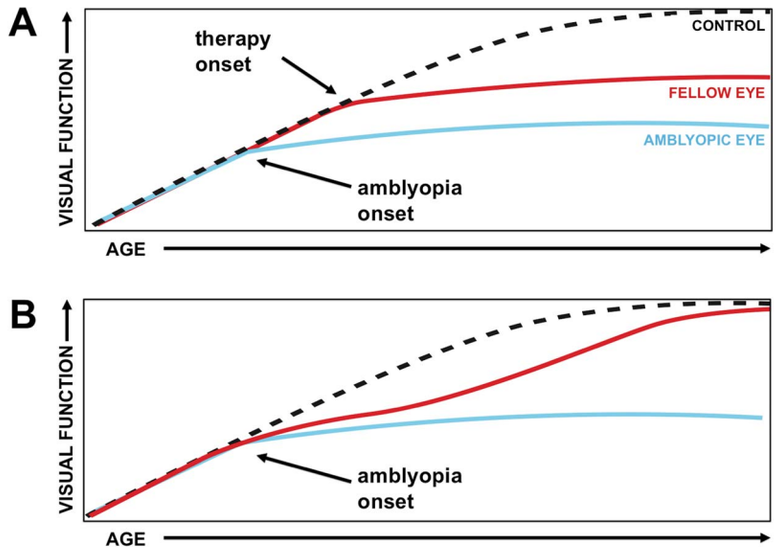

Figure 1. (**A**) Representation of the development of a given visual function as a child matures. The *dashed black line* represents maturation in a control eye; *red*, the fellow eye; *blue*, the amblyopic eye. If the development of fellow eye sensitivity for a given visual function is unaffected by amblyopia but disrupted by occlusion therapy, typical visual development in the fellow eye should be observed until the onset of occlusion therapy, and abnormal sensitivity following this. (**B**) If the fellow eye is impacted by amblyopia, fellow eye sensitivity will be affected immediately, before the onset of treatment. Fellow eye sensitivity may or may not return to the level of controls. If the fellow eye sensitivity does return to normal levels, as depicted above, this may occur naturally but with a prolonged maturation period relative to controls, or as a function of occlusion therapy.

with the fellow eye may be disrupted along with those of the amblyopic eye. However, as the fellow eye's input is not obstructed in strabismus or anisometropia, it continues to mature in response to visual stimulation and experience. In this case, the maturation of the fellow eye may be delayed, such that children with amblyopia show deficits in their fellow eye relative to controls, but not as severe as those in the amblyopic eye. Under this model, fellow eye deficits should be observed after amblyopia onsets, before the initiation of treatment, and should onset concurrent with deficits in the amblyopic eye.

Additionally, these fellow eye deficits may resolve naturally as children continue to develop, with full maturation at a later age than control children. If this were the case, adults with amblyopia should be less likely to present with fellow eye deficits than children, regardless of whether they have undergone amblyopia treatment. Alternately, these fellow eye deficits may resolve only if these children are treated with occlusion therapy, in which case fellow eye deficits should be less prevalent in people of any age who have been successfully treated for amblyopia, compared with those who were less successfully treated, or those who never underwent treatment at all.

Fellow Eye Deficits Occur at Any Level of Visual Processing Involving Binocular Cortex

Fellow eye deficits arise through mechanisms that are difficult to directly evaluate psychophysically in humans. For example, we might predict that fellow eye deficits will arise for any tasks that rely on binocular cortical areas of the brain, because these binocular neurons have undergone atypical development. A monocular visual disruption early in life may cause these binocular cells to develop abnormally, leading to deficits in performance when viewing stimuli with the fellow eye. This is not a simple explanation to evaluate, however, because the first stage where binocular input is combined occurs in striate visual cortex (V1), a fairly early stage in visual processing. In the macaque, most – though not all – layers of the striate cortex contain binocularly innervated cells.[63,64] As such, brains are truly binocular systems: even under monocular viewing conditions, processes that begin with monocular computations will necessarily pass through downstream cortical areas that are binocularly sensitive. Even optotype acuity (acuity for naming letters or symbols), which shows no deficits in the fellow eye by definition, displays binocular summation in normal observers,[65] meaning acuity is better when viewing an optotype chart with two eyes, rather than one. This implies the involvement of binocular cortex (though not necessarily binocular mechanisms) in optotype acuity at some stage of processing. Observers with amblyopia do not show such an advantage,[66] at least for optotypes presented to each eye at equally high contrast.

For simplicity, we can consider binocularly sensitive cells in two categories. First, some cells respond preferentially to stimulation in overlapping receptive fields in both eyes, as is the case for disparity detectors in stereoscopic vision that are used for computing relative differences between two eyes.[67] Though their connections and response properties are immature, many binocular cells in macaque V1 are sensitive to interocular disparity information in infancy.[68] By adulthood, disparity-sensitive cells are abundant throughout a typically developed visual cortex, including V1, V2, V3A, V4, V5/MT+, and a range of intraparietal areas.[69–74] Though not all of these areas necessarily contribute to the perception of stereoscopic depth,[75] they require concordant information between the two eyes in order to respond. It is not surprising then that many children with anisometropic and/or strabismic amblyopia have poor stereopsis as a result of disrupted binocular development,[76,77] even after treatment for amblyopia.[42] Because disparity processing cannot be evaluated independently for amblyopic and fellow eyes, we will not consider tasks that rely on disparity selectivity, though cortical regions underlying these tasks are undoubtedly involved in a range of other perceptual tasks.

Another form of binocular cell comes in the form of those that respond regardless of the eye of stimulation, and these are of interest when considering fellow eye deficits. In a typically

?1

Investigative Ophthalmology & Visual Science

developed visual system, these cells are insensitive to the eye of origin and will respond whether a stimulus is presented to the left or right eye. A well-studied example of this is V5/MT+, which contains motion-sensitive cells that fire whether motion is shown to the left or to the right eye: most MT cells in healthy macaques will fire regardless of eye of origin.[78–80] Psychophysically, an effective demonstration of this is the motion aftereffect, a phenomenon wherein viewing a moving pattern for a prolonged period of time leads to perception of motion in the opposite direction when staring at a test pattern. The motion aftereffect demonstrates partial[81,82] or even complete[83,84] interocular transfer, such that adapting to a motion stimulus with one eye will lead to a motion aftereffect perceived in the other eye, indicating that some regions involved with perception of motion may be insensitive to eye of input. The abnormal visual development that accompanies amblyopia may disrupt these kinds of binocular cells: for instance, many cells lose their binocular sensitivity in amblyopic macaques, with a stronger preference for fellow eye stimulation[85,86] (though see Ref. 87). It is possible that the fellow eye simply takes command of these regions, and these formerly binocular cells become effectively monocular. For example, Wiesel[88] proposed that the shrinkage observed for a deprived eye's ocular dominance columns leaves room for fellow eye expansion through axonal reorganization into unoccupied regions of cortex. If this were the case, we would predict little or no deficit in fellow eye processing. However, the deficits seen in binocular functions imply a widespread disruption of visual processing in these regions. Thus, we might predict that fellow eye deficits become more prominent as information is processed beyond the striate cortex in regions that increasingly involve binocular cortex and are able to process input from either eye, regardless of upstream structural changes. While aspects of vision may not be reduced in the fellow eye to the same extent as the amblyopic eye, deficits in the fellow eye may be more likely to arise for visual functions that rely on cortical areas that are responsive to input from either eye, with more severe deficits for aspects of vision that are increasingly binocular in the sense that they are not sensitive to input eye. Moreover, we would predict that more severe amblyopia should be associated with greater fellow eye deficits, because the amblyopia would have a deeper impact on binocular regions.

Fellow Eye Deficits Reflect an Adaptive Mechanism That Equates the Sensitivity of the Two Eyes

Another possibility is that fellow eye deficits reflect an adaptive mechanism that decreases the sensitivity of the fellow eye in response to the reduced sensitivity of the amblyopic eye. In amblyopia, an increase in disordered or unreliable input to one eye due to amblyogenic factors leads to a decrease in sensitivity to the visual information delivered by that eye. If an adaptive central mechanism is intact, this may be accompanied by a complementary reduction in sensitivity for the fellow eye, in order to alleviate competition between the two eyes, or to attenuate the suppression of the amblyopic eye by the fellow eye. Under this model, the lack of a fellow eye deficit is associated with greater interocular differences in sensitivity, which may lead to stronger interocular suppression, and this may represent more severe amblyopia. If the visual system is effective at reducing the fellow eye's sensitivity, greater fellow eye deficits in childhood might be associated with more successful resolution of amblyopia. It is even possible that early fellow eye deficits are protective factors that may prevent amblyopia from developing in the first place.

The proposed mechanisms outlined above are not all mutually exclusive. For example, a slower maturation of fellow eye sensitivity (section 1.1.2.) may provide the time for adaptive mechanisms to yield a beneficial outcome (section 1.1.4.). In this review, we consider deficits in five visual tasks – positional acuity, contrast sensitivity, spatial integration, global motion perception, and motion-defined form perception – commonly reported for the amblyopic eye. We review the evidence for fellow eye deficits in each task, and if these deficits are consistently present, we consider whether they may arise from abnormal binocular processing, adaptive mechanisms, and/or the effects of occlusion therapy and aging. ?2

Positional Acuity

Hyperacuity is a general term describing the ability normal observers have to obtain spatial vision thresholds smaller than would be expected based on the resolution limits of the retina.[89] A commonly studied type of hyperacuity in amblyopia is the ability to detect a difference in the relative location of at least two elements (Figs. 2A–F). Collectively, these tasks measure a hyperacuity that will be referred to as positional acuity (also known as Vernier acuity for some tasks). An alignment threshold, the smallest offset between two elements that can be detected, can quantify positional acuity. Positional acuity is thought to be cortically mediated: thresholds are resistant to retinal image degradation[90,91] and target movement across the retina.[92] Positional acuity shows a significant binocular summation advantage,[93,94] meaning thresholds are better when viewing stimuli binocularly compared with monocularly. While this may reflect summation mechanisms downstream of the cortical site of positional acuity processing, alignment thresholds are elevated in one eye when stimuli are masked or flanked by objects presented to the other eye,[95] suggesting interaction between the two eyes, beyond summation, is possible. In infants, Vernier acuity surpasses the resolution of grating acuity (the ability to distinguish a patch of black and white stripes) at 3 months of age[96] or even earlier.[97] The development of positional acuity is likely dependent on development of cortical columns in striate cortex.[98] Alignment thresholds of typically developing children are not adult-like until 5 years of age[99] or later,[100,101] and have shown full maturation as late as age 14 years.[102] Other kinds of hyperacuity tasks, like the ability to detect minor perturbations in a circle, may not reach maturity until even later in life.[103]

Positional Acuity Deficits in the Amblyopic Eye

Deficits in positional acuity are prevalent when viewing stimuli with the amblyopic eye. Alignment thresholds are typically elevated relative to controls[46,104] or to the fellow eye,[105,106] with thresholds in adult amblyopic eyes similar to those of 3- to 4-year-old control children.[100] Additionally, the subjective point of alignment between the two compared positions is shifted to one side of the true aligned position.[107–109] Some studies have found that the amblyopic eye deficit cannot be predicted from contrast sensitivity, grating resolution, or letter acuity,[109] while others have shown a relationship with contrast sensitivity[46] or letter acuity.[105,106] These differences may reflect methodologic factors such as the size, contrast, or configuration of the stimulus used. The amblyopic deficit is particularly worse at very short viewing durations,[109] and has shown to be more disrupted in strabismic than in anisometropic amblyopia[100,105,106,108,110–113] and in observers with more severely compromised binocular function.[76,114] Adults with amblyopia do not show a robust binocular summation effect for positional acuity.[115] Positional acuity deficits in anisometropic amblyopia cannot be accounted for by increased blur or reduced signal input.[116] Alignment thresholds can improve after occlusion

Investigative Ophthalmology & Visual Science

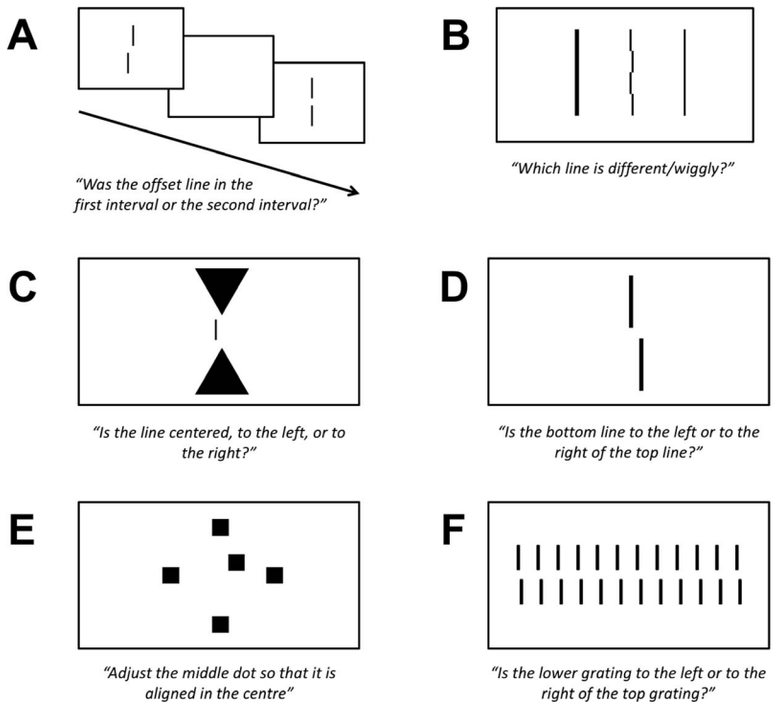

FIGURE 2. Examples of stimuli used to measure alignment thresholds for assessing positional acuity. Stimuli are recreated from (**A**) Freeman & Bradley,[46] (**B**) Carkeet et al.,[100] (**C**) Bedell et al.,[107] (**D**) Rentschler & Hilz,[109] (**E**) McGraw et al.,[121] and (**F**) Levi & Klein.[105,106]

therapy in children, with greatest improvement shown in children with greatest deficits.[117] Thresholds can also improve with practice for adults, though the magnitude of this effect is smaller in untrained orientations.[118]

Positional Acuity Deficits in the Fellow Eye

Evidence for the positional acuity of the fellow eye has been mixed, but largely suggests there is not a robust deficit with fellow eye viewing. While two early studies found alignment thresholds in the fellow eye of adult observers to be approximately 5 arcsec better than those of monocularly-viewing controls,[46,109] no further studies have uncovered a benefit to the fellow eye in positional acuity. In fact, most investigations suggest the positional acuity of the fellow eye remains intact. No difference was found between controls and the fellow eye in positional acuity at the retina, with a very small fellow eye deficit in the nasal periphery.[119] No difference was found in alignment thresholds for the fellow eye of a young adult with congenital cataract and his normally sighted twin.[120] Moreover, no difference in vertical or horizontal alignment thresholds was found between age-matched controls and the fellow eye of children with amblyopia who had not yet undergone treatment[121] or who had a variety of treatment histories.[108]

While fellow eye deficits do not appear to be prevalent, some evidence implicates strabismus, rather than anisometropia, in poor fellow eye performance. Some studies have reported fellow eye deficits for strabismic, but not anisometropic, amblyopia in adults[112] and children.[122] Strabismic amblyopia can be associated with poor fixation stability in the fellow eye,[123,124] so it is possible that the positional uncertainty implied by elevated thresholds is due to unsteady eye movements. This is unlikely; however, positional acuity is not affected by retinal image motion in normal viewers.[92] Moreover, thresholds in the amblyopic eye are not elevated by nystagmic eye movements[104,106] or presentations too brief for an eye movement to occur,[107] nor do they differ between steady and unsteady fixators.[108] If poor fixation does not account for poor positional acuity in the amblyopic eye, it seems unlikely to account for poor positional acuity in the fellow eye. A second factor leading to positional acuity deficits in the fellow eye may be the presence of strabismus on its own, rather than amblyopia. For example, Bedell et al.[107] assessed line displacement thresholds in adults with strabismic amblyopia, adults with strabismus but not amblyopia, and controls. The affected eyes of observers in the strabismus groups were significantly elevated compared with controls, with amblyopic eyes showing even larger thresholds than strabismus-only eyes. However, the fellow eye of 43% of people with amblyopia and people with strabismus only had abnormally elevated displacement thresholds. Moreover, adults with strabismus show elevated alignment thresholds in their fellow eye regardless of depth of amblyopia.[125] This may account for the good performance of patients studied by Freeman and Bradley,[46] who only assessed fellow eyes in anisometropic amblyopia.

Mechanisms Underlying Deficits in Positional Acuity

The mechanisms supporting positional acuity are likely in striate cortex[126] with no need for additional downstream processing.[127] Westheimer[128] showed that positional acuity cannot be limited by spatial constraints imposed by ocular dominance columns, so the imbalance in ocular dominance columns observed in animal models of severe amblyopia noted previously (e.g., Refs. 47–52) does not, on its own, imply an impact on fellow eye alignment thresholds. In support of this, human participants who have been enucleated (i.e., have had one eye surgically removed) within

Investigative Ophthalmology & Visual Science

the first few years of life show no benefits to positional acuity in the remaining eye compared with monocularly tested controls.[125] While enucleation does not model the interocular suppression that accompanies amblyopia, this indicates that the availability of increased cortical area or responsiveness is not sufficient for improvements in alignment thresholds. Instead, the spatial distortions (expansion, contraction, or warping of parts of the visual field) and spatial uncertainty (poor precision) that accompanies amblyopia may account for poor alignment thresholds.[104,107,123] It has been demonstrated that while spatial uncertainty (poor precision) is prevalent in the amblyopic eye of participants with either etiological subtype, spatial distortions are more likely to occur in viewers with strabismus, and not in those with anisometropia,[129,130] at least when contrast sensitivity deficits are controlled for.[131]

If elevated thresholds in the deprived eye are associated with amblyopia through one mechanism (spatial uncertainty), while elevated alignment thresholds in both eyes are associated with strabismus through another mechanism (spatial distortions), this may produce the pattern of results observed above: observers with anisometropic amblyopia would show deficits in the amblyopic eye only, while those with strabismic amblyopia would show deficits in both eyes, with an even more severe deficit in the amblyopic eye. A potential mechanism for fellow eye deficits in strabismus may be anomalous retinal correspondence, a condition that can occur when points on the retina of the fellow fixating eye do not perfectly match to points on the deviated eye.[132] In this case, positional information from the fellow eye may be influenced by the corresponding spatial distortions introduced by the deviated eye.[129,133] However, the fellow eyes of strabismic observers do not show clear spatial distortions compared with control observers.[129,130] Consistent with this, Fronius et al.[108] found no deficits in the fellow eyes of children with strabismic amblyopia who showed elevated thresholds using their amblyopic eye. Thus, this cannot be a full account of fellow eye deficits in positional acuity in strabismus. Moreover, most observers studied by Rentschler and Hilz[109] had strabismic amblyopia, and it remains unclear what mechanism would lead to superior positional acuity thresholds for these participants than those of control observers.

In summary, while amblyopia appears to cause deficits in positional acuity in the amblyopic eye, it does not appear to lead to robust deficits in the fellow eye. Subtle deficits may arise as a consequence of strabismus, rather than amblyopia, though further research is necessary to confirm the conditions under which these deficits arise. Because positional acuity can be solved by purely monocular mechanisms in striate cortex, and amblyopic deficits in binocular summation likely reflect downstream disruptions in binocular interactions at processing stages after positional differences are resolved, this is consistent with the notion that fellow eye deficits should only be observed for visual tasks that are subserved by binocular mechanisms. In macaques, the difference between amblyopic and fellow eye positional thresholds is reduced when the effective contrast of the test stimuli is equated between the two eyes,[111] which suggests that a fellow eye deficit would theoretically provide an advantage for alleviating suppression; the fact that a deficit in the fellow eye is not commonly reported may reflect that interocular differences in hyperacuities are not obvious or large enough to require such an adaptation. Finally, no studies have directly investigated the effects of occlusion therapy on alignment thresholds in the fellow eye, so it remains a question whether treatment impacts positional acuity in this eye. However, little evidence suggests we should predict a change.

Contrast Sensitivity

Contrast sensitivity is the ability to differentiate boundaries of different luminance. Typically, contrast detection thresholds (where a smaller number means greater sensitivity) are measured and converted into sensitivities (where a larger number means greater sensitivity). The contrast sensitivity function describes the ability of the visual system to detect differences in contrast of gratings at different spatial frequencies, quantified by cycles (stripes) per degree of visual angle (Fig. 3A). Sensitivity to contrast can also be assessed with a letter chart by presenting letters at a fixed size with decreasing contrast (Fig. 3C).[134] Contrast sensitivity does not reflect one single function; sensitivity can be affected by factors at the level of the retina, the lateral geniculate nucleus, or the cortex.[135] A typical contrast sensitivity function for adults has a peak around 4 cyc/deg. Contrast sensitivity increases rapidly in the first few months of life.[136] While the contrast sensitivity function generally retains the same shape throughout development,[137] it is reduced at all spatial frequencies in 4-year olds[138] and though differences after around age 8 can be small,[139] may not reach adult levels until adolescence.[140] Contrast sensitivity shows a similar prolonged development in macaques.[141]

Contrast Sensitivity Deficits in the Amblyopic Eye

Depending on the study, contrast sensitivity has been found to be reduced in the amblyopic eye at all spatial frequencies, at high spatial frequencies only, or in a combination of these two patterns (Fig. 3B).[142–146] Amblyopic macaques show similar deficiencies in their amblyopic eyes.[86,111] Contrast sensitivity deficits in amblyopia exist both at the fovea and in the periphery.[147] These deficits are sometimes found to correlate with visual acuity of the amblyopic eye, though not always.[148–151] Macaques with amblyopia show deficits in discriminating between gratings of suprathreshold contrast, and these deficits cannot be accounted for by their contrast detection thresholds.[152] Low-contrast letter acuity can improve with occlusion therapy.[117] However, deficits in contrast sensitivity in the amblyopic eye may persist after successful treatment (i.e., 20/20 visual acuity),[36,151] although some children have shown improvements in sensitivity to mid to high spatial frequencies in the amblyopic eye after treatment even when they demonstrate no gains in visual acuity.[153]

Contrast Sensitivity Deficits in the Fellow Eye

Evidence for the integrity of contrast sensitivity in the fellow eye is mixed. Early studies assumed the fellow eye did not show any deficits in contrast sensitivity. Some studies have used the fellow eye of patients as a control to determine whether the amblyopic eye demonstrates a deficient contrast sensitivity,[142–144,146,149] a technique that may mask deficits in the fellow eye. Some have compared interocular differences between the eyes of patients with the interocular differences between eyes of controls (e.g., Refs. 154, 155), which does not allow comment on fellow eye performance on its own and may confound poor fellow eye performance with good amblyopic eye performance. However, because the typical contrast sensitivity function in a healthy eye is well-studied, these studies can comment on the shape of the fellow eye's function, and it is often reported to be normal in both shape and amplitude.[142,144,149] Sjöstrand[146] described the contrast sensitivity of children aged 4- to 12-years old with anisometropic or strabismic amblyopia as "within or slightly below the normal range," though this comment was made with reference to the known adult contrast sensitivity function rather than a control

Investigative Ophthalmology & Visual Science

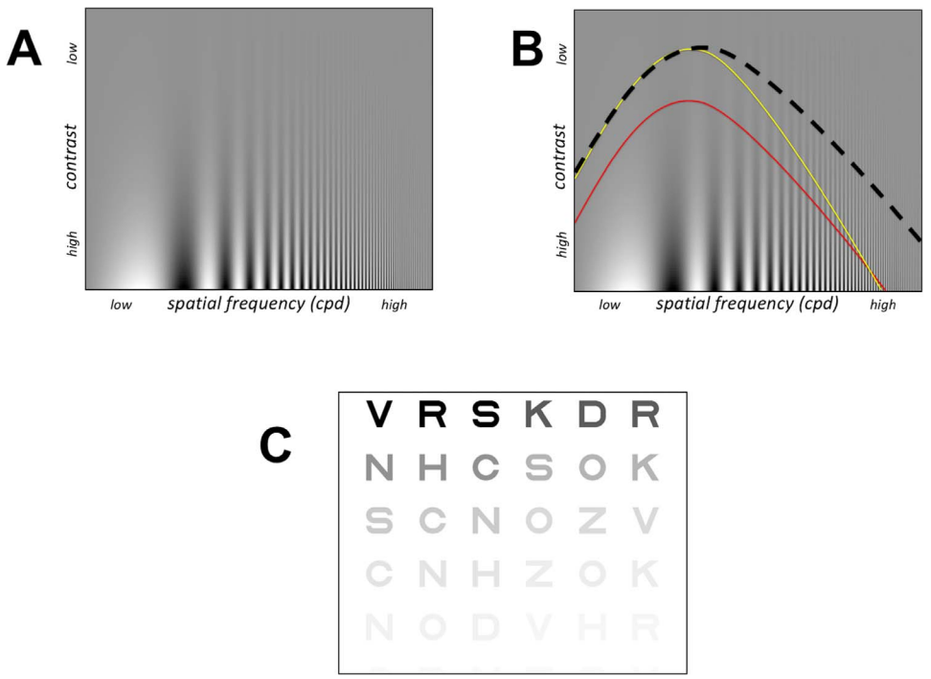

Figure 3. (**A**) An example of the range of spatial frequencies (in cycles per degree of visual angle) and contrast levels assessed with contrast sensitivity tasks. As contrast decreases, stripes become less visible; however, visibility is not constant across all spatial frequencies. The function that describes stripe visibility is the contrast sensitivity function. (**B**) A representation of a contrast sensitivity function for a typical adult is shown in *black dashed lines*. Stripes above the line are not visible to the observer. The *red line* represents a contrast sensitivity function that is depressed at all spatial frequencies. The *yellow line* represents a contrast sensitivity function that is depressed at high spatial frequencies only. (**C**) Letter contrast sensitivity is assessed with an eye chart using letters of the same size but decreasing contrast. In the Pelli-Robson contrast sensitivity chart,[134] letters of decreasing contrast are presented in groups of three; the contrast of the last triplet on which a viewer can correctly identify two of the three letters is their contrast sensitivity.

group of age-matched children, so it is not clear if this observation reflects immaturities or true deficits. Another study of children with amblyopia found that the fellow eye of these children performed as well as or better than a group of control children with a mean age of 10 years[35]; however, these patients had a mean age two years older than the control group and better visual acuity in their fellow eyes, which may explain their superior performance. Patients with strabismus, whether or not they have amblyopia, have shown significantly reduced letter contrast acuity in the fellow eye compared with monocularly viewing controls,[156] so receiving disordered binocular input of any kind during critical periods of development may be at the root of fellow eye deficits. On the other hand, under some conditions, the contrast sensitivity function of the fellow eye of adults with strabismic amblyopia has been shown to be normal compared with controls (e.g., Ref. 143). Other studies have shown that for amblyopia due to unilateral congenital cataract, contrast sensitivity functions in the fellow eye of children who had undergone treatment were found to be depressed at high spatial frequencies,[157] so these deficits cannot be accounted for solely by strabismus.

Deficits in contrast sensitivity for the fellow eye are not likely to be related to the occlusion of this eye during treatment for amblyopia. Contrast sensitivity was assessed in children with amblyopia undergoing full-time occlusion therapy, and shown to be reduced in the occluded eye after 8 weeks of occlusion,[158] indicating fellow eye sensitivity may be negatively impacted as consequence of amblyopia treatment. However, sensitivity returned to pretreatment levels at a 6-month follow-up visit during which no occlusion was conducted, so this effect may be short-lived. Alternately, letter contrast sensitivity of the fellow eye has shown to improve in the fellow eye during a pretreatment period of glasses wearing prior to occlusion[159] even in participants with plano (non-corrective) lenses over the fellow eye. No further improvement was shown during or after treatment. No age-matched control group was available in these studies to determine whether the initial contrast sensitivity of the fellow eye was abnormal, however.

Further evidence indicates that deficits in the fellow eye do exist prior to the onset of treatment, and that these deficits may be resolved with occlusion therapy. Two studies found that the amblyopic and fellow eyes showed abnormal contrast during, or prior to beginning, treatment compared with age-matched controls.[160,161] While contrast sensitivity in the amblyopic eye was deficient at all spatial frequencies, contrast sensitivity of the fellow eye, which had normal visual acuity, was deficient at high spatial frequencies only. In a subset of children assessed after occlusion therapy, contrast sensitivity had improved in both eyes, with the fellow eye performing at the level of age-matched controls. Moreover, children who had poorer acuity outcomes in the amblyopic eye following therapy had poorer contrast sensitivity in the fellow eye. Wali et al.[161] additionally noted that the contrast sensitivity of the amblyopic and fellow eyes was significantly correlated, indicating a shared mechanism. Finally, another study[162] assessed contrast sensitivity in children with amblyopia who fell into one of three groups: patients who had never had occlusion therapy, patients undergoing occlusion therapy (with worse than 20/20 vision in the amblyopic eye), and patients who had finished occlusion therapy successfully (20/20 vision or better in the amblyopic eye). All three patient groups had significantly poorer contrast sensitivity in both eyes compared to the controls, at all spatial frequencies; however,

Investigative Ophthalmology & Visual Science

patients who had successfully completed occlusion therapy had better contrast sensitivity in the fellow eye at high spatial frequencies relative to the remaining group of patients.

Mechanisms Underlying Deficits in Contrast Sensitivity

Reduction in contrast sensitivity in amblyopia is assumed to have a neural origin: researchers have ruled out factors such as defocus,[154] and unstable eye fixations.[163] Similar to positional acuity, we can consider what happens to striate cortex to generate a prediction for what might happen to the contrast sensitivity of the fellow eye. Contrast sensitivity deficits are associated with a reduction in the width of the corresponding ocular dominance columns in macaques,[164] so we may expect the fellow eye to have a corresponding increase in sensitivity. In support of this, participants who have undergone enucleation early in life have better contrast sensitivity thresholds[165] and letter contrast acuity[156] than monocularly viewing controls, suggesting a cortical reorganization following monocular deprivation that can increase the sensitivity of the fellow eye (although they do have deficits in motion perception – discussed below in section 6.3.). In fact, compared with controls viewing binocularly, these observers have similar contrast sensitivity[165] and letter contrast acuity,[166] indicating an upper limit to benefits equal to that of binocular summation in a typical visual system. In less severe forms of binocular disruption, as is the case with anisometropic or strabismic amblyopia, humans have shown normal spacing of ocular dominance columns,[167,168] except in the periphery,[169] although structure may not imply function: a reduction of contrast sensitivity in the amblyopic eye is associated with reduced activity in humans.[170] Still, monocular contrast sensitivity was found to be better in the amblyopic and the fellow eye for those with poor stereopsis, compared with those with good stereopsis and comparable acuity.[76] These authors[76] suggest that neurons formerly dedicated to binocular interactions are able to rearrange to support monocular sensitivity, which remains consistent with equal spacing of ocular dominance columns. Thus, we may anticipate no deficits in the contrast sensitivity of the fellow eye, and possibly superior performance.

However, there may be a functional role for a reduction in contrast sensitivity of the fellow eye. In contrast to animal models with severe deprivation amblyopia or monocular observers, an anisometropic or strabismic amblyopic eye continues to receive some visual input. One mechanism for suppression in amblyopia is the higher contrast sensitivity of the fellow eye, which interferes with contrast detection in the amblyopic eye.[171] Poorer fellow eye contrast sensitivity may be indicative of deeper or more treatment-resistant amblyopia due to amblyopia's impact on the development of binocularly sensitive cortical regions, but this shared mechanism may act to keep fellow eye sensitivity reduced while the acuity of the amblyopic eye remains poor. Thus, given the reduction in contrast sensitivity of the amblyopic eye, a corresponding reduction in sensitivity of the fellow eye may be adaptive for relieving, or at least lessening, suppression. Both binocular summation and interocular transfer (an elevated contrast threshold in one eye after adapting to a stimulus of the same spatial frequency presented to the other eye) have been observed in people with amblyopia at the spatial frequencies for which the two eyes have equal or near-equal contrast sensitivity, but not at the spatial frequencies for which the two eyes have very different sensitivities.[145,172,173] This leads to the intriguing possibility that observers who have reduced contrast sensitivity in the fellow eye may show less interference or suppression of the amblyopic eye. In support of this, Baker et al.[174] have shown that while amblyopic observers do not have normal binocular summation when shown equal contrast in the two eyes, they do have normal binocular summation when stimuli are matched to be perceived as equal contrast, by reducing the contrast of the fellow eye until it perceptually matches that of the amblyopic eye. Moreover, visual tasks that target this contrast imbalance by presenting dichoptic stimuli at perceptually matched contrast levels have been shown to improve visual acuity in the amblyopic eye.[175] Taken together, these results suggest that equated contrast sensitivity can promote binocular interactions, or at least reveal residual binocularity in a visual system that would otherwise show suppression of the visual input from the amblyopic eye by the fellow eye. Thus, a reduction in contrast sensitivity of the fellow eye, if it occurs naturally, might be an adaptation for reducing suppression and promoting normal binocular function. Studies assessing contrast sensitivity during treatment indicate that occluding the fellow eye does not damage contrast sensitivity in this eye,[160–162] though they do not clearly indicate whether deficits in the fellow eye exist prior to occlusion therapy.

If there are deficits in the contrast sensitivity function of fellow eyes of people with amblyopia, why are they not always revealed? A few factors may account for why earlier studies that have investigated contrast sensitivity in the fellow eye did not report deficits: for example, studies that report normal function have tended to study adults using method of adjustment or limits (e.g., Refs. 142–144) while those showing fellow eye deficits have tended to study children using charts with forced-choice alternatives (e.g., Refs. 160–162). Substantive differences are not likely to arise from using subjective versus forced-choice methods in measuring contrast sensitivity in amblyopia,[154] so it is likely that the different populations under study are showing true differences in the contrast sensitivity of the fellow eye. Two reasons may account for the differences observed in children vs. adults. First, it is possible that adults participating in amblyopia research may be more likely to have undergone treatment earlier in life. The positive effects of occlusion therapy on fellow eye contrast deficits observed in children likely persist beyond childhood, and so these deficits are not detected in adults. This cannot be a full explanation, however, because untreated adults have demonstrated normal contrast sensitivity in the fellow eye.[144] Second, there may be a developmental component to the contrast sensitivity function of the fellow eye. In other words, reduced sensitivity in the fellow eye during childhood may be a mechanism for plasticity and a greater ability for recovery early in life rather later in adulthood. This may manifest in the form of a prolonged developmental time course for the contrast sensitivity function of the fellow eye, which may eventually reach adult-like levels but at a later age than typically developing controls.

In summary, children, and less consistently adults, with amblyopia show clear contrast sensitivity deficits in the fellow eye. These deficits are not caused by occlusion therapy, and tend to be selective for high spatial frequencies, though they may appear at all spatial frequencies. Evidence supports the notion that fellow eye deficits in contrast sensitivity are linked to the integrity of the amblyopic eye: contrast sensitivity in the fellow eye can increase in children who are given prescription glasses, even when only the amblyopic eye receives a refractive correction[159]; fellow eye contrast sensitivity after treatment is better for children who have good amblyopic eye acuity outcomes than those who do not[160,161]; and fellow eye contrast sensitivity correlates with amblyopic eye contrast sensitivity.[161] Taken together, these studies strongly suggest a functional role of fellow eye deficits in amblyopia. To determine if this is the case, a number of additional hypotheses

Investigative Ophthalmology & Visual Science

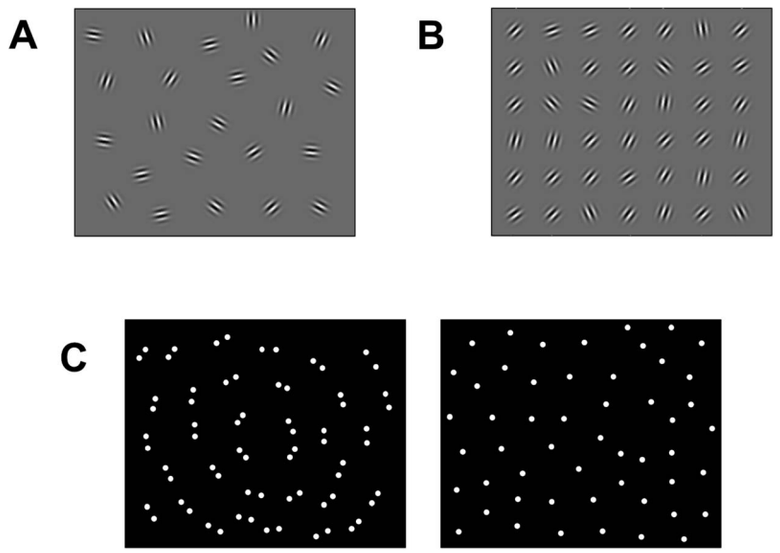

FIGURE 4. (**A**) An example stimulus that can be used in contour integration tasks. Gabor patches are oriented such that a circle or oval can be identified in the center portion of this image. An observer may be asked to identify which of two images contains the contour, or to identify the portion of the image that contains the contour. Increased orientation noise and decreased spacing among patches can make this task harder. (**B**) An example of a stimulus used in a global orientation task where Gabor patches are tilted clockwise. Lines or other textures may also be used in these stimuli. Observers are typically asked to discriminate the orientation (e.g., clockwise or counter-clockwise; horizontal or vertical). (**C**) An example of a concentric Glass pattern with high coherence. Observers are typically presented with a Glass pattern (*left*) and a noise pattern (*right*), and must identify which contains the coherent pattern. Pattern coherence is decreased in order to obtain a coherence threshold.

need to be tested: first, weaker suppression should be correlated with greater fellow eye deficits in contrast sensitivity. To our knowledge, no one has directly investigated this possibility. Second, worse contrast sensitivity in the fellow eye should predict better visual acuity in the amblyopic eye later in life – though it is unclear at this stage if these deficits should lead to more successful treatment outcomes, or if they may act as protective factors that preclude the need for occlusion therapy in the first place. Finally, a longitudinal study will help resolve whether these deficits reflect a prolonged development of contrast sensitivity in amblyopia compared with controls that reaches typical adult-like performance regardless of treatment status.

Spatial Integration

Spatial integration refers to the general ability to combine visual cues in a stimulus spanning a large area of the visual field for a cohesive percept. This information is distributed across multiple receptive fields, presumed to be subserved by facilitatory long-range lateral connections between orientation-tuned cortical cells in V1.[176,177] Contour integration, global orientation discrimination, and Glass pattern detection are all tasks that require integration of elements across the visual field (Fig. 4). Contour integration tasks assess the ability to detect collinear elements over large retinal distances, often using an array of Gabor patches with varying levels of orientation noise (Fig. 4A). This task typically requires the participant to detect a contour in the form of a path or an oval. Because Gabor patches belonging to the target and the distractors are evenly spaced, the only cue to contour in these stimuli is the orientation of the patches. Global orientation tasks assess the ability to detect or discriminate the overall direction of tilt in a pattern made up of correlated elements (Fig. 4B), usually Gabor patches or lines. Typically, an observer reports the orientation of the pattern (e.g., clockwise or counter-clockwise; horizontal or vertical). Noise patches may be randomly oriented, or the entire array of patches may have a mean orientation with a SD. Similarly, this task requires the integration of local elements across space. Glass pattern consist of an array of dot pairs that are spatially displaced to create translational or concentric patterns (Fig. 4C). Noise is added by breaking some of the dot pairs and randomly plotting their positions. Dot coherence is reduced until the observer can no longer discriminate a Glass pattern from a full noise pattern. On their own, local dot pairs cannot signal the global pattern, so observers must be able to integrate across the field to detect a coherent stimulus.

Three-month-old infants are sensitive to correlated orientations in Gabor patch arrays,[178–180] and 3-year-old children can discriminate the global orientation of a dense array of lines among distractors at similar levels to adults.[181] Sensitivity for translational and concentric Glass patterns becomes adult-like between the ages of 6 and 9 years,[182] and contour detection thresholds improve until at least age 14 years.[183,184] In developing macaques, contour integration[185] and Glass pattern detection[186] mature between 2 to 3 years of age, a developmental human age equivalent[187] of 8 to 12 years.

Spatial Integration Deficits in the Amblyopic Eye

Spatial integration is known to be deficient in the amblyopic eye. Some evidence implicates a greater deficit for strabismic than anisometropic amblyopia[188]: when stimulus visibility is controlled for, path detection is still impaired in strabismic amblyopia[189] but not in anisometropic amblyopia.[190] Adults with amblyopia also show deficits on oval contour detection tasks, particularly when more orientation noise is present,[191] and on dotted line detection tasks when noise is present.[192] These deficits are not due to poor acuity or contrast sensitivity, but may be due to difficulties in the amblyopic visual system with separating noise elements from signal elements.[193] Similar results have been found in patients with anisometropic or

strabismic amblyopia for contour detection[194] and global orientation discrimination.[195,196] Glass pattern detection is impaired in strabismic amblyopia[39] and deprivation amblyopia.[197] When characterized by interocular threshold differences, contour detection has also been shown in children with anisometropic amblyopia who have not yet received therapy, and greater interocular contour detection thresholds have been shown to correlate with greater interocular acuity differences.[198] This suggests that depth of amblyopia may play a role in the severity of contour integration deficits. Contour detection thresholds in the amblyopic eye of children with anisometropic, strabismic, or mixed amblyopia can improve after occlusion therapy.[199]

Spatial Integration Deficits in the Fellow Eye

As with contrast sensitivity, spatial integration deficits in the fellow eye have been described only relatively recently. Some studies of contour integration have used the fellow eye as a control for the amblyopic eye,[189,190] while others have calculated interocular differences in contour detection thresholds[198] which, as discussed, may mask fellow eye deficits because a lower interocular difference may reflect poorer fellow eye rather than better amblyopic eye performance. Deficits in contour integration[191] and global orientation discrimination[195] have been shown to be present, but less severe, in the fellow eyes of adults with anisometropic or strabismic amblyopia. Similarly, amblyopic macaques have shown deficits in contour detection[200] and Glass pattern detection[201] in both eyes, with the fellow eye deficits being less severe. Sampling efficiency, an indicator of the amount of information an observer can extract from a stimulus, has also been shown to be worse in both the amblyopic and fellow eyes compared with controls.[202,203]

Most evidence indicates that it is not likely that occlusion therapy causes deficits to occur in the fellow eye. On one hand, adult observers with strabismus who did not currently have amblyopia showed contour detection deficits in both eyes.[191] This group was defined based on their current acuity, so it is unclear if this population included treated patients with a history of amblyopia. From this result only, we might conclude that successful treatment for amblyopia can lead to fellow eye deficits in spatial integration. However, another study designed to monitor contour integration throughout occlusion therapy indicates that successful treatment for visual acuity in the amblyopic eye is associated with an improvement in contour integration for the fellow eye.[199] Here, it was found that contour detection thresholds were elevated in both the amblyopic and fellow eyes of children before starting occlusion therapy, with deficits in the amblyopic eye significantly worse than those in the fellow eye. The interocular difference in contour detection thresholds approached those of controls by 4 weeks of treatment, stabilizing after 8 weeks. At a 4-month follow-up, interocular differences in visual acuity were still present despite equal contour detection thresholds. Given that contour integration shows a protracted period of development,[183,184] it may be that this visual skill shows more plasticity than visual acuity recovery, with a long sensitive period for recovery. Though contour detection thresholds were effectively equal between the two eyes of treated children with amblyopia, thresholds of the amblyopic and fellow eye were still elevated relative to controls, indicating that the visual system stabilizes with equal performance, and not necessarily good performance. While not strong evidence, this is consistent with the notion that a fellow eye deficit prior to treatment may provide an advantage to the amblyopic visual system by reducing the magnitude of interocular differences.

Mechanisms Underlying Deficits in Spatial Integration

Cortical mechanisms for spatial integration are distributed across many levels of visual processing. Kovács et al.[184] proposed that the prolonged refinement of contour detection thresholds into adolescence may reflect the later maturation of horizontal connections within V1. Burkhalter et al.[204] have argued that because ocular dominance columns and binocularity are established before the horizontal connections in some V1 layers, these connections may not begin to mature until after these regions can detect binocularly correlated input. If this is the case, an early disruption of binocular development may impact normal development of the lateral connections in V1 that subserve contour integration in the amblyopic eye, and possibly the fellow eye as well. In the macaque, feedback projections to V1 are ubiquitous in V2.[205] Kiorpes and Bassin[185] have argued that the later maturation of these connections[206] indicates that these feedback connections, rather than connections within V1 only, may be more important for contour integration. Importantly, strabismic macaques with amblyopia show a reduction in V2 relative to V1 activity,[207] implicating a disruption to these connections. Macaques with anisometropic amblyopia show disordered organization of orientation-selective subfields in V2 driven by both the amblyopic and the fellow eye.[208] Thus, disruptions in the V1 to V2 reciprocal connections that organize V2 receptive fields, which involve binocular mechanisms (though not exclusively), may account for deficits in contour integration in both the amblyopic and fellow eye. These connections may underlie an adaptive mechanism that works to achieve the equilibrium in spatial integration abilities observed by Chandna et al.,[199] rather than control-like performance levels.

In addition to these areas of early visual cortex, the higher-level object-sensitive lateral occipital complex is sensitive to collinear Gabor patches,[209–211] likely reflecting feedback related to figure interpretation or context.[177] This area is disparity-sensitive,[212,213] and as such, responds to input from both eyes. Thus, contour integration may involve mechanisms that require normal binocular development, both in early visual cortex and in higher cortical areas. This decrease in the range of interactions that can be integrated by the fellow eye may be an adaptation to equate the sensitivity of the amblyopic and fellow eyes. On the other hand, feed-forward mechanisms could disrupt the development of the lateral occipital cortex and impact contour integration in both the amblyopic and fellow eyes.

In summary, deficits in spatial integration as a result of amblyopia are prevalent in the fellow eye, though they are not as severe as those observed in the amblyopic eye. They are not limited to one etiological subtype of amblyopia. Because these deficits are observed in children before initiating occlusion therapy, they are not a consequence of amblyopia treatment. In fact, treatment may be beneficial for mitigating the deficit in both the amblyopic and fellow eyes. These deficits likely arise from binocularly sensitive regions in primary visual cortex, as well as downstream areas. The evidence for whether these deficits reflect an adaptive mechanism, however, is not strong. While there is some suggestion that spatial integration improvements for the amblyopic eye stop once they reach the level of the fellow eye, rather than control performance,[199] additional research is necessary to reveal whether these fellow eye deficits are advantageous prior to treatment. For example, do spatial integration deficits in the fellow eye predict better outcomes after occlusion therapy? Are they associated with weaker interocular suppression? Like contrast sensitivity, there is some indication that fellow eye deficits are more prevalent in children, so it is important to determine if these deficits exist in

Investigative Ophthalmology & Visual Science

childhood as a consequence of slower development, or as indicators of better acuity outcomes later in life for those without treatment for amblyopia.

Global Motion Perception

Global motion perception, put simply, is the ability to perceive a set of stimuli moving in a coherent direction. A common way to assess global motion is with a random dot animation that contains signal dots moving coherently in the same direction and noise dots moving in random directions (Fig. 5); sometimes, researchers use Gabor elements or spatially filtered dots in order to carefully control the spatial frequency content of the stimulus. Typically a translational (left/right or up/down) motion pattern is used, though radial (expanding/contracting) and rotational (clockwise/counterclockwise) patterns may also be assessed. Using these stimuli, a coherence threshold is measured, which represents the minimum proportion of signal dots needed to perceive coherent motion. Visual evoked potentials indicate that infants are sensitive to coherent global motion by 5 months of age,[214,215] though cortical activity patterns are not adult-like at this age. Depending on the stimulus used, global motion coherence thresholds in children can reach adult-like values before age 5 years[181,216] or as late as age 15 years.[217] Global motion perception may develop sooner in life for fast than for slow stimulus speeds[216,218] (but see Ref. 217), though in healthy children[216] and developing macaques,[186,219] mature performance can also depend on spatiotemporal (Δx, Δt) stimulus parameters rather than motion speed per se.

Global Motion Perception Deficits in the Amblyopic Eye

The amblyopic eye of observers shows deficits in global motion perception relative to controls[196,220–224] though this deficit is not robust – some studies have found no deficits in the amblyopic eye.[40,197] This may depend on stimulus parameters, because not all global motion stimuli elicit abnormal coherence thresholds in amblyopia.[222] Children[222] and macaques[225] with amblyopia show motion sensitivity functions that are both depressed overall, and shifted to faster speeds or larger dot displacements (Δx). These properties are mirrored in the visual evoked potential responses of adults with amblyopia[226] and neural response functions in MT of macaques with amblyopia.[85] Observers with amblyopia have also shown deficits in second-order (contrast-defined) global motion perception that were not correlated with first-order (luminance-defined) global motion deficits[223] and deficits in discriminating rotational or radial flow patterns that were not correlated with deficits in discriminating translational flow patterns,[224] implicating possibly independent mechanisms for these deficits. Some work has suggested that the integration of local motion signals into a global percept is intact, rather, the ability to segregate noise dots from signal dots prior to integration may be impacted.[193,227] Global motion deficits cannot be fully accounted for by stimulus visibility due to poor acuity or contrast sensitivity deficits in the amblyopic eye.[196,222,223,227,228]

Global Motion Perception Deficits in the Fellow Eye

Deficits in the fellow eye of observers with amblyopia have been identified that appear to be similar to those discovered in the amblyopic eye, but less severe in nature. While Aaen-Stockdale et al.[229] found first- and second-order deficits in both eyes that appeared to be present to a similar extent, there is more evidence to suggest that fellow eye deficits are slightly attenuated. This has been found to be the case in adults with amblyopia for first- and second-order global motion patterns,[223] and for translational, rotational, and radial global motion patterns.[224] Similarly, when contrast sensitivity deficits are controlled for in in both eyes, persistent fellow eye deficits are present in adults that are smaller in magnitude than amblyopic eye deficits.[229]

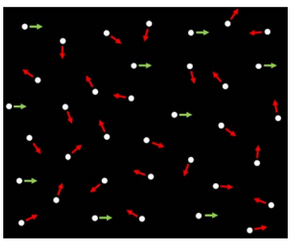

Figure 5. A schematic of a typical random dot patch used in assessing global motion coherence thresholds. Signal dots, indicated by the *green arrows* pointing to the *right*, move together in the same direction. Noise dots, indicated by the *red arrows*, move in random directions. The participant's task is to indicate the direction in which they see the dot pattern move. The coherence of the stimulus is reduced by removing signal dots and adding noise dots.

However, not all studies of global motion have identified deficits in the fellow eyes of observers with amblyopia. Ho et al.[230] and Wang et al.[231] identified a few children with elevated global motion thresholds in the fellow eye, but no overall group deficit. However, the amblyopic eye was not tested in these observers. In children, deficits in the fellow eye were only present for stimuli with spatiotemporal parameters that produced deficits in the amblyopic eye.[222] Thus, it is not clear if a deficit in the fellow eye should be expected for the stimuli used by these previous studies,[230,231] given that deficits in the amblyopic eye may not have been revealed by these stimuli. Ho et al.[40] tested both eyes of children with amblyopia using a stimulus similar to those studies, and while a few individuals with elevated thresholds were identified, group performance for either eye was not different from controls. Thus, the lack of an overall group deficit in the fellow eyes of children assessed by these previous studies[230,231] may not be surprising.

Few clinical factors have been identified that predict elevated deficits in the fellow eye. While no studies to date have assessed global motion perception in children before the onset of occlusion therapy, no significant relationship has been found between duration of occlusion therapy and global motion deficits in either eye of children[222] or in the fellow eye of adults.[229] Moreover, fellow eye deficits in global motion perception are not likely to be confined to one subtype of amblyopia. One study[40] noted that only patients with anisometropic amblyopia had abnormally high coherence thresholds in amblyopic and/or fellow eyes. On the other hand, developing macaques with strabismic, but not anisometropic, amblyopia demonstrated fellow eye deficits.[225] However, other studies have found no significant differences in children with strabismic versus anisometropic amblyopia in children[222] or adults.[223,224]

Mechanisms Underlying Deficits in Global Motion Perception

While there are debates over the exact computational mechanisms by which it is accomplished (see Refs. 232–234 for review), the perception of global motion is generally considered to consist of two stages: a computation of motion vectors at

Investigative Ophthalmology & Visual Science

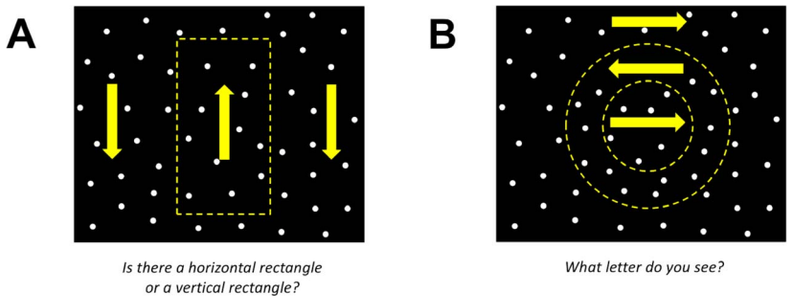

FIGURE 6. Examples of stimuli used in motion-defined form tasks. In these stimuli, dots within the shape move in one direction, while dots outside of the shape move in the opposite direction. In some versions of this task, the dots outside of the shape move randomly. No dashed border is actually present in the stimulus. Minimum speed thresholds can be obtained by reducing the speed of the moving dots until the participant can no longer correctly identify the form. Likewise, coherence thresholds can be obtained by reducing the coherence of the moving dots (similar to global motion, above). (**A**) A motion-defined form task using rectangle orientation. The participant's task is to indicate whether the rectangle is positioned horizontally or vertically. (**B**) A motion-defined letter task. The participant's task is to indicate which letter is present, in this case the letter O.

local positions in direction-sensitive V1 cells with small receptive fields,[235,236] and integration of these local vectors in MT cells with large receptive fields[236,237] for an overall, global percept of motion. Area MT in healthy macaques represents only the binocular area of the visual field,[238] and MT is sensitive to binocular disparity.[79] Moreover, MT cells appear to be able to integrate motion and disparity signals.[239,240] Consistent with this, motion coherence thresholds and stereoacuity are correlated in young children,[241,242] possibly reflecting parallel development of these two visual functions as MT and its connections with other regions mature. Cells in macaque MT respond to motion presented to either eye.[78,79] Finally, there is no binocular summation advantage for coherence thresholds in healthy observers.[243] Taken together, this body of evidence indicates that the disruption of typical binocular development may lead to impaired motion processing in either eye, due to abnormal maturation of these regions, even when a motion task does not rely on stereoscopic processing. From this, we may predict that observers with amblyopia will show deficits to global motion processing when using the fellow eye.

The evidence from fellow eye deficits in global motion perception suggests that visual functions that rely on binocular development will be deficient when binocular development is disrupted, irrespective of the eye receiving stimulus input. Not all global motion stimuli can evoke elevated coherence thresholds in the fellow eye, a pattern that mirrors that of the amblyopic eye. Moreover, fellow eye deficits do not appear on tasks that do not reveal deficits in the amblyopic eye. However, fellow eye deficits may be less pronounced than those of the amblyopic eye, suggesting that the amblyopic deficit may reflect a combination of an early-stage monocular deficiency that does not affect input originating from the fellow eye, and a later-stage binocular deficiency that impacts motion processing regardless of eye of origin. If this is the case, it is unlikely that fellow eye deficits represent an adaptive mechanism to attenuate competition between the two eyes, representing instead a consequence of abnormal maturation of the binocular visual system. While this explanation would predict deficient fellow eye performance in children prior to the onset of occlusion therapy, no studies have directly investigated global motion perception before undergoing treatment in order to rule this out. No studies have followed children with amblyopia through occlusion therapy to document changes in global motion as a function of treatment, but because global motion deficits persist even after successful resolution of visual acuity in the amblyopic eye, it appears these deficits cannot be resolved with occlusion therapy. Fellow eye deficits persist into adulthood, and so the deficits observed in children do not simply reflect a slower maturation of the visual system and instead a robust disruption of the binocular system. Thus, while deficits in global motion perception may not be treatable with occlusion therapy, it is possible that treatments which target binocular function, like dichoptic training,[32,33,244] may alleviate these deficits. If this were the case, improvements to global motion coherence thresholds in both eyes of children and adults with amblyopia should be observed with binocular treatment.

Motion-Defined Form Perception

Motion-defined form stimuli (sometimes referred to as kinetic form or form-from-motion) involve first-order motion information to create a second-order boundary (also known as a motion contrast) to create shapes (Fig. 6). Motion-defined form stimuli always represent two-dimensional figures, in contrast to the similarly named structure-from-motion stimuli, which represent three-dimensional surfaces or objects. It is not known if motion-defined form thresholds, like global motion thresholds, fail to show binocular summation at high contrast levels. Infants as young as 3 months are sensitive to motion-defined shapes.[245] Similar to global motion perception, mature performance on motion-defined form tasks can vary by stimuli. For motion-defined form perception, minimum speed thresholds for motion-defined letter[246] and shape[181] discrimination are adult-like by age 7 years, while coherence thresholds on motion-defined Landolt C orientation discrimination tasks are not adult-like until age 15 years.[247] Consistent with this, evidence from event-related potential latencies indicates processing efficiency for motion-defined form stimuli is slower in 16-year-olds compared with adults.[248] Children reach adult-like coherence thresholds for motion-defined form stimuli created with fast-moving dots earlier in life than those created with slow-moving dots.[37]

Motion-Defined Form Perception Deficits in the Amblyopic Eye

While motion-defined form perception is not as widely studied in amblyopia as the four visual functions discussed previously, large deficits are characteristic of the amblyopic eye. Elevated minimum speed[249] and coherence[37,38] thresholds have been identified in children with amblyopia. While performance on motion-defined form discrimination tasks deteriorates with poorer visual acuity,[250] children in these studies[37,38,249] had completed treatment for amblyopia and even those with good visual acuity in their amblyopic eyes performed worse than

their age-matched controls. Similar to global motion perception, deficits in motion-defined form perception are persistent at slow speeds only,[37] implicating the mechanisms underlying these deficits may be, in part, shared. Motion-defined form deficits appear to be present prior to treatment: in a group of children with amblyopia, motion-defined form coherence thresholds were elevated in the amblyopic eye at the initiation of occlusion therapy, and remained elevated at 1-year follow-up.[38] Few adults with amblyopia have been assessed for motion-defined form perception, but deficits appear to remain in the amblyopic eye in adulthood.[249]

Motion-Defined Form Perception Deficits in the Fellow Eye

Children with amblyopia have elevated motion-defined form thresholds when viewing stimuli with the normally-sighted fellow eye.[37,38,230,231,249] Similar to global motion, motion-defined form thresholds in the fellow eye are typically elevated compared with controls but less so than the amblyopic eye.[37,38] Fellow eye deficits are not associated with deficient high- or low-contrast letter acuity,[37,249] stereoacuity,[37,230,231] or maximum motion displacement thresholds.[230] There is no evidence to suggest that fellow eye deficits are more prevalent in any one amblyopic subtype.[37,38] Fellow eye deficits are observed only for speeds where amblyopic eye deficits are observed,[37] highlighting the binocular nature of motion-defined form disruption. Importantly, however, children who show similar global motion coherence thresholds to their age-matched control peers can still have elevated motion-defined form thresholds,[230,231] so this deficit is not purely a function of motion processing deficits. Wang et al.[231] showed that stationary texture-defined form perception was also impaired in the fellow eye, suggesting that shape extraction is a primary deficiency in these observers, even when viewing motion-defined form stimuli.

No clear or consistent clinical characteristics appear to be associated with fellow eye deficits in motion-defined form perception. Deficits are not likely to be due to occlusion therapy: as in the amblyopic eye, coherence thresholds in the fellow eye were found to be elevated at the onset of occlusion therapy.[38] While thresholds had improved at 1-year follow up, the amount of improvement was equivalent to that of the control children, so this likely reflects an age effect rather than the effect of treatment. Moreover, in these children, duration of occlusion therapy was not associated with deficits in either eye, and deficits in either eye did not predict treatment outcomes. Unlike with the amblyopic eye, however, fellow eye deficits may not persist into adulthood: of five adults with amblyopia assessed for motion-defined form perception, only one demonstrated a deficit in the fellow eye.[249]

Mechanisms Underlying Deficits in Motion-Defined Form Perception

Motion-defined form processing involves a network of early, dorsal, and ventral cortical regions. In the cat, striate cortex is sensitive to motion contrast or motion-defined contours.[251–253] In the macaque, V2 but not V1 can distinguish the orientation of kinetic boundaries.[254] Regions sensitive to kinetic boundaries or motion-defined shapes in nonhuman primates include areas V4[255,256] and MT.[257,258] In humans, motion-defined form stimuli also activate V5/MT+.[257,259–262] As such, fellow eye deficits in motion-defined form perception may primarily arise from the same mechanisms as global motion perception. On the other hand, they may also arise as a function of deficits in form processing. For example, lesions to ventral-occipital,[263] ventral-temporal,[264] or parieto-temporal[265] regions can selectively disrupt motion-defined form processing without interruption to motion processing. Moreover, deficits to motion-defined form have been documented in enucleated observers who have global motion coherence thresholds within the normal range.[266] Regions in nonhuman primates shown to be sensitive to shapes defined by a variety of cues, including but not limited to motion-defined boundaries, include the superior temporal sulcus[267] and inferior temporal cortex.[268] Human neuroimaging has implicated the lateral occipital complex,[259,260,269] fusiform gyri,[262,270,271] inferior temporal gyri,[259,262,271] lingual gyri, and regions of the occipital gyri[248,270,271] in kinetic or motion-defined form perception.

There needs to be more done to determine the implications of motion-defined form deficits in the fellow eye. Of primary importance is to clarify the interpretation of motion-defined form deficits regardless of which eye they are demonstrated in. For example, because performance on this task has not been found to correlate with global motion coherence thresholds in amblyopia, it appears that these deficits do not necessarily follow from global motion deficits. However, studies that have found motion-defined form deficits have not identified global motion deficits in the same group of participants, so it may not be surprising that a correlation between the two has not been established. This should be explored in future work. The fact that both tasks share similar speed tuning suggests a shared mechanism, at least in part. If deficiencies in motion-defined form perception stem from deficiencies in motion processing, then they may simply be grouped in with the implications of global motion processing discussed above.

However, the shape perception aspect of motion-defined form tasks involves additional visual functions, such as extracting cue-invariant form information and segregating figure from ground. While one study, reviewed above,[231] has demonstrated deficient texture-defined form processing in the fellow eye of children with amblyopia, few studies have investigated form processing abilities in observers with amblyopia using other nonluminance boundary cues, such as color-defined form. Thus, further work should also seek to explore whether deficiencies in motion-defined form processing extend to further cues, or if they are isolated to kinetic information. Of interest to note is that the object-sensitive lateral occipital cortex is implicated in some of the spatial integration tasks discussed above, which also show fellow eye deficits. Deficits in motion-defined form, then, could reflect a combination of the deficits observed in the amblyopic eye at early stages and both eyes at later stages of global motion processing, along with deficits in both eyes to cue-invariant form processing. If deficits on this task do arise from multiple stages of processing, this may explain why they have been more robustly identified for motion-defined form than global motion. Still, of the five visual functions discussed in this paper, deficits in motion-defined form perception are the least extensively studied in amblyopia. Though motion-defined form deficits do not appear to resolve along with acuity from treatment for amblyopia, deficits in the fellow eye are not likely to be induced by occlusion therapy. This is further supported by the observation of motion-defined form deficits in enucleated individuals,[266] who have never undergone occlusion. It is possible that fellow eye deficits in motion-defined form perception resolve by adulthood naturally. However, only one study has assessed motion-defined form in adults with amblyopia, so this needs to be confirmed with additional studies.

Summary

In unilateral amblyopia, the fellow eye has good visual acuity by definition. Despite this, deficits are prevalent across a range

Investigative Ophthalmology & Visual Science

of visual functions when observers with amblyopia use the fellow eye. These visual functions include contrast sensitivity, spatial integration, global motion, and motion-defined form perception, which are all shown to be deficient in the amblyopic eye as well. On the other hand, positional hyperacuity tasks, which are impacted in the amblyopic eye, do not appear to be robustly deficient in the fellow eye. Like visual acuity, positional acuity may be mediated by monocular mechanisms that do not show a deficit in the fellow eye of observers with amblyopia. However, positional acuity deficits in the fellow eye may be associated with strabismus, with or without amblyopia.

Deficits in the Fellow Eye Are Unlikely to be Caused by Occlusion Therapy

There is little support for the notion that these fellow eye deficits occur as a result of treatment for amblyopia (section 1.1.1.). Though macaques who have not been treated for amblyopia do show fellow eye deficits,[225] global motion perception in the fellow eye of humans has not been adequately assessed prior to treatment. However, prior to or at the onset of occlusion therapy, fellow eye deficits have been documented for contrast sensitivity,[159–162] spatial integration,[199] and motion-defined form.[38] While this evidence is promising, it comes from only a handful of studies. It has traditionally been difficult to assess performance in the fellow eye prior to treatment onset for a number of reasons. First, conducting psychophysical assessments across a range of tasks can take a long time, and when the purpose of the study is to track deficits in the amblyopic eye through occlusion therapy, assessment of the fellow eye is often omitted. In theory, designing studies that assess only the fellow eye through occlusion therapy may solve this, but confirming that deficits exist in the amblyopic eye is important for understanding whether deficits in the fellow eye should be expected. Second, children are often very young when they first undergo occlusion therapy, and so it is not easy to have them conduct psychophysical tasks in a laboratory environment. Some studies have used, for example, preferential looking techniques to determine contrast sensitivity functions (e.g., Ref. 136) or eye-tracking techniques to determine global motion thresholds (e.g., Ref. 241) in children too young to play psychophysical games. However, these techniques can still be time consuming.

Deficits in the Fellow Eye Are Unlikely to be Caused by Slowed Maturation

There is also little evidence for the notion that these fellow eye deficits occur in children only as a result of delayed maturation (section 1.1.2.), though this idea must be more definitively ruled out with further research. Studies on contrast sensitivity have shown that adults can demonstrate normal contrast sensitivity functions in their fellow eyes,[142–144] but no studies have purposely assessed children and adults at the same time on the same contrast sensitivity test to explore this hypothesis. There is also some indication in spatial integration tasks that deficits are more prevalent in children[199] than adults,[191] though this impression may be simply because fewer studies have been conducted on adults. Adults have been shown to have normal thresholds in the fellow eye on a motion-defined form perception task where the fellow eye of children showed elevated thresholds,[249] but this study had a small sample size and motion-defined form thresholds have not been assessed in adults with amblyopia since. A targeted investigation that is designed to compare the performance of children and adults with amblyopia with controls – or even better, a longitudinal study that documents fellow eye deficits throughout development – may help clarify why not all studies have uncovered fellow eye deficits in amblyopia, particularly with adults. Important to keep in mind is that these deficits may resolve in adulthood as a result of delayed maturation, or they may resolve as a function of treatment. In particular, contrast sensitivity[160,161] and spatial integration[199] have shown to improve with occlusion therapy. Motion-defined form thresholds, on the other hand, show the same level of improvement as controls,[38] indicating that motion-defined form perception continues to improve over time as a function of maturation, and not as a function of treatment.

Fellow Eye Deficits May Be More Likely for Processes Involving Binocular Cortex

Fellow eye deficits may originate from the altered development of binocular cortical areas (section 1.1.3.). The most convincing evidence for this comes from global motion perception deficits in the fellow eye.[222–224,228,229] As discussed, deficits in global motion and motion-defined form processing appear more prevalent than lower-level functions like contrast sensitivity and especially positional acuity, which does not appear to be impacted in the fellow eye of observers with amblyopia. Regions involved in motion perception respond to moving stimuli regardless of eye of origin.[78,79] The development of these regions is disrupted when visual input between the two eyes is not equal during critical periods, and this abnormal development is reflected in poorer performance of the fellow eye relative to control eyes for global motion tasks. This may also be reflected in the poorer performance of fellow eyes in motion-defined form tasks,[37,38,230,249] which recruit additional regions that likely participate in cue-invariant form processing. More research is required to explore whether this is a motion-specific phenomenon, however, or whether this reflects a generalized disruption that affects other tasks. In contrast to targeting a visual function achieved by a bilateral system that is recruited when either eye is stimulated, another fruitful way to assess this may be targeting a lateralized area involved in processing visual stimuli regardless of eye of origin. For example, the fusiform face area is classically right-lateralized,[272,273] and left hemisphere activation may reflect complementary, rather than redundant, processes supporting face processing.[274] Indeed, face processing has been shown to be abnormal in amblyopia.[275–277] However, these studies often use the fellow eye as a comparison so it is not yet clear if face processing fits this proposed model.

Fellow Eye Deficits May Reflect an Adaptive Mechanism to Equate Interocular Sensitivity

Finally, there is evidence that fellow eye deficits may reflect an adaptive mechanism (section 1.1.4). This evidence primarily comes from spatial vision tasks that can be solved relatively early in the processing hierarchy: contrast sensitivity and spatial integration. As discussed, matching the contrast sensitivity of the two eyes appears to promote or at least reveal binocular interactions.[174] Thus, a mechanism to reduce the sensitivity of the fellow eye, were it in place, would be beneficial to the binocular visual system. Fellow eye deficits in contrast sensitivity appear greatest at high spatial frequencies,[157,160,161] where the amblyopic eye deficits are also most prevalent. For both contrast sensitivity and spatial integration, in which fellow eye deficits exist prior to occlusion therapy, the performance of the fellow eye can improve following an improvement in visual acuity for the amblyopic eye.[160,161,199] Contour integration performance in the fellow eye improves with treatment and stabilizes not at control levels of performance, but when interocular differences in contour

Investigative Ophthalmology & Visual Science

integration are minimal.[199] Global motion and motion-defined form perception deficits in the fellow eye do not appear to improve with positive outcomes in occlusion therapy[37,38,222,230,231,249]; however, these visual functions do not improve in the amblyopic eye, either. At this point, while there is promising evidence consistent with the idea of adaptive mechanism particularly for spatial visual functions, no causal links have been established to suggest that fellow eye deficits can have a direct impact on the severity of amblyopia.

Conclusions

In total, there is not enough evidence to completely rule out any one of these four potential mechanisms for fellow eye deficits in amblyopia. Indeed, they are not necessarily mutually exclusive. Overall, however, it seems unlikely that occlusion therapy is causing fellow eye deficits. While there is some indication that fellow eye deficits are greater in children than in adults, not enough research has been conducted to confirm whether this is the case or what the mechanism for this might be. It is clear that fellow eye deficits persist for visual functions that rely on binocular regions of cortex that have received disordered input from one eye during development, but the evidence for this so far cannot distinguish between the possibility that this should be the case for motion perception, or that this should be the case for any visual functions that are solved after eye of origin information is discarded. Finally, there is evidence consistent with the idea that fellow eye deficits could reflect an adaptive mechanism that attempts to equate the sensitivity of the two eyes in order to mitigate the effects of amblyopia on the developing visual system. However, this evidence has thus far been indirectly inferred. Moreover, fellow eye deficits may reflect mechanisms not considered here – evidence from infantile strabismus, for example, indicates that congenital impairment of binocular function is possible,[278,279] which would also account for deficits in the fellow eye. These possibilities highlight the importance of planning studies to directly investigate the role of fellow eye deficits in the amblyopic visual system, and how they change over time in relationship to the sensitivity of the amblyopic eye.

Clinically, while it has been practical to diagnose and treat amblyopia as a monocular disorder of visual acuity, fellow eye deficits are an important reminder that more effective treatments for amblyopia may target its binocular origin. In addition to improving visual acuity, treatments that involve the integration of information between the two eyes, usually during perceptual training or game playing, have been shown to reduce interocular suppression between the eyes and/or improve stereoacuity[175,244,280–285] (see Refs. 286, 287 for reviews), indicating dichoptic techniques may be better at promoting binocular interactions. However, training techniques that do not require binocular integration have also shown positive effects on binocular function.[288–290] A recent meta-analysis indicated that while these treatments do work, no single technique has shown a greater advantage.[291] Moreover, while dichoptic training can lead to improved visual acuity in children,[292] it may not be more successful than traditional occlusion therapy.[293] Importantly, these studies have not assessed the impact of these treatments on the visual function of the fellow eye. Contrast sensitivity[160–162] and spatial integration[199] can improve in the fellow eye following occlusion therapy, and while we would predict similar gains following successful treatment by other methods, this has not been formally assessed. Amblyopic and fellow eye deficits in motion-defined form perception[38] are not alleviated by occlusion therapy, so it would be useful to use this task as an outcome measure for these new treatments to determine whether they have a deeper impact on the visual system than the current gold standard.

This paper explored fellow eye deficits in five visual tasks that have been extensively studied in amblyopia. However, children and adults with amblyopia have demonstrated abnormalities in the fellow eye for a range of additional tasks not discussed here: for example, in foveal function,[294] pupillary response amplitudes,[295] fixational eye movement patterns,[296,297] smooth pursuit,[123] saccadic latency,[298] visual evoked potentials to both form and motion stimuli,[226,299–302] blur discrimination,[303] global shape perception,[304] orientation adaptation,[305] line bisection,[306] the extraction of three-dimensional structure,[307] maximum motion displacement thresholds,[308,309] single-object tracking,[40] multiple-object tracking,[40,41] scene perception,[310] perception of the McGurk effect,[311] and visual decision-making.[312] Many of these visual functions have been assessed during fellow eye viewing in only a handful of studies, so more work is needed to determine how robust these deficits are and the conditions under which they occur. A complete account of how amblyopia impacts the developing visual system must be able to predict the tasks on which fellow eye deficits will be observed – or not.

Acknowledgements

Disclosure: **K. Meier**, None; **D. Giaschi**, None

References

1. Attebo K, Mitchell P, Cumming R, Smith W, Jolly N, Sparkes R. Prevalence and causes of amblyopia in an adult population. *Ophthalmology*. 1998;105:154–159.
2. Caca I, Cingu AK, Sahin A, et al. Amblyopia and refractive errors among school-aged children with low socioeconomic status in southeastern Turkey. *J Pediatr Ophthalmol Strabismus*. 2013;50:37–43.
3. Chia A, Dirani M, Chan YH, et al. Prevalence of amblyopia and strabismus in young Singaporean Chinese children. *Invest Ophthalmol Vis Sci*. 2010;51:3411–3417.
4. Høeg TB, Moldow B, Ellervik C, et al. Danish Rural Eye Study: the association of preschool vision screening with the prevalence of amblyopia. *Acta Ophthalmol*. 2015;93:322–329.
5. Multi-ethnic Pediatric Eye Disease Study Group. Prevalence of amblyopia and strabismus in African American and Hispanic children ages 6 to 72 months the multi-ethnic pediatric eye disease study. *Ophthalmology*. 2008;115:1229–1236.e1.
6. Robaei D, Kifley A, Rose KA, Mitchell P. Impact of amblyopia on vision at age 12 years: findings from a population-based study. *Eye*. 2008;22:496–502.
7. Robaei D, Rose KA, Ojaimi E, Kifley A, Martin FJ, Causes Mitchell P. and associations of amblyopia in a population-based sample of 6-year-old Australian children. *Arch Ophthalmol*. 2006;124:878–884.
8. Holmes JM, Clarke MP. Amblyopia. *Lancet*. 2006;367:1343–1351.
9. von Noorden GK. Binocular vision and ocular motility. St. Louis, MO: Mosby; 1990.
10. Sengpiel F. Plasticity of the visual cortex and treatment of amblyopia. *Curr Biol*. 2014;24:R936–R940.
11. Fells P. Richardson Cross lecture 1989 amblyopia–an historical perspective. *Eye*. 1990;4(Pt 6):775–786.
12. Flynn JT, Woodruff G, Thompson JR, et al. The therapy of amblyopia: an analysis comparing the results of amblyopia therapy utilizing two pooled data sets. *Trans Am Ophthalmol Soc*. 1999;97:373–395.

13. Leiba H, Shimshoni M, Oliver M, Gottesman N, Levartovsky S. Long-term follow-up of occlusion therapy in amblyopia. *Ophthalmology*. 2001;108:1552–1555.
14. Erdem E, Cınar GY, Somer D, Demir N, Burcu A, Ornek F. Eye patching as a treatment for amblyopia in children aged 10-16 years. *Jpn J Ophthalmol*. 2011;55:389–395.
15. Mintz-Hittner HA, Fernandez KM. Successful amblyopia therapy initiated after age 7 years: compliance cures. *Arch Ophthalmol*. 2000;118:1535–1541.
16. Mohan K, Saroha V, Sharma A. Successful occlusion therapy for amblyopia in 11- to 15-year-old children. *J Pediatr Ophthalmol Strabismus*. 2004;41:89–95.
17. Park KH, Hwang JM, Ahn JK. Efficacy of amblyopia therapy initiated after 9 years of age. *Eye*. 2004;18:571–574.
18. Pediatric Eye Disease Investigator Group. A prospective, pilot study of treatment of amblyopia in children 10 to <18 years old. *Am J Ophthalmol*. 2004;137:581–583.
19. Kishimoto F, Fujii C, Shira Y, Hasebe K, Hamasaki I, Ohtsuki H. Outcome of conventional treatment for adult amblyopia. *Jpn J Ophthalmol*. 2014;58:26–32.
20. Simmers AJ, Gray LS. Improvement of visual function in an adult amblyope. *Optom Vis Sci*. 1999;76:82–87.
21. Fulton AB, Mayer DL. Esotropic children with amblyopia: effects of patching on acuity. *Graefes Arch Clin Exp Ophthalmol*. 1988;226:309–312.
22. Fronius M, Cirina L, Ackermann H, Kohnen T, Diehl CM. Efficiency of electronically monitored amblyopia treatment between 5 and 16 years of age: new insight into declining susceptibility of the visual system. *Vision Res*. 2014;103:11–19.
23. Holmes JM, Lazar EL, Melia BM, et al. Effect of age on response to amblyopia treatment in children. *Arch Ophthalmol*. 2011;129:1451–1457.
24. Wick B, Wingard M, Cotter S, Scheiman M. Anisometropic amblyopia: is the patient ever too old to treat. *Optom Vis Sci*. 1992;69:866–878.
25. Bavelier D, Levi DM, Li RW, Dan Y, Hensch TK. Removing brakes on adult brain plasticity: from molecular to behavioral interventions. *J Neurosci*. 2010;30:14964–14971.
26. Levi DM. Perceptual learning in adults with amblyopia: a reevaluation of critical periods in human vision. *Dev Psychobiol*. 2005;46:222–232.
27. Fahle M. Perceptual learning: specificity versus generalization. *Curr Opin Neurobiol*. 2005;15:154–160.
28. Levi DM, Li RW. Perceptual learning as a potential treatment for amblyopia: a mini-review. *Vision Res*. 2009;49:2535–2549.
29. Farivar R, Thompson B, Mansouri B, Hess RF. Interocular suppression in strabismic amblyopia results in an attenuated and delayed hemodynamic response function in early visual cortex. *J Vis*. 2011;11(14):1–12.
30. Sengpiel F, Blakemore C. The neural basis of suppression and amblyopia in strabismus. *Eye*. 1996;10(Pt 2):250–258.
31. Sengpiel F, Blakemore C, Kind PC, Harrad R. Interocular suppression in the visual cortex of strabismic cats. *J Neurosci*. 1994;14(Pt 2):6855–6871.
32. Hess RF, Thompson B, Baker DH. Binocular vision in amblyopia: structure, suppression and plasticity. *Ophthalmic Physiol Opt*. 2014;34:146–162.
33. Birch EE. Amblyopia and binocular vision. *Prog Retin Eye Res*. 2013;33:67–84.
34. Wong AM. New concepts concerning the neural mechanisms of amblyopia and their clinical implications. *Can J Ophthalmol*. 2012;47:399–409.
35. Cascairo MA, Mazow ML, Holladay JT, Prager T. Contrast visual acuity in treated amblyopia. *Binocul Vis Strabismus Q*. 1997;12:167–174.
36. Huang C, Tao L, Zhou Y, Lu ZL. Treated amblyopes remain deficient in spatial vision: a contrast sensitivity and external noise study. *Vision Res*. 2007;47:22–34.
37. Hayward J, Truong G, Partanen M, Giaschi D. Effects of speed, age, and amblyopia on the perception of motion-defined form. *Vision Res*. 2011;51:2216–2223.
38. Giaschi D, Chapman C, Meier K, Narasimhan S, Regan D. The effect of occlusion therapy on motion perception deficits in amblyopia. *Vision Res*. 2015;114:122–134.
39. Rislove EM, Hall EC, Stavros KA, Kiorpes L. Scale-dependent loss of global form perception in strabismic amblyopia. *J Vis*. 2010;10(12):25.
40. Ho CS, Paul PS, Asirvatham A, Cavanagh P, Cline R, Giaschi DE. Abnormal spatial selection and tracking in children with amblyopia. *Vision Res*. 2006;46:3274–3283.
41. Secen J, Culham J, Ho C, Giaschi D. Neural correlates of the multiple-object tracking deficit in amblyopia. *Vision Res*. 2011;51:2517–2527.
42. Giaschi D, Lo R, Narasimhan S, Lyons C, Wilcox LM. Sparing of coarse stereopsis in stereodeficient children with a history of amblyopia. *J Vis*. 2013;13(10):1–15.
43. Lewis TL, Maurer D. Multiple sensitive periods in human visual development: evidence from visually deprived children. *Dev Psychobiol*. 2005;46:163–183.
44. Lewis TL, Maurer D. Effects of early pattern deprivation on visual development. *Optom Vis Sci*. 2009;86:640–646.
45. Varadharajan S, Hussaindeen JR. Visual acuity deficits in the fellow eyes of children with unilateral amblyopia. *J AAPOS*. 2012;16:41–45.
46. Freeman RD, Bradley A. Monocularly deprived humans: nondeprived eye has supernormal Vernier acuity. *J Neurophysiol*. 1980;43:1645–1653.
47. LeVay S, Wiesel TN, Hubel DH. The development of ocular dominance columns in normal and visually deprived monkeys. *J Comp Neurol*. 1980;191:1–51.
48. Hubel DH, Wiesel TN, LeVay S. Functional architecture of area 17 in normal and monocularly deprived macaque monkeys. *Cold Spring Harb Symp Quant Biol*. 1976;40:581–589.
49. Hubel DH, Wiesel TN, LeVay S. Plasticity of ocular dominance columns in monkey striate cortex. *Philos Trans R Soc Lond B Biol Sci*. 1977;278:377–409.
50. Hubel DH, Wiesel TN. The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J Physiol*. 1970;206:419–436.
51. Olson CR, Freeman RD. Progressive changes in kitten striate cortex during monocular vision. *J Neurophysiol*. 1975;38:26–32.
52. Shatz CJ, Stryker MP. Ocular dominance in layer IV of the cat's visual cortex and the effects of monocular deprivation. *J Physiol*. 1978;281:267–283.
53. Barrett BT, Bradley A, McGraw PV. Understanding the neural basis of amblyopia. *Neuroscientist*. 2004;10:106–117.
54. Mitchell DE, Duffy KR. The case from animal studies for balanced binocular treatment strategies for human amblyopia. *Ophthalmic Physiol Opt*. 2014;34:129–145.
55. Kandel GL, Grattan PE, Bedell HE. Are the dominant eyes of amblyopes normal? *Am J Optom Physiol Opt*. 1980;57:1–6.
56. Kaye SB, Chen SI, Price G, et al. Combined optical and atropine penalization for the treatment of strabismic and anisometropic amblyopia. *J AAPOS*. 2002;6:289–293.
57. Kutschke PJ, Scott WE, Keech RV. Anisometropic amblyopia. *Ophthalmology*. 1991;98:258–263.
58. Longmuir S, Pfeifer W, Scott W, Olson R. Effect of occlusion amblyopia after prescribed full-time occlusion on long-term visual acuity outcomes. *J Pediatr Ophthalmol Strabismus*. 2013;50:94–101.

Investigative Ophthalmology & Visual Science

59. North RV, Kelly ME. Atropine occlusion in the treatment of strabismic amblyopia and its effect upon the non-amblyopic eye. *Ophthalmic Physiol Opt*. 1991;11:113–117.
60. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. *Arch Ophthalmol*. 2002;120:268–278.
61. Simons K, Stein L, Sener EC, Vitale S, Guyton DL. Full-time atropine, intermittent atropine, and optical penalization and binocular outcome in treatment of strabismic amblyopia. *Ophthalmology*. 1997;104:2143–2155.
62. Levi D, Carkeet A. Amblyopia: a consequence of abnormal visual development. In: Simons K, ed. *Early Visual Development, Normal and Abnormal*. New York: Oxford University Press; 1993:391–408.
63. Hubel DH, Wiesel TN. Receptive fields and functional architecture of monkey striate cortex. *J Physiol*. 1968;195:215–243.
64. Hubel DH, Wiesel TN. Laminar and columnar distribution of geniculo-cortical fibers in the macaque monkey. *J Comp Neurol*. 1972;146:421–450.
65. Cagenello R, Arditi A, Halpern DL. Binocular enhancement of visual acuity. *J Opt Soc Am A*. 1993;10:1841–1848.
66. Vedamurthy I, Suttle CM, Alexander J, Asper LJ. Interocular interactions during acuity measurement in children and adults, and in adults with amblyopia. *Vision Res*. 2007;47:179–188.
67. Cumming BG, DeAngelis GC. The physiology of stereopsis. *Annu Rev Neurosci*. 2001;24:203–238.
68. Chino YM, Smith EL, Hatta S, Cheng H. Postnatal development of binocular disparity sensitivity in neurons of the primate visual cortex. *J Neurosci*. 1997;17:296–307.
69. DeAngelis GC, Newsome WT. Organization of disparity-selective neurons in macaque area MT. *J Neurosci*. 1999;19:1398–1415.
70. Durand JB, Nelissen K, Joly O, et al. Anterior regions of monkey parietal cortex process visual 3D shape. *Neuron*. 2007;55:493–505.
71. Gonzalez F, Perez R. Neural mechanisms underlying stereoscopic vision. *Prog Neurobiol*. 1998;55:191–224.
72. Peterhans E, von der Heydt R. Functional organization of area V2 in the alert macaque. *European J Neurosci*. 1993;5:509–524.
73. Tsao DY, Vanduffel W, Sasaki Y, et al. Stereopsis activates V3A and caudal intraparietal areas in macaques and humans. *Neuron*. 2003;39:555–568.
74. Watanabe M, Tanaka H, Uka T, Fujita I. Disparity-selective neurons in area V4 of macaque monkeys. *J Neurophysiol*. 2002;87:1960–1973.
75. DeAngelis GC, Cumming BG, Newsome WT. Cortical area MT and the perception of stereoscopic depth. *Nature*. 1998;394:677–680.
76. McKee SP, Levi DM, Movshon JA. The pattern of visual deficits in amblyopia. *J Vis*. 2003;3(5):380–405.
77. Weakley DR. The association between nonstrabismic anisometropia, amblyopia, and subnormal binocularity. *Ophthalmology*. 2001;108:163–171.
78. Kiorpes L, Walton PJ, O'Keefe LP, Movshon JA, Lisberger SG. Effects of early-onset artificial strabismus on pursuit eye movements and on neuronal responses in area MT of macaque monkeys. *J Neurosci*. 1996;16:6537–6553.
79. Maunsell JH, van Essen DC. Functional properties of neurons in middle temporal visual area of the macaque monkey. II. Binocular interactions and sensitivity to binocular disparity. *J Neurophysiol*. 1983;49:1148–1167.
80. Zeki SM. Functional organization of a visual area in the posterior bank of the superior temporal sulcus of the rhesus monkey. *J Physiol*. 1974;236:549–573.
81. Moulden B. After-effects and the integration of patterns of neural activity within a channel. *Philos Trans R Soc Lond B Biol Sci*. 1980;290:39–55.
82. Wade NJ, Swanston MT, de Weert CM. On interocular transfer of motion aftereffects. *Perception*. 1993;22:1365–1380.
83. Nishida S, Ashida H, Sato T. Complete interocular transfer of motion aftereffect with flickering test. *Vision Res*. 1994;34:2707–2716.
84. Raymond JE. Complete interocular transfer of motion adaptation effects on motion coherence thresholds. *Vision Res*. 1993;33:1865–1870.
85. El-Shamayleh Y, Kiorpes L, Kohn A, Movshon JA. Visual motion processing by neurons in area MT of macaque monkeys with experimental amblyopia. *J Neurosci*. 2010;30:12198–12209.
86. Kiorpes L, Kiper DC, O'Keefe LP, Cavanaugh JR, Movshon JA. Neuronal correlates of amblyopia in the visual cortex of macaque monkeys with experimental strabismus and anisometropia. *J Neurosci*. 1998;18:6411–6424.
87. Shooner C, Hallum LE, Kumbhani RD, et al. Population representation of visual information in areas V1 and V2 of amblyopic macaques. *Vision Res*. 2015;114:56–67.
88. Wiesel TN. Postnatal development of the visual cortex and the influence of environment. *Nature*. 1982;299:583–591.
89. Westheimer G. Diffraction theory and visual hyperacuity. *Am J Optom Physiol Opt*. 1976;53:362–364.
90. Stigmar G. Blurred visual stimuli. II. The effect of blurred visual stimuli on Vernier and stereo acuity. *Acta Ophthalmol*. 1971;49:364–379.
91. Williams RA, Enoch JM, Essock EA. The resistance of selected hyperacuity configurations to retinal image degradation. *Invest Ophthalmol Vis Sci*. 1984;25:389–399.
92. Westheimer G, McKee SP. Visual acuity in the presence of retinal-image motion. *J Opt Soc Am*. 1975;65:847–850.
93. Banton T, Levi DM. Binocular summation in Vernier acuity. *J Opt Soc Am A*. 1991;8:673–680.
94. Lindblom B, Westheimer G. Binocular summation of hyperacuity tasks. *J Opt Soc Am A*. 1989;6:585–589.
95. Mussap AJ, Levi DM. Binocular processes in Vernier acuity. *J Opt Soc Am A*. 1995;12:225–233.
96. Shimojo S, Birch EE, Gwiazda J, Held R. Development of Vernier acuity in infants. *Vision Res*. 1984;24:721–728.
97. Manny RE, Klein SA. The development of Vernier acuity in infants. *Curr Eye Res*. 1984;3:453–462.
98. Stanley OH. Cortical development and visual function. *Eye*. 1991;5(Pt 1):27–30.
99. Zanker J, Mohn G, Weber U, Zeitler-Driess K, Fahle M. The development of Vernier acuity in human infants. *Vision Res*. 1992;32:1557–1564.
100. Carkeet A, Levi DM, Manny RE. Development of Vernier acuity in childhood. *Optom Vis Sci*. 1997;74:741–750.
101. Kim E, Enoch JM, Fang MS, et al. Performance on the three-point Vernier alignment or acuity test as a function of age: measurement extended to ages 5 to 9 years. *Optom Vis Sci*. 2000;77:492–495.
102. Skoczenski AM, Norcia AM. Late maturation of visual hyperacuity. *Psychol Sci*. 2002;13:537–541.
103. Wang YZ, Morale SE, Cousins R, Birch EE. Course of development of global hyperacuity over lifespan. *Optom Vis Sci*. 2009;86:695–700.
104. Bedell HE, Flom MC. Monocular spatial distortion in strabismic amblyopia. *Invest Ophthalmol Vis Sci*. 1981;20:263–268.
105. Levi DM, Klein S. Hyperacuity and amblyopia. *Nature*. 1982;298:268–270.

Investigative Ophthalmology & Visual Science

106. Levi DM, Klein S. Differences in Vernier discrimination for grating between strabismic and anisometropic amblyopes. *Invest Ophthalmol Vis Sci*. 1982;23:398–407.
107. Bedell HE, Flom MC, Barbeito R. Spatial aberrations and acuity in strabismus and amblyopia. *Invest Ophthalmol Vis Sci*. 1985;26:909–916.
108. Fronius M, Sireteanu R, Zubcov A. Deficits of spatial localization in children with strabismic amblyopia. *Graefes Arch Clin Exp Ophthalmol*. 2004;242:827–839.
109. Rentschler I, Hilz R. Amblyopic processing of positional information. Part I: Vernier acuity. *Exp Brain Res*. 1985;60:270–278.
110. Birch EE, Swanson WH. Hyperacuity deficits in anisometropic and strabismic amblyopes with known ages of onset. *Vision Res*. 2000;40:1035–1040.
111. Kiorpes L, Kiper DC, Movshon JA. Contrast sensitivity and Vernier acuity in amblyopic monkeys. *Vision Res*. 1993;33:2301–2311.
112. Levi DM, Klein SA. Vernier acuity, crowding and amblyopia. *Vision Res*. 1985;25:979–991.
113. Levi DM, Waugh SJ, Beard BL. Spatial scale shifts in amblyopia. *Vision Res*. 1994;34:3315–3333.
114. Agrawal R, Conner IP, Odom JV, Schwartz TL, Mendola JD. Relating binocular and monocular vision in strabismic and anisometropic amblyopia. *Arch Ophthalmol*. 2006;124:844–850.
115. Vedamurthy I, Suttle CM, Alexander J, Asper LJ. A psychophysical study of human binocular interactions in normal and amblyopic visual systems. *Vision Res*. 2008;48:1522–1531.
116. Watt RJ, Hess RF. Spatial information and uncertainty in anisometropic amblyopia. *Vision Res*. 1987;27:661–674.
117. Simmers AJ, Gray LS, McGraw PV, Winn B. Functional visual loss in amblyopia and the effect of occlusion therapy. *Invest Ophthalmol Vis Sci*. 1999;40:2859–2871.
118. Levi DM, Polat U, Hu YS. Improvement in Vernier acuity in adults with amblyopia. Practice makes better. *Invest Ophthalmol Vis Sci*. 1997;38:1493–1510.
119. Osuobeni EP. Monocular Vernier acuity in normally binocular, monocular, and amblyopic subjects. *Optom Vis Sci*. 1992;69:550–555.
120. Johnson CA, Post RB, Chalupa LM, Lee TJ. Monocular deprivation in humans: a study of identical twins. *Invest Ophthalmol Vis Sci*. 1982;23:135–138.
121. McGraw PV, Winn B, Whitaker D, McFadzean R. Positional acuity in amblyopia: does a perceptual consequence of neural recruitment exist. *Ophthalmic Physiol Opt*. 1998;18:423–429.
122. Cox JF, Suh S, Leguire LE. Vernier acuity in amblyopic and nonamblyopic children. *J Pediatr Ophthalmol Strabismus*. 1996;33:39–46.
123. Bedell HE, Flom MC. Bilateral oculomotor abnormalities in strabismic amblyopes: evidence for a common central mechanism. *Doc Ophthalmol*. 1985;59:309–321.
124. Schor C, Hallmark W. Slow control of eye position in strabismic amblyopia. *Invest Ophthalmol Vis Sci*. 1978;17:577–581.
125. Reed MJ, Steinbach MJ, Ono H, Kraft S, Gallie B. Alignment ability of strabismic and eye enucleated subjects on the horizontal and oblique meridians. *Vision Res*. 1995;35:2523–2528.
126. Kapadia MK, Gilbert CD, Westheimer G. A quantitative measure for short-term cortical plasticity in human vision. *J Neurosci*. 1994;14:451–457.
127. Westheimer G. The spatial sense of the eye. Proctor lecture. *Invest Ophthalmol Vis Sci*. 1979;18:893–912.
128. Westheimer G. Do ocular-dominance columns set spatial limits for hyperacuity processing. *Vision Res*. 1982;22:1349–1352.
129. Fronius M, Sireteanu R. Monocular geometry is selectively distorted in the central visual field of strabismic amblyopes. *Invest Ophthalmol Vis Sci*. 1989;30:2034–2044.
130. Lagrèze WD, Sireteanu R. Two-dimensional spatial distortions in human strabismic amblyopia. *Vision Res*. 1991;31:1271–1288.
131. Hess RF, Holliday IE. The spatial localization deficit in amblyopia. *Vision Res*. 1992;32:1319–1339.
132. 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.
133. Sireteanu R, Lagrèze WD, Constantinescu DH. Distortions in two-dimensional visual space perception in strabismic observers. *Vision Res*. 1993;33:677–690.
134. Pelli DG, Robson JG, Wilkins AJ. The design of a new letter chart for measuring contrast sensitivity. *Clin Vis Sci*. 1988;2:187–199.
135. Shapley R, Lennie P. Spatial frequency analysis in the visual system. *Annu Rev Neurosci*. 1985;8:547–583.
136. Banks MS, Salapatek P. Acuity and contrast sensitivity in 1-, 2-, and 3-month-old human infants. *Invest Ophthalmol Vis Sci*. 1978;17:361–365.
137. Movshon JA, Kiorpes L. Analysis of the development of spatial contrast sensitivity in monkey and human infants. *J Opt Soc Am A*. 1988;5:2166–2172.
138. Atkinson J, French J, Braddick O. Contrast sensitivity function of preschool children. *Br J Ophthalmol*. 1981;65:525–529.
139. Derefeldt G, Lennerstrand G, Lundh B. Age variations in normal human contrast sensitivity. *Acta Ophthalmol*. 1979;57:679–690.
140. Beazley LD, Illingworth DJ, Jahn A, Greer DV. Contrast sensitivity in children and adults. *Br J Ophthalmol*. 1980;64:863–866.
141. Boothe RG, Kiorpes L, Williams RA, Teller DY. Operant measurements of contrast sensitivity in infant macaque monkeys during normal development. *Vision Res*. 1988;28:387–396.
142. Hess RF, Campbell FW, Greenhalgh T. On the nature of the neural abnormality in human amblyopia; neural aberrations and neural sensitivity loss. *Pflugers Arch*. 1978;377:201–207.
143. Hess RF, Howell ER. The threshold contrast sensitivity function in strabismic amblyopia: evidence for a two type classification. *Vision Res*. 1977;17:1049–1055.
144. Levi DM, Harwerth RS. Spatio-temporal interactions in anisometropic and strabismic amblyopia. *Invest Ophthalmol Vis Sci*. 1977;16:90–95.
145. Pardhan S, Gilchrist J. Binocular contrast summation and inhibition in amblyopia. The influence of the interocular difference on binocular contrast sensitivity. *Doc Ophthalmol*. 1992;82:239–248.
146. Sjöstrand J. Contrast sensitivity in children with strabismic and anisometropic amblyopia. A study of the effect of treatment. *Acta Ophthalmol*. 1981;59:25–34.
147. Katz LM, Levi DM, Bedell HE. Central and peripheral contrast sensitivity in amblyopia with varying field size. *Doc Ophthalmol*. 1984;58:351–373.
148. Abrahamsson M, Sjöstrand J. Contrast sensitivity and acuity relationship in strabismic and anisometropic amblyopia. *Br J Ophthalmol*. 1988;72:44–49.
149. Howell ER, Mitchell DE, Keith CG. Contrast thresholds for sine gratings of children with amblyopia. *Invest Ophthalmol Vis Sci*. 1983;24:782–787.

Investigative Ophthalmology & Visual Science

150. Koskela PU, Alanko HI. Correlations between visual acuity, grating acuity and contrast sensitivity in amblyopia. *Acta Ophthalmol*. 1990;68(S195):91–93.
151. Rogers GL, Bremer DL, Leguire LE. The contrast sensitivity function and childhood amblyopia. *Am J Ophthalmol*. 1987; 104:64–68.
152. Kiper DC, Kiorpes L. Suprathreshold contrast sensitivity in experimentally strabismic monkeys. *Vision Res*. 1994;34: 1575–1583.
153. Lennerstrand G, Lundh BL. Improvement of contrast sensitivity from treatment for amblyopia. *Acta Ophthalmol*. 1980;58:292–294.
154. Bradley A, Freeman RD. Contrast sensitivity in anisometropic amblyopia. *Invest Ophthalmol Vis Sci*. 1981;21:467–476.
155. Loshin DS, Levi DM. Suprathreshold contrast perception in functional amblyopia. *Doc Ophthalmol*. 1983;55:213–236.
156. Reed MJ, Steeves JK, Steinbach MJ, Kraft S, Gallie B. Contrast letter thresholds in the non-affected eye of strabismic and unilateral eye enucleated subjects. *Vision Res*. 1996;36: 3011–3018.
157. Lewis TL, Maurer D, Tytla ME, Bowering ER, Brent HP. Vision in the "good" eye of children treated for unilateral congenital cataract. *Ophthalmology*. 1992;99:1013–1017.
158. Koskela PU, Hyvärinen L. Contrast sensitivity in amblyopia. III. Effect of occlusion. *Acta Ophthalmol*. 1986;64:386–390.
159. Moseley MJ, Fielder AR, Irwin M, Jones HS, Auld RJ. Effectiveness of occlusion therapy in ametropic amblyopia: a pilot study. *Br J Ophthalmol*. 1997;81:956–961.
160. Leguire LE, Rogers GL, Bremer DL. Amblyopia: the normal eye is not normal. *J Pediatr Ophthalmol Strabismus*. 1990; 27:32–38.
161. Wali N, Leguire LE, Rogers GL, Bremer DL. CSF interocular interactions in childhood ambylopia. *Optom Vis Sci*. 1991; 68:81–87.
162. Chatzistefanou KI, Theodossiadis GP, Damanakis AG, Ladas ID, Moschos MN, Chimonidou E. Contrast sensitivity in amblyopia: the fellow eye of untreated and successfully treated amblyopes. *J AAPOS*. 2005;9:468–474.
163. Higgins KE, Daugman JG, Mansfield RJ. Amblyopic contrast sensitivity: insensitivity to unsteady fixation. *Invest Ophthalmol Vis Sci*. 1982;23:113–120.
164. Crawford ML, Harwerth RS. Ocular dominance column width and contrast sensitivity in monkeys reared with strabismus or anisometropia. *Invest Ophthalmol Vis Sci*. 2004;45:3036–3042.
165. Nicholas JJ, Heywood CA, Cowey A. Contrast sensitivity in one-eyed subjects. *Vision Res*. 1996;36:175–180.
166. Reed MJ, Steeves JK, Steinbach MJ. A comparison of contrast letter thresholds in unilateral eye enucleated subjects and binocular and monocular control subjects. *Vision Res*. 1997; 37:2465–2469.
167. Horton JC, Hocking DR. Pattern of ocular dominance columns in human striate cortex in strabismic amblyopia. *Vis Neurosci*. 1996;13:787–795.
168. Horton JC, Stryker MP. Amblyopia induced by anisometropia without shrinkage of ocular dominance columns in human striate cortex. *Proc Natl Acad Sci U S A*. 1993;90:5494–5498.
169. Adams DL, Sincich LC, Horton JC. Complete pattern of ocular dominance columns in human primary visual cortex. *J Neurosci*. 2007;27:10391–10403.
170. Goodyear BG, Nicolle DA, Humphrey GK, Menon RS. BOLD fMRI response of early visual areas to perceived contrast in human amblyopia. *J Neurophysiol*. 2000;84:1907–1913.
171. Harrad RA, Hess RF. Binocular integration of contrast information in amblyopia. *Vision Res*. 1992;32:2135–2150.
172. Selby SA, Woodhouse JM. The spatial frequency dependence of interocular transfer in amblyopes. *Vision Res*. 1981;21: 1401–1408.
173. Holopigian K, Blake R, Greenwald MJ. Selective losses in binocular vision in anisometropic amblyopes. *Vision Res*. 1986;26:621–630.
174. Baker DH, Meese TS, Mansouri B, Hess RF. Binocular summation of contrast remains intact in strabismic amblyopia. *Invest Ophthalmol Vis Sci*. 2007;48:5332–5338.
175. Hess RF, Mansouri B, Thompson B. A new binocular approach to the treatment of amblyopia in adults well beyond the critical period of visual development. *Restor Neurol Neurosci*. 2010;28:793–802.
176. Gilbert CD. Adult cortical dynamics. *Physiol Rev*. 1998;78: 467–485.
177. Li Z. A neural model of contour integration in the primary visual cortex. *Neural Comput*. 1998;10:903–940.
178. Braddick O, Birtles D, Wattam-Bell J, Atkinson J. Motion- and orientation-specific cortical responses in infancy. *Vision Res*. 2005;45:3169–3179.
179. Gerhardstein P, Kovacs I, Ditre J, Feher A. Detection of contour continuity and closure in three-month-olds. *Vision Res*. 2004;44:2981–2988.
180. Norcia AM, Pei F, Bonneh Y, Hou C, Sampath V, Pettet MW. Development of sensitivity to texture and contour information in the human infant. *J Cogn Neurosci*. 2005;17:569–579.
181. Parrish EE, Giaschi DE, Boden C, Dougherty R. The maturation of form and motion perception in school age children. *Vision Res*. 2005;45:827–837.
182. Lewis TL, Ellemberg D, Maurer D, Dirks M, Wilkinson F, Wilson HR. A window on the normal development of sensitivity to global form in Glass patterns. *Perception*. 2004; 33:409–418.
183. Hadad B, Maurer D, Lewis TL. The effects of spatial proximity and collinearity on contour integration in adults and children. *Vision Res*. 2010;50:772–778.
184. Kovács I, Kozma P, Feher A, Benedek G. Late maturation of visual spatial integration in humans. *Proc Natl Acad Sci U S A*. 1999;96:12204–12209.
185. Kiorpes L, Bassin SA. Development of contour integration in macaque monkeys. *Vis Neurosci*. 2003;20:567–575.
186. Kiorpes L, Price T, Hall-Haro C, Movshon JA. Development of sensitivity to global form and motion in macaque monkeys (Macaca nemestrina). *Vision Res*. 2012;63:34–42.
187. Boothe RG, Dobson V, Teller DY. Postnatal development of vision in human and nonhuman primates. *Annu Rev Neurosci*. 1985;8:495–545.
188. Bonneh YS, Sagi D, Polat U. Local and non-local deficits in amblyopia: acuity and spatial interactions. *Vision Res*. 2004; 44:3099–3110.
189. Hess RF, McIlhagga W, Field DJ. Contour integration in strabismic amblyopia: the sufficiency of an explanation based on positional uncertainty. *Vision Res*. 1997;37:3145–3161.
190. Hess RF, Demanins R. Contour integration in anisometropic amblyopia. *Vision Res*. 1998;38:889–894.
191. Kovács I, Polat U, Pennefather PM, Chandna A, Norcia AM. A new test of contour integration deficits in patients with a history of disrupted binocular experience during visual development. *Vision Res*. 2000;40:1775–1783.
192. Mussap AJ, Levi DM. Amblyopic deficits in detecting a dotted line in noise. *Vision Res*. 2000;40:3297–3307.
193. Mansouri B, Hess RF. The global processing deficit in amblyopia involves noise segregation. *Vision Res*. 2006;46: 4104–4117.

Investigative Ophthalmology & Visual Science

194. Levi DM, Yu C, Kuai SG, Rislove E. Global contour processing in amblyopia. *Vision Res*. 2007;47:512–524.
195. Simmers AJ, Bex PJ. The representation of global spatial structure in amblyopia. *Vision Res*. 2004;44:523–533.
196. Simmers AJ, Ledgeway T, Hess RF. The influences of visibility and anomalous integration processes on the perception of global spatial form versus motion in human amblyopia. *Vision Res*. 2005;45:449–460.
197. Ellemberg D, Lewis TL, Maurer D, Brar S, Brent HP. Better perception of global motion after monocular than after binocular deprivation. *Vision Res*. 2002;42:169–179.
198. Chandna A, Pennefather PM, Kovács I, Norcia AM. Contour integration deficits in anisometropic amblyopia. *Invest Ophthalmol Vis Sci*. 2001;42:875–878.
199. Chandna A, Gonzalez-Martin JA, Norcia AM. Recovery of contour integration in relation to logMAR visual acuity during treatment of amblyopia in children. *Invest Ophthalmol Vis Sci*. 2004;45:4016–4022.
200. Kozma P, Kiorpes L. Contour integration in amblyopic monkeys. *Vis Neurosci*. 2003;20:577–588.
201. Kiorpes L. Visual processing in amblyopia: animal studies. *Strabismus*. 2006;14:3–10.
202. Husk JS, Hess RF. Global processing of orientation in amblyopia. *Vision Res*. 2013;82:22–30.
203. Mansouri B, Allen HA, Hess RF. Detection, discrimination and integration of second-order orientation information in strabismic and anisometropic amblyopia. *Vision Res*. 2005; 45:2449–2460.
204. Burkhalter A, Bernardo KL, Charles V. Development of local circuits in human visual cortex. *J Neurosci*. 1993;13:1916–1931.
205. Gattass R, Sousa AP, Mishkin M, Ungerleider LG. Cortical projections of area V2 in the macaque. *Cereb Cortex*. 1997; 7:110–129.
206. Burkhalter A. Development of forward and feedback connections between areas V1 and V2 of human visual cortex. *Cereb Cortex*. 1993;3:476–487.
207. Bi H, Zhang B, Tao X, Harwerth RS, Smith EL, Chino YM. Neuronal responses in visual area V2 (V2) of macaque monkeys with strabismic amblyopia. *Cereb Cortex*. 2011;21: 2033–2045.
208. Tao X, Zhang B, Shen G, et al. Early monocular defocus disrupts the normal development of receptive-field structure in V2 neurons of macaque monkeys. *J Neurosci*. 2014;34: 13840–13854.
209. Altmann CF, Bülthoff HH, Kourtzi Z. Perceptual organization of local elements into global shapes in the human visual cortex. *Curr Biol*. 2003;13:342–349.
210. Kourtzi Z, Huberle E. Spatiotemporal characteristics of form analysis in the human visual cortex revealed by rapid event-related fMRI adaptation. *Neuroimage*. 2005;28:440–452.
211. Kourtzi Z, Tolias AS, Altmann CF, Augath M, Logothetis NK. Integration of local features into global shapes: monkey and human FMRI studies. *Neuron*. 2003;37:333–346.
212. Cottereau BR, McKee SP, Ales JM, Norcia AM. Disparity-tuned population responses from human visual cortex. *J Neurosci*. 2011;31:954–965.
213. Ip IB, Minini L, Dow J, Parker AJ, Bridge H. Responses to interocular disparity correlation in the human cerebral cortex. *Ophthalmic Physiol Opt*. 2014;34:186–198.
214. Hou C, Gilmore RO, Pettet MW, Norcia AM. Spatio-temporal tuning of coherent motion evoked responses in 4-6 month old infants and adults. *Vision Res*. 2009;49:2509–2517.
215. Shirai N, Birtles D, Wattam-Bell J, et al. Asymmetrical cortical processing of radial expansion/contraction in infants and adults. *Dev Sci*. 2009;12:946–955.
216. Meier K, Giaschi D. The maturation of global motion perception depends on the spatial and temporal offsets of the stimulus. *Vision Res*. 2014;95:61–67.
217. Hadad BS, Maurer D, Lewis TL. Long trajectory for the development of sensitivity to global and biological motion. *Dev Sci*. 2011;14:1330–1339.
218. Narasimhan S, Giaschi D. The effect of dot speed and density on the development of global motion perception. *Vision Res*. 2012;62:102–107.
219. Kiorpes L, Movshon JA. Development of sensitivity to visual motion in macaque monkeys. *Vis Neurosci*. 2004;21:851–859.
220. Kiorpes L, Tang C, Movshon JA. Factors limiting contrast sensitivity in experimentally amblyopic macaque monkeys. *Vision Res*. 1999;39:4152–4160.
221. Knox PJ, Ledgeway T, Simmers AJ. The effects of spatial offset, temporal offset and image speed on sensitivity to global motion in human amblyopia. *Vision Res*. 2013;86:59–65.
222. Meier K, Sum B, Giaschi D. Global motion perception in children with amblyopia as a function of spatial and temporal stimulus parameters. *Vision Res*. 2016;127:18–27.
223. Simmers AJ, Ledgeway T, Hess RF, McGraw PV. Deficits to global motion processing in human amblyopia. *Vision Res*. 2003;43:729–738.
224. Simmers AJ, Ledgeway T, Mansouri B, Hutchinson CV, Hess RF. The extent of the dorsal extra-striate deficit in amblyopia. *Vision Res*. 2006;46:2571–2580.
225. Kiorpes L, Tang C, Movshon JA. Sensitivity to visual motion in amblyopic macaque monkeys. *Vis Neurosci*. 2006;23: 247–256.
226. Hou C, Pettet MW, Norcia AM. Abnormalities of coherent motion processing in strabismic amblyopia: visual-evoked potential measurements. *J Vis*. 2008;8(4):2.1–12.
227. Hess RF, Mansouri B, Dakin SC, Allen HA. Integration of local motion is normal in amblyopia. *J Opt Soc Am A Opt Image Sci Vis*. 2006;23:986–992.
228. Aaen-Stockdale C, Hess RF. The amblyopic deficit for global motion is spatial scale invariant. *Vision Res*. 2008;48:1965–1971.
229. Aaen-Stockdale C, Ledgeway T, Hess RF. Second-order optic flow deficits in amblyopia. *Invest Ophthalmol Vis Sci*. 2007; 48:5532–5538.
230. Ho CS, Giaschi DE, Boden C, Dougherty R, Cline R, Lyons C. Deficient motion perception in the fellow eye of amblyopic children. *Vision Res*. 2005;45:1615–1627.
231. Wang J, Ho CS, Giaschi DE. Deficient motion-defined and texture-defined figure-ground segregation in amblyopic children. *J Pediatr Ophthalmol Strabismus*. 2007;44:363–371.
232. Braddick O, Qian N. The organization of global motion and transparency. In: Zanker JM, Zeil J, eds. *Motion Vision: Computational, Neural, and Ecological Constraints*. Berlin Heidelberg New York: Springer Verlag; 2001:85–112. ?3
233. Derrington AM, Allen HA, Delicato LS. Visual mechanisms of motion analysis and motion perception. *Annu Rev Psychol*. 2004;55:181–205.
234. Snowden RJ, Verstraten FAJ. Motion transparency: making models of motion perception transparent. *Trends Cogn Sci*. 1999;3:369–377.
235. Albright TD. Direction and orientation selectivity of neurons in visual area MT of the macaque. *J Neurophysiol*. 1984;52: 1106–1130.
236. Gattass R, Gross CG. Visual topography of striate projection zone (MT) in posterior superior temporal sulcus of the macaque. *J Neurophysiol*. 1981;46:621–638.

Investigative Ophthalmology & Visual Science

237. Mikami A, Newsome WT, Wurtz RH. Motion selectivity in macaque visual cortex. II. Spatiotemporal range of directional interactions in MT and V1. *J Neurophysiol*. 1986;55:1328–1339.
238. Gattass R, Nascimento-Silva S, Soares JG, et al. Cortical visual areas in monkeys: location, topography, connections, columns, plasticity and cortical dynamics. *Philos Trans R Soc Lond B Biol Sci*. 2005;360:709–731.
239. Bradley DC, Qian N, Andersen RA. Integration of motion and stereopsis in middle temporal cortical area of macaques. *Nature*. 1995;373:609–611.
240. Krug K, Parker AJ. Neurons in dorsal visual area V5/MT signal relative disparity. *J Neurosci*. 2011;31:17892–17904.
241. Yu T-Y, Jacobs RJ, Anstice NA, Paudel N, Harding JE, Thompson B. Global motion perception in 2-year-old children: A method for psychophysical assessment and relationships with clinical measures of visual function. *Invest Ophthalmol Vis Sci*. 2013;54:8408–8419.
242. Chakraborty A, Anstice NS, Jacobs RJ, et al. Global motion perception is independent from contrast sensitivity for coherent motion direction discrimination and visual acuity in 4.5-year-old children. *Vision Res*. 2015;115(Pt A):83–91.
243. Hess RF, Hutchinson CV, Ledgeway T, Mansouri B. Binocular influences on global motion processing in the human visual system. *Vision Res*. 2007;47:1682–1692.
244. Vedamurthy I, Nahum M, Huang SJ, et al. A dichoptic custom-made action video game as a treatment for adult amblyopia. *Vision Res*. 2015;114:173–187.
245. Kaufmann-Hayoz R, Kaufmann F, Stucki M. Kinetic contours in infants' visual perception. *Child Dev*. 1986;57:292–299.
246. Giaschi D, Regan D. Development of motion-defined figure-ground segregation in preschool and older children, using a letter-identification task. *Optom Vis Sci*. 1997;74:761–767.
247. Schrauf M, Wist ER, Ehrenstein WH. Development of dynamic vision based on motion contrast. *Exp Brain Res*. 1999;124:469–473.
248. Bucher K, Dietrich T, Marcar VL, et al. Maturation of luminance- and motion-defined form perception beyond adolescence: a combined ERP and fMRI study. *Neuroimage*. 2006;31:1625–1636.
249. Giaschi DE, Regan D, Kraft SP, Hong XH. Defective processing of motion-defined form in the fellow eye of patients with unilateral amblyopia. *Invest Ophthalmol Vis Sci*. 1992;33:2483–2489.
250. Zwicker AE, Hoag RA, Edwards VT, Boden C, Giaschi DE. The effects of optical blur on motion and texture perception. *Optom Vis Sci*. 2006;83:382–390.
251. Gharat A, Baker CL. Motion-defined contour processing in the early visual cortex. *J Neurophysiol*. 2012;108:1228–1243.
252. Hammond P, Smith AT. Sensitivity of complex cells in cat striate cortex to relative motion. *Brain Res*. 1984;301:287–298.
253. Kastner S, Nothdurft HC, Pigarev IN. Neuronal responses to orientation and motion contrast in cat striate cortex. *Vis Neurosci*. 1999;16:587–600.
254. Marcar VL, Raiguel SE, Xiao D, Orban GA. Processing of kinetically defined boundaries in areas V1 and V2 of the macaque monkey. *J Neurophysiol*. 2000;84:2786–2798.
255. Handa T, Inoue M, Mikami A. Neuronal activity during discrimination of shapes defined by motion in area V4. *Neuroreport*. 2010;21:532–536.
256. Mysore SG, Vogels R, Raiguel SE, Orban GA. Processing of kinetic boundaries in macaque V4. *J Neurophysiol*. 2006;95:1864–1880.
257. Handa T, Katai S, Kuno R, Unno S, Inoue M, Mikami A. Differential activity to shapes under shape-from-motion condition in macaque middle temporal area. *Neuroscience*. 2008;156:1118–1135.
258. Marcar VL, Xiao DK, Raiguel SE, Maes H, Orban GA. Processing of kinetically defined boundaries in the cortical motion area MT of the macaque monkey. *J Neurophysiol*. 1995;74:1258–1270.
259. Schoenfeld MA, Woldorff M, Düzel E, Scheich H, Heinze HJ, Mangun GR. Form-from-motion: MEG evidence for time course and processing sequence. *J Cogn Neurosci*. 2003;15:157–172.
260. Vachon P, Voss P, Lassonde M, et al. Global motion stimuli and form-from-motion stimuli: common characteristics and differential activation patterns. *Int J Neurosci*. 2009;119:1584–1601.
261. Vaina LM, Sikoglu EM, Soloviev S, et al. Functional and anatomical profile of visual motion impairments in stroke patients correlate with fMRI in normal subjects. *J Neuropsychol*. 2010;4(Pt 2):121–145.
262. Wang J, Zhou T, Qiu M, et al. Relationship between ventral stream for object vision and dorsal stream for spatial vision: an fMRI + ERP study. *Hum Brain Mapp*. 1999;8:170–181.
263. Blanke O, Brooks A, Mercier M, et al. Distinct mechanisms of form-from-motion perception in human extrastriate cortex. *Neuropsychologia*. 2007;45:644–653.
264. Cowey A, Vaina LM. Blindness to form from motion despite intact static form perception and motion detection. *Neuropsychologia*. 2000;38:566–578.
265. Regan D, Giaschi D, Sharpe JA, Hong XH. Visual processing of motion-defined form: selective failure in patients with parietotemporal lesions. *J Neurosci*. 1992;12:2198–2210.
266. Steeves JK, González EG, Gallie BL, Steinbach MJ. Early unilateral enucleation disrupts motion processing. *Vision Res*. 2002;42:143–150.
267. Unno S, Handa T, Nagasaka Y, Inoue M, Mikami A. Modulation of neuronal activity with cue-invariant shape discrimination in the primate superior temporal sulcus. *Neuroscience*. 2014;268:221–235.
268. Sáry G, Vogels R, Orban GA. Cue-invariant shape selectivity of macaque inferior temporal neurons. *Science*. 1993;260:995–997.
269. Grill-Spector K, Kushnir T, Edelman S, Itzchak Y, Malach R. Cue-invariant activation in object-related areas of the human occipital lobe. *Neuron*. 1998;21:191–202.
270. Giaschi D. The processing of motion-defined form. In: Harris L, Jenkin M, eds. *Seeing Spatial Form*. New York: Oxford University Press, 2006:101–119.
271. Gulyás B, Heywood CA, Popplewell DA, Roland PE, Cowey A. Visual form discrimination from color or motion cues: functional anatomy by positron emission tomography. *Proc Natl Acad Sci U S A*. 1994;91:9965–9969.
272. Kanwisher N, Yovel G. The fusiform face area: a cortical region specialized for the perception of faces. *Philos Trans R Soc Lond B Biol Sci*. 2006;361:2109–2128.
273. Rossion B, Joyce CA, Cottrell GW, Tarr MJ. Early lateralization and orientation tuning for face, word, and object processing in the visual cortex. *Neuroimage*. 2003;20:1609–1624.
274. Meng M, Cherian T, Singal G, Sinha P. Lateralization of face processing in the human brain. *Proc Biol Sci*. 2012;279:2052–2061.
275. Bankó ÉM, Körtvélyes J, Németh J, Weiss B, Vidnyánszky Z. Amblyopic deficits in the timing and strength of visual cortical responses to faces. *Cortex*. 2013;49:1013–1024.
276. Cattaneo Z, Vecchi T, Monegato M, Pece A, Merabet LB, Carbon CC. Strabismic amblyopia affects relational but not featural and Gestalt processing of faces. *Vision Res*. 2013;80:19–30.

Investigative Ophthalmology & Visual Science

277. Lerner Y, Pianka P, Azmon B, et al. Area-specific amblyopic effects in human occipitotemporal object representations. *Neuron*. 2003;40:1023–1029.
278. Ing MR. Surgical alignment prior to six months of age for congenital esotropia. *Trans Am Ophthalmol Soc*. 1995;93: 135–141.
279. Kelly KR, Felius J, Ramachandran S, John BA, Jost RM, Birch EE. Congenitally impaired disparity vergence in children with infantile esotropia. *Invest Ophthalmol Vis Sci*. 2016;57: 2545–2551.
280. Ding J, Levi DM. Recovery of stereopsis through perceptual learning in human adults with abnormal binocular vision. *Proc Natl Acad Sci U S A*. 2011;108:E733–E741.
281. Hess RF, Babu RJ, Clavagnier S, Black J, Bobier W, Thompson B. The iPod binocular home-based treatment for amblyopia in adults: efficacy and compliance. *Clin Exp Optom*. 2014; 97:389–398.
282. Hess RF, Mansouri B, Thompson B. Restoration of binocular vision in amblyopia. *Strabismus*. 2011;19:110–118.
283. Knox PJ, Simmers AJ, Gray LS, Cleary M. An exploratory study: prolonged periods of binocular stimulation can provide and effective treatment for childhood amblyopia. *Invest Ophthalmol Vis Sci*. 2012;53:817–824.
284. Li J, Thompson B, Lam CS, et al. The role of suppression in amblyopia. *Invest Ophthalmol Vis Sci*. 2011;52:4169–4176.
285. Vedamurthy I, Knill DC, Huang SJ, et al. Recovering stereo vision by squashing virtual bugs in a virtual reality environment. *Philos Trans R Soc Lond B Biol Sci*. 2016; 371:1–13.
286. Hess RF, Thompson B. Amblyopia and the binocular approach to its therapy. *Vision Res*. 2015;114:4–16.
287. Levi DM, Knill DC, Bavelier D. Stereopsis and amblyopia: a mini-review. *Vision Res*. 2015;114:17–30.
288. Chen Z, Li J, Liu J, et al. Monocular perceptual learning of contrast detection facilitates binocular combination in adults with anisometropic amblyopia. *Sci Rep*. 2016;6:1–12.
289. Ooi TL, Su YR, Natale D, He ZJ. A push-pull treatment for strengthening the 'lazy eye' in amblyopia. *Curr Biol*. 2013; 23:R309–R310.
290. Zhang JY, Cong LJ, Klein SA, Levi DM, Yu C. Perceptual learning improves adult amblyopic vision through rule-based cognitive compensation. *Invest Ophthalmol Vis Sci*. 2014; 55:2020–2030.
291. Tsirlin I, Colpa L, Goltz HC, Wong AM. Behavioral training as new treatment for adult amblyopia: A meta-analysis and systematic review. *Invest Ophthalmol Vis Sci*. 2015;56: 4061–4075.
292. Birch EE, Li SL, Jost RM, et al. Binocular iPad treatment for amblyopia in preschool children. *J AAPOS*. 2015;19:6–11.
293. Holmes JM, Manh VM, Lazar EL, et al. Effect of a binocular iPad game vs part-time patching in children aged 5 to 12 years with amblyopia: A randomized clinical trial. *JAMA Ophthalmol*. 2016;134:1391.
294. Agervi P, Nilsson M, Martin L. Foveal function in children treated for amblyopia. *Acta Ophthalmol*. 2010;88:222–226.
295. Barbur JL, Hess RF, Pinney HD. Pupillary function in human amblyopia. *Ophthalmic Physiol Opt*. 1994;14:139–149.
296. González 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.
297. Shaikh AG, Otero-Millan J, Kumar P, Ghasia FF. Abnormal fixational eye movements in amblyopia. *PLoS One*. 2016;11: e0149953.
298. Perdziak M, Witkowska DK, Gryncewicz W, Ober JK. Not only amblyopic but also dominant eye in subjects with strabismus show increased saccadic latency. *J Vis*. 2016;16: 1–12.
299. Davis AR, Sloper JJ, Neveu MM, Hogg CR, Morgan MJ, Holder GE. Differential changes of magnocellular and parvocellular visual function in early- and late-onset strabismic amblyopia. *Invest Ophthalmol Vis Sci*. 2006;47:4836–4841.
300. Davis AR, Sloper JJ, Neveu MM, Hogg CR, Morgan MJ, Holder GE. Differential changes in color and motion-onset visual evoked potentials from both eyes in early- and late-onset strabismic amblyopia. *Invest Ophthalmol Vis Sci*. 2008;49: 4418–4426.
301. Watts PO, Neveu MM, Holder GE, Sloper JJ. Visual evoked potentials in successfully treated strabismic amblyopes and normal subjects. *J AAPOS*. 2002;6:389–392.
302. Zhang W, Zhao K. Multifocal VEP difference between early- and late-onset strabismus amblyopia. *Doc Ophthalmol*. 2005;110:173–180.
303. Simmers AJ, Bex PJ, Hess RF. Perceived blur in amblyopia. *Invest Ophthalmol Vis Sci*. 2003;44:1395–1400.
304. Liu L, Wang K, Liao B, Xu L, Han S. Perceptual salience of global structures and the crowding effect in amblyopia. *Graefes Arch Clin Exp Ophthalmol*. 2004;242:566–570.
305. Rentschler I, Hilz R. Abnormal orientation selectivity in both eyes of strabismic amblyopes. *Exp Brain Res*. 1979;37:187–191.
306. Thiel A, Sireteanu R. Strabismic amblyopes show a bilateral rightward bias in a line bisection task: evidence for a visual attention deficit. *Vision Res*. 2009;49:287–294.
307. Husk JS, Farivar R, Hess RF. Amblyopic deficits in processing structure-from-motion. *J Vis*. 2012;12(4):1–12.
308. Ho CS, Giaschi DE. Deficient maximum motion displacement in amblyopia. *Vision Res*. 2006;46:4595–4603.
309. Ho CS, Giaschi DE. Stereopsis-dependent deficits in maximum motion displacement in strabismic and anisometropic amblyopia. *Vision Res*. 2007;47:2778–2785.
310. Mirabella G, Hay S, Wong AM. Deficits in perception of images of real-world scenes in patients with a history of amblyopia. *Arch Ophthalmol*. 2011;129:176–183.
311. Narinesingh C, Wan M, Goltz HC, Chandrakumar M, Wong AM. Audiovisual perception in adults with amblyopia: a study using the McGurk effect. *Invest Ophthalmol Vis Sci*. 2014;55:3158–3164.
312. Farzin F, Norcia AM. Impaired visual decision-making in individuals with amblyopia. *J Vis*. 2011;11(14):1–10.

Investigative Ophthalmology & Visual Science

Queries for iovs-58-03-28

Author: This article has been lightly edited for grammar, style, and usage. Please compare against your original document and make changes on these pages. Please limit your corrections to substantive changes that affect meaning. If no change is required in response to a question, please write "OK as set" in the margin. Copy editor

Author: Carefully check the spelling and order of the author names and check the affiliations for all of the authors.

Author: Make sure that ALL funding/financial support is listed in the information following the Acknowledgments.

Author: Check the bottom of the first page to make sure the license shown is the license you prefer. (The two options are the Creative Commons Attribution-NonCommercial-NoDerivatives license and the Creative Commons Attribution license.)

1. Author: In the Fellow Eye Deficits Occur at Any Level of Visual Processing Involving Binocular Cortex section, paragraph 2, sentence 4, please define "MT." Copy editor
2. Author: For in-text references calling out specific sections (e.g., section 1.1.2.), please go through and adjust these call outs using headings. Journal does not use section numbers. Copy editor
3. Author: For reference 232, please include only one city for the publisher. Copy editor