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Temporal integration of visual signals in lens compensation (a review)

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Abstract

Postnatal eye growth is controlled by visual signals. When wearing a positive lens that causes images to be focused in front of the retina (myopic defocus), the eye reduces its rate of ocular elongation and increases choroidal thickness to move the retina forward to meet the focal plane of the eye. When wearing a negative lens that causes images to be focused behind the retina (hyperopic defocus), the opposite happens. This review summarizes how the retina integrates the constantly changing visual signals in a non-linear fashion to guide eye growth in chicks: (1a) When myopic or hyperopic defocus is interrupted by a daily episode of normal vision, normal vision is more effective in reducing myopia caused by hyperopic defocus than in reducing hyperopia caused by myopic defocus; (1b) when the eye experiences alternating myopic and hyperopic defocus, the eye is more sensitive to myopic defocus than to hyperopic defocus and tends to develop hyperopia, even if the duration of hyperopic defocus is much longer than the duration of myopic defocus; (2) when the eye experiences brief, repeated episodes of defocus by wearing either positive or negative lenses, lens compensation depends on the frequency and duration of individual episodes of lens wear, not just the total daily duration of lens wear; and (3) further analysis of the time constants for the hypothesized internal emmetropization signals show that, while it takes approximately the same amount of time for the signals to rise and saturate during lens-wearing episodes, the decline of the signals between episodes depends strongly on the sign of defocus and the ocular component. Although most extensively studied in chicks, the nonlinear temporal integration of visual signals has been found in other animal models. These findings may help explain the complex etiology of myopia in school-aged children and suggest ways to slow down myopia progression.

Keywords

Myopia; hyperopia; axial length; choroid; emmetropization; temporal integration

After decades of studies on myopia conducted on various animals, including tree shrews (Sherman et al. 1977; Norton and Rada 1995), rhesus monkeys (Wiesel and Raviola 1977; von Noorden and Crawford 1978; Hung et al. 1995), chicks (Schaeffel et al. 1988; Irving et al. 1992), marmosets (Troilo and Judge 1993; Whatham and Judge 2001), guinea pigs (McFadden et al. 2004), and mice (Tejedor and de la Villa 2003; Schaeffel et al. 2004), it has become clear that the growth of the eye, like the growth of other organs in our body, is

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under homeostatic control, and that the homeostatic control mechanism depends, at least in part, on visual signals that exert strong control over the axial length of the eye (Wallman and Winawer 2004).

To see far objects clearly, the focal length of the eye needs to match its physical length, so the images will be focused on the photoreceptors in the retina, a state known as emmetropia. When presented with defocus (i.e., when an image is not focused on the photoreceptors), the eye has a short term focusing mechanism (accommodation) and a long-term focusing mechanism (emmetropization). Emmetropization is the capacity to compensate for defocus by changing both the rate of ocular elongation and the thickness of the choroid (a vascular layer lying between the retinal pigment epithelium and sclera) to bring the retina closer to the focal plane. When the image is focused in front of the retina (so called “myopic defocus”, since the eye is now functionally myopic) by wearing a positive lens, the eye reduces its rate of ocular elongation and increases choroidal thickness to move the retina forward to meet the focal plane (Figure 1). Given enough time, the eye will restore emmetropia with the positive lens in place, and will therefore appear hyperopic without the lens. The opposite happens when wearing a negative lens that focuses images behind the retina (“hyperopic defocus”, Figure 1).

Among the species used in myopia research, chicks are the most commonly used, mostly because, compared with other species, chicks have been shown to be able to compensate for the widest range of defocus within a relatively short period of time (Irving et al. 1992). Indeed, young chick eyes have two distinguishing traits facilitating compensation: Their eyes (which grow at a relatively steady rate when measured until at least 42 days old (Gottlieb et al. 1987) change their rate of growth within a day or two to compensate for both myopic and hyperopic defocus, and their choroids show large changes in thickness to compensate for both myopic and hyperopic defocus (Wallman et al. 1995). Indeed, compensatory changes in choroidal thickness have been found in tree shrews (Siegwart and Norton 1998), marmosets (Troilo et al. 2000), rhesus macaques (Hung et al. 2000), guinea pigs (Howlett and McFadden 2006; Howlett and McFadden 2009), and even in humans (Chakraborty et al. 2012; Woodman et al. 2012). However, the magnitude of change in choroidal thickness found in primates is much smaller than that found in chicks. These two compensatory components (axial length and choroidal thickness) have different temporal dynamics in chicks: Choroidal compensation happens more rapidly (within a few hours), whereas axial compensation takes a day or two to occur (Zhu et al. 2005).

In real life, every region of the retina experiences a dynamic mixture of myopic and hyperopic defocus, changing constantly depending on one’s fixation point, accommodative state, and the surrounding environment. Because the pattern of defocus in the retina changes rapidly over space and time, but the compensatory growth mechanism is relatively slow, the eye faces a significant challenge: The eye must integrate visual information over space and time to infer whether it needs to increase its length (or accelerate growth), reduce its length (or slow its growth), or to maintain its current size (or growth rate). To better understand the emmetropization mechanism, it is essential to study the eye’s response not only to the average level of defocus but also to the variations in magnitude and type of defocus that occur naturally at each region of the retina during normal emmetropization, i.e., to study the temporal integration of visual signals.

This review summarizes studies on the temporal integration of visual signals. Significantly, experimental results have led to a greater appreciation of the fact that the temporal integration of different types of retinal defocus is decidedly non-linear. This review also asks the question if or how a strategy of lens wear in children might be able to exploit these nonlinearities to slow down or even arrest myopic progression.

The linear model of temporal integration of visual signals

It is now clear that the retina can use visual signals it receives to guide eye growth towards emmetropization through a local mechanism (Wallman et al. 1987; Diether and Schaeffel 1997), even after the connection to the brain has been severed by optic nerve section (Troilo and Wallman 1991; Wildsoet and Wallman 1995). Given the massive number of visual signals the retina receives during every waking moment, how does the retina process these visual signals to guide eye growth? Flitcroft (1998) proposed that the retina simply averages visual signals over a period of time to guide eye growth toward emmetropization. Wallman and Winawer (2004) then described a simple linear model of emmetropization in which internal emmetropization signals rise and fall in a linear fashion (Figure 2A). Imagine an emmetropic eye experiencing several brief episodes of defocus with darkness between these episodes: If the eye experiences two episodes of myopic defocus (of the same magnitude and duration), the hypothesized internal emmetropization signal would rise in the direction guiding compensation for myopic defocus in a linear fashion during exposure, incrementing like a counter, and remain stable between exposures (during darkness). If the eye then experiences an equally long period of hyperopic defocus, the signal would start going to the opposite direction guiding compensation for hyperopic defocus, decrementing again like a counter. If such a linear model accurately describes the retina's response to defocus (assuming that the retina weighs myopic and hyperopic defocus equally), then one can infer that: (1) Equal duration of myopic and hyperopic defocus would cancel each other out, leaving no accumulated signal, and thus normal eye growth; and (2) a more stringent test of linearity would examine the specific temporal dynamics with the prediction that the final magnitude of the signal (and the final compensation) depends on the total exposure to defocus that the retina experiences over time each day.

The non-linear model of temporal integration of visual signals

Results from previous studies, however, argue against this linear model. Indeed, there is strong evidence indicating three nonlinearities in the temporal integration of defocus:

1a. The retina does not weigh myopic and hyperopic defocus equally: Short periods of normal vision reduce experimental myopia caused by wearing negative lenses or occluders but have minimal effects on experimental hyperopia caused by wearing positive lenses

It has been shown that a short period of "normal vision" (viewing without any lens or occluder on the eye) each day cancels myopia from wearing negative lenses or occluders during the rest of the day (Napper et al. 1995; Schmid and Wildsoet 1996); by contrast, it takes a much longer period of normal vision to cancel out hyperopia from wearing positive lenses during the rest of the day (Schmid and Wildsoet 1996). Specifically, in chicks, a daily episode of normal vision of as little as 2 to 3 hours (17% to 25% of the light phase) reduced myopia caused by wearing occluders (Napper et al. 1995) or negative lenses (Schmid and Wildsoet 1996) the remainder of the day (9 to 10 hours) by more than 95%. This phenomenon has also been found in tree shrews (Shaikh et al. 1999) and monkeys (Smith et al. 2002; Wensveen et al. 2006; Kee et al. 2007). Hyperopia caused by myopic defocus, on the other hand, is much more resilient in chicks: A daily episode of 3 hours of normal vision (25% of the light phase) reduced hyperopia caused by wearing positive lenses the remainder of the day (9 hours, 75% of the light phase) by only 10% (Schmid and Wildsoet 1996). Furthermore, chicks that wore a positive lens for only 3 hours per day and no lens for the remaining 9 hours per day, still developed a significant hyperopic shift (Schmid and Wildsoet 1996). When the percentage of myopia from each treatment paradigm (the final refractive error after wearing either negative lenses or occluders interrupted by normal

vision as a percentage of the final refractive error after wearing these devices uninterrupted) in chicks, tree shrews, and rhesus monkeys is plotted against the duration of daily normal vision, a strikingly consistent trend is found across different species (Figure 3): It is clear that as little as 2 hours of daily normal vision reduced myopia progression by approximately 80% in all these different species (Smith et al. 2002). This suggests that the “diluted” response to wearing negative lenses or occluders might reflect an evolutionarily preserved strategy to prevent the eye from elongating too much in response to episodes of hyperopic defocus (Smith et al. 2002).

1b. When positive and negative lenses are worn alternately, the eye is more responsive to myopic defocus and develops hyperopia

In chicks, when positive and negative lenses are worn alternately, the eye is more responsive to myopic defocus and develops hyperopia, rather than averaging out the defocus of the opposite signs (Winawer and Wallman 2002; Zhu et al. 2003; Winawer et al. 2005). Specifically, when Winawer and Wallman (2002) put positive and negative lenses alternately on chick eyes for equal duration per episode (with darkness between episodes), the eyes developed hyperopia, despite wearing negative lenses for the same duration (Figure 4). When negative lenses were worn 5 times longer than positive lenses per episode, eyes still became hyperopic (Winawer and Wallman 2002). In an extreme case, only four 2-minute long daily episodes of positive lens wear canceled out the effect of wearing negative lenses the remainder of the day, and caused hyperopia (Zhu et al. 2003)(Figure 4). Similar protective effects of myopic defocus were also found in tree shrews when young tree shrews wore positive lenses binocularly (McBrien et al. 2012), but were absent when older tree shrews wore positive lenses monocularly (Norton et al. 2006). On the other hand, myopic defocus was found to be less protective than normal vision in rhesus monkeys, possibly because the degree of imposed myopic defocus was too large (Kee et al. 2007).

In the real world, of course, the eyes do not experience any type of defocus for a sustained period of time, because of temporal fluctuation of defocus, depending on one’s fixation point, accommodative state, and the surrounding environment. Therefore, to better mimic the visual experience in the real world, Winawer *et al.* (2005) designed a two-drum system that could project myopic and hyperopic defocus in chicks’ eyes in rapid succession in a fraction of a second (Figure 5). The chick was placed at the center of the inner drum made of a metal scrim. When the light source inside the inner drum was turned on and the light source outside the inner drum (between the inner drum and the outer drum) was turned off, the metal scrim appeared bright and opaque but the outer drum was dark and invisible from the point of view of the chick inside the inner drum. By contrast, when the light source inside the inner drum was turned off and the light source outside the inner drum was turned on, the metal scrim became dark and invisible to the chick while the outer drum appeared bright. When the chick was wearing a positive lens while sitting at the center of the inner drum (under cycloplegia), the inner and outer drums would project hyperopic defocus and myopic defocus, respectively (Figure 5A). Therefore, by switching rapidly between the light sources inside and outside the inner drum, the authors were able to project myopic and hyperopic defocus in rapid succession to the lens-wearing eye (the fellow control eye had normal vision in a chamber).

Similar to previous findings, the authors found that myopic defocus had a dominating effect on lens compensation. Equal duration of brief myopic and hyperopic defocus (from 0.5 seconds to 15 minutes each) in rapid succession still caused hyperopia, and bigger hyperopic shifts were found with slower alternations. Unequal duration of brief myopic and hyperopic defocus (5 minutes of myopic defocus and 25 minutes of hyperopic defocus) also caused hyperopia. But, when the duration of myopic defocus was too short (0.5 seconds of myopic

defocus and 2.5 seconds of hyperopic defocus), there was no obvious compensation, possibly because both myopic and hyperopic defocus cancelled each other out.

Taken together, these findings support the hypothesis that, instead of using the “average” defocus signal over a period of time to guide emmetropization, the controller in the retina is much more sensitive to myopic defocus than to hyperopic defocus in the guidance of eye growth.

2. Lens compensation depends on the frequency and duration of individual episodes of lens-wear, not just the total exposure of lens wear per day

In chicks, lens compensation has been found to depend on both the frequency of exposure to defocus and on the duration of each exposure, not just on the total duration of lens wear.

Schwahn and Schaeffel (1997) studied the effects of brief, repeated flickering lights on lens compensation and form deprivation myopia (FDM) in chicks. Chicks, wearing either positive or negative lenses, were raised in flickering lights of different frequencies (6 and 12 Hz) and duty cycles (an index of the relative durations of the light period and the subsequent dark period of a flicker cycle, expressed as the percentage of the flicker cycle that is occupied by the light period, 4% to 75%). The duration of each light pulse ranged from a minimum of 3 milliseconds (produced by a 4% duty cycle at 12 Hz) to a maximum of 83 milliseconds (produced by a 50% duty cycle at 6 Hz). Despite the extremely short duration of each light pulse, chick eyes still partially compensated for defocus, although the magnitude of compensation was less compared that found in the normal lighting condition (no flicker). Similar results have been found in other studies (Crewther and Crewther 2002; Crewther and Crewther 2003; Crewther et al. 2006).

Winawer and Wallman (2002) gave chicks brief, repeated episodes of either positive or negative lens wear, with dark intervals between lens-wearing episodes. The chicks in different groups had the same total duration of lens wear per day, but with different durations of lens-wearing episodes at different frequencies, from 2 seconds every 2 minutes (the highest frequency, and the shortest lens-wearing episodes and the shortest dark intervals between lens wear) to 28 minutes every day (the lowest frequency, and the longest lens-wearing episodes and the longest dark intervals between lens wear). More frequent lens-wearing episodes (shorter duration per episode and shorter dark interval between episodes) caused more robust lens compensation, compared with less frequent lens-wearing episodes (longer duration per episode and longer dark interval). When the duration of each lens-wearing episode was less than a minute, however, very little compensation ensued.

Taken together, these findings also suggest that the temporal integration of visual signals is not simply a linear function and that the magnitude of lens compensation is not necessarily simply proportional to the total duration of lens wear. Ohngemach et al. (2001) discovered that the sensitivity to deprivation myopia varies over the day and that intermittent periods of normal vision inhibit deprivation myopia more if they occur in the evening than in the morning. It is possible that the emmetropization signal rises and saturates quickly during each lens-wearing episode (within a matter of minutes), and declines slowly between episodes, i.e., the nonlinear model of the hypothesized internal emmetropization signal (Figure 2B)(Flitcroft 1999); Wallman and Winawer 2004; Zhu and Wallman 2009b). Not only do these separate signals rise and decay in a non-linear fashion, but the effects of the two signals add together in a non-linear manner.

3. Lens compensation strongly depends on the sign of defocus and the ocular component

In light of previous findings, it would be important to further analyze the temporal properties in lens compensation. Since it is still unclear which signaling molecules or biochemical pathways are responsible for the hypothesized internal emmetropization signal, Zhu and Wallman (2009b) conducted two experiments to study the effects of the signal on axial length and choroidal thickness, and tried to infer the temporal properties of the rise and fall of the signal from the experimental results. The authors tried to find: (1) How brief they could make brief, repeated episodes of lens-wear (with darkness in between successive periods of lens wear) and still generate a robust response to lens wear; and (2) how long they could make the period of darkness between successive episodes of lens wear and still generate a robust response to lens wear. Consequently, in these experiments, the total duration of lens wear was different between different lens-wearing paradigms.

For several days, chicks were exposed to brief, repeated periods of either positive or negative lens wear, with a period of darkness between successive periods of lens wear in both experiments. In the first experiment, the authors varied the lens-wearing duration, and kept the frequency of lens wear constant (from 10 seconds to 10 minutes per hour). The axial and choroidal compensation resulting from each particular treatment paradigm were compared to those resulting from wearing lenses without any interruptions. The authors specifically calculated the “rise time” for both positive and negative lens wear: How long each brief repeated episode of lens wear should be to generate 50% of the maximum response to uninterrupted lens wear. In the second experiment, the authors held the duration of each repeated episode of lens wear constant (0.5 hour per episode to ensure signal saturation), and varied the dark interval between lens wear (from 0.5 to 47.5 hours). The authors studied the “fall time”: How long each dark interval between lens wear should be for the emmetropization signal to decline sufficiently during the dark interval so that it can produce only 50% of the maximum response to uninterrupted lens wear. The authors showed that the rise times were very similar for both axial length and choroidal thickness for both positive and negative lenses: It takes a couple of minutes (1 to 4 minutes) for the emmetropization signal to rise to 50% maximum potency. The fall times for axial length, however, was drastically different for positive and negative lenses: It took 24 hours for the emmetropization signal to decay by 50% for positive lenses, but only 0.4 hours for negative lenses (Figure 4). The fall times for choroidal thickness were also different for positive (6.7 hours) and negative (3.2 hours) lenses, even though the difference between the two was not as big as that found for axial length. Schwahn and Schaeffel (1997) found that the suppression of negative lens-induced myopia was correlated with the dark phase duration, but the suppression of positive lens-induced hyperopia was not, further supporting different fall-times for positive and negative lens compensation.

In summary, it seems that the controller in the retina does not just simply average out the defocus it experiences over a period of time and use the “mean defocus” to guide eye growth. Rather, there is a more complicated homeostatic controlling mechanism that generates a signal that rises and eventually saturates during defocus and decays slowly between episodes of defocus. The time constants for this signal are drastically different for axial length and choroidal thickness for positive and negative lens wear.

Furthermore, rather than the single emmetropization signal postulated in the linear model, it is likely that separate biochemical signals mediate the response to myopic defocus (growth inhibition) and hyperopic defocus (growth stimulation). In general, it is very hard to inhibit positive lens compensation compared with negative lens compensation, either visually or pharmacologically. First, as mentioned before, compensation for positive and negative lens shows distinctively different temporal dynamics (Schmid and Wildsoet 1996; Schwahn and Schaeffel 1997; Winawer and Wallman 2002; Zhu et al. 2003; Zhu et al. 2005; Zhu and Wallman 2009b) and circadian rhythms (Nickla et al. 1998). Second, except for insulin,

various pharmacological agents, such as muscarinic antagonists, dopamine agonists, and neurotoxins against catecholamines, all block only myopia, not hyperopia (as recently reviewed by Ganesan and Wildsoet (2010)).

All in all, there are three nonlinearities in the temporal integration of visual signals in lens compensation: (1) The retina is more sensitive to myopic defocus than to hyperopic defocus, suggested by the findings that when myopic or hyperopic defocus is interrupted by a daily episode of normal vision, normal vision is more effective in reducing myopia caused by hyperopic defocus than in reducing hyperopia caused by myopic defocus, and that when the eye experiences alternating myopic and hyperopic defocus, the eye is more responsive to myopic defocus than to hyperopic defocus and tends to develop hyperopia, even if the duration of hyperopic defocus is much longer than the duration of myopic defocus. (2) When the eye experiences brief, repeated episodes of defocus by wearing either positive or negative lenses, lens compensation depends on the frequency and duration of the lens wear, not just the total duration of lens wear per day. (3) Further analysis of the time constants for the hypothesized internal emmetropization signals show that, while it takes approximately the same amount of time for the signals to rise and saturate during lens-wearing episodes, the decline of the signals between episodes depends strongly on the sign of defocus and the ocular component.

Significance of temporal properties of the non-linear model of the hypothesized internal emmetropization signal

The temporal properties of the non-linear model of the hypothesized internal emmetropization signal help explain why short but frequent episodes of lens wear is more effective in causing lens compensation, compared with long but infrequent episodes of lens wear, while the total duration of daily lens exposure was kept the same. Compared with long but infrequent lens-wearing episodes, short but frequent exposures to defocus are more effective in generating the emmetropization signal because the short episodes can also cause the signal to rise and saturate, while the short dark intervals between frequent exposures prevent the signal from declining between lens-wearing episodes. Extremely short lens-wearing episodes (each less than a minute in duration), by contrast, do not give the emmetropization signal enough time to rise during episodes. Thus, no compensation takes place.

The long fall time of axial length for positive lenses found in chicks also helps explain why hyperopia is the “favored” result of compensation, even when the duration of positive lens wear is much shorter than that of negative lens wear.

The different fall times for axial length and choroidal thickness for positive and negative lens wear help explain the dissociation between axial and choroidal compensation previously discovered by Winawer and Wallman (2002).

Specifically, when chicks wore spectacle lenses without interruption, axial and choroidal compensation occurred simultaneously, at least during the first few days of lens treatment. This was not necessarily the case during intermittent lens wear (with periods of darkness between lens-wearing episodes): If episodes of intermittent positive or negative lens wear were brief and frequent, both increased axial elongation and choroidal thinning (after wearing negative lenses) and axial inhibition and choroidal thickening (after wearing positive lenses) were found, similar to results with uninterrupted lens wear. But, if lens treatment was not frequent enough (when the duration of dark intervals between lens-wearing episodes were too long), only axial inhibition (after wearing positive lenses) and choroidal thinning (after wearing negative lenses) could still be found after several days of

lens treatment (Winawer and Wallman 2002; Zhu and Wallman 2009b). A similar dissociation of axial and choroidal compensation was also found either when chicks' daily rhythms were interrupted by repeated light exposure during the night (Kee et al. 2001), or when chicks wore a weak diffuser over a positive lens (Park, 2003). It has been proposed that a signal cascade, which originates in the retina and passes through the retinal pigment epithelium and the choroid and eventually reaches the sclera, controls choroidal thickness and the scleral extracellular matrix biosynthesis, thus controlling ocular growth, as reviewed by Wallman and Winawer (2004). Given the different fall times for choroidal thickness and axial length, it is possible that there are two independent signals originated in the retina that control choroidal and axial compensation via independent mechanisms. On the other hand, Zhu and Wallman (2005) has shown that a transient choroidal thickening does take place right after each episode of positive lens wear (which could be missed if measured several hours later), and Nickla (2006; 2007; 2010) has shown that this transient choroidal thickening is necessary in reducing the rate of ocular elongation.

Understanding the temporal integration of visual signals can help us understand the etiology of myopia in school-aged children, and develop effective therapies to reduce myopic progression. If the findings on the temporal integration of visual signals found in chicks generalize to human myopia, they suggest that the temporal pattern of defocus, for example from nearwork such as reading, may play a larger role in determining one's myopic progression than the total amount of time one spends doing nearwork.

It is widely observed that myopia is highly associated with the level of education (Rosenfield and Gilmartin 1998), and it has often been suggested that the aspect of education associated with myopia might be prolonged hyperopic defocus during reading. However, the correlation between the degree of myopic development and the total amount of near work (during which the eye is subjected to hyperopic defocus) per day is weak (Saw et al. 1996; Tan et al. 2000; Saw et al. 2001; Mutti et al. 2002; Saw et al. 2002), indicating that the total duration of reading per day may not capture the most important factor in determining myopic development. Indeed, the findings on the temporal integration of visual signals suggest that the temporal dynamics of near work (e.g., the duration of study and, especially, the length of breaks in between) should be further analyzed to predict whether a child will develop myopia, and may even help predict the speed of myopia progression.

Integration of simultaneous myopic and hyperopic defocus

In addition to the temporal integration of alternating myopic and hyperopic defocus, it is important to study the effect of simultaneous myopic and hyperopic defocus. It has been shown that presenting chick eyes with simultaneously competing myopic and hyperopic defocus, using either mixed astigmatic (toric) lenses with opposite lens powers on the two perpendicular meridians (McLean and Wallman 2003), lens-cone devices with two target planes (Diether and Wildsoet 2005) or dual-power lenses that had different combinations of lens powers (Tse et al. 2007), caused hyperopia, confirming the dominating effect of myopic defocus in chicks. Moreover, Benavente-Perez et al. (2012) reported similar results in marmosets by using multi-zone contact lenses with alternating powers. Therefore, it seems that when the retina experiences myopic and hyperopic defocus simultaneously, myopic defocus still dominates compensation, although to a smaller degree than when the eye experiences myopic and hyperopic defocus in succession. In the future studies of temporal and spatial integration of visual signal, one should analyze defocus from four dimensions: The sign of the defocus, the magnitude of the defocus, the spatial location of the defocus, and the duration of the defocus, to better control its effects on emmetropization (Tse et al. 2007).

Remaining questions

There are still many questions remaining to be answered regarding the temporal integration of visual signals. For example, what signaling pathways are responsible for the integration of visual signals? A number of signaling molecules have been suggested to be involved in emmetropization, e.g., glucagon (Fischer et al. 1999; Feldkaemper and Schaeffel 2002; Vessey et al. 2005a; Vessey et al. 2005b; Fischer et al. 2008; Zhu and Wallman 2009a) and retinoic acid (Seko et al. 1996; Mertz and Wallman 2000; McFadden et al. 2004), but it is not clear how these molecules work together to accurately control eye growth towards emmetropization.

Another question to ask would be: Does the non-linearity in the temporal integration of visual signals found in chicks also exist in primates or humans? If it does, to what extent? Also, is the signaling pathway in humans, assuming its existence, the same as that in chicks? In fact, the results found in animal studies lead to a puzzle about the development of human myopia: If myopic defocus protected against the development of myopia in humans, it would be very hard for school-aged children to develop myopia, as long as they had frequent brief breaks from near work, since very brief periods of myopic defocus would be sufficient to prevent myopia. So, why does myopic defocus seem less potent in arresting axial elongation in children than in chicks? One possibility is that school-aged children are beyond the age when myopic defocus can cancel out the effect of hyperopic defocus. A more optimistic possibility is that the pattern of temporal integration in children is different from the pattern found in chicks. Because the chick eye is growing so fast, the chick's emmetropization mechanism may have evolved to be sensitive to myopic defocus and to shut down axial elongation for several hours after only a few minutes of exposure to myopic defocus. Because the child's eye is growing relatively slowly, the human emmetropization mechanism may require relatively long periods of exposure to more extreme myopic defocus before it will shut down axial elongation for hours or days.

Although alternating periods of myopic defocus and hyperopic defocus tend to produce slight hyperopia in chicks, this effect has not been found in children. However, projecting myopic defocus onto the peripheral retina (while allowing the central retina to receive clear images) may produce somewhat similar effects in chicks and in children. Placing dual-zone spectacle lenses on chicks, Liu and Wildsoet (2011) have shown that projecting myopic defocus onto the peripheral retina reduced axial elongation and caused hyperopia. In fact, myopic defocus slowed down axial elongation more effectively when that myopic defocus was confined to the peripheral retina rather than when the same amount of myopic defocus was projected onto the entire retina. Interestingly, recent studies have also shown that both dual-focus soft contact lenses (Anstice and Phillips 2011) and contact lenses with progressive positive power in the periphery (Sankaridurg et al. 2011) can reduce the rate of axial elongation in childhood myopia. Both the dual-zone contact lens and a contact lens with progressive positive power in the periphery projected myopic defocus onto the peripheral retina, allowing the child to retain clear foveal vision and still receive a sufficiently strong dose of myopic defocus on the peripheral retina to slow down axial elongation. Furthermore, Phillips (2005) has shown that, when dominant eyes of school-aged children were corrected for distance and fellow eyes were undercorrected, myopia progression in the fellow eyes was significantly slower than in the distance-corrected dominant eyes, suggesting that the myopic defocus the fellow undercorrected eyes experienced at all levels of accommodation (driven by the dominant eye) reduced myopia progression. By confining myopic defocus to the peripheral retina of both eyes or to the entire retina of only one eye, clinicians may be able to slow down axial elongation in both eyes or in one eye respectively, while still enabling a child to have high acuity distance vision in the central visual field. Slowing down the progression of myopia and even

preventing the development of myopia in school-aged children, perhaps, may not be a dream after all.

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- Myopic defocus is more potent than hyperopic defocus in guiding eye growth.
- Lens compensation depends on the frequency and duration of episodes of defocus.
- Lens compensation also depends on the sign of defocus and the ocular component.
- These findings may help explain the etiology of myopia in school-aged children.

A. Before compensation

B. After compensation

Figure 1.

Schematics of ocular compensation for defocus of opposite signs. (A) shows an emmetropic eye with a schematic representation of the myopic and hyperopic defocus produced by wearing a positive and negative spectacle lens, respectively. (B) shows ocular compensation: The eye reduces axial length and increases choroidal thickness to compensate for the positive lens, and increases axial length and reduces choroidal thickness to compensate for the negative lens. In either case, the eye becomes emmetropic again with the spectacle lens in place, since the image is now again focused on the retina. Adapted from Wallman and Winawer (Neuron, 2004;43:447-68).

Figure 2. Schematics for the linear model (A) and one type of the non-linear model (B) for the hypothesized internal emmetropization signal. The linear model (A) proposes that the signal is linearly related to the duration of defocus, and that signals produced by defocus of opposite signs cancel out each other. The non-linear model (B) proposes that the signal rises slowly and eventually saturates (provided the episode is long enough) and decays toward zero during periods of darkness between episodes. Adapted from Zhu and Wallman (*Invest Ophthalmol Vis Sci.*, 2009;50:37–46).

Figure 3.

The relationship between myopia and the amount of normal vision per day across different species. A similar amount of relative myopia (the final refractive error after wearing either negative lenses or occluders interrupted by normal vision, as a percentage of the final refractive error after wearing these devices uninterrupted) was found in various species wearing either negative lenses or diffusers interrupted by different amounts of normal vision. It is clear that 2 hours of daily normal vision reduced myopia by approximately 80% in different species. Adapted from Smith *et al.* (Invest Ophthalmol Vis Sci., 2002;43:291-9).

Figure 4.

The effect of brief, repeated episodes of positive lens wear on refractive error in chicks. Wearing positive lenses for brief, repeated episodes caused hyperopia, even though the eyes wore negative lenses for either the same duration (the bar on the left) or the rest of the day (the bar on the right). The blue and red arrows indicate the change in refraction (relative to control eyes) produced when the chicks wore only positive and negative lenses, respectively.

Figure 5.

Two-drum system. (A) The schematics of the two-drum system (top view). The inner and outer drums project hyperopic and myopic defocus to chick's lens-wearing eye, respectively. (B) and (C): Photographs of the inner scrim with the outer drum in the background. To the chick inside, the inner surface of the metal scrim appears opaque when illuminated from the inside (B), and clear when illuminated from the outside (C). Note that these photographs depict the effect of lighting on the appearance of the two drums, as viewed from outside the inner drum (not from the chick's perspective): When the outside surface of the inner drum appears transparent (B) or opaque (C) from the photographer's point of view, the inside surface of the inner drum will appear opaque (B) or invisible (C) from the chick's viewpoint inside the drum. Adapted from Winawer et al. (Vision Res. 2005;45:1667-77).

Figure 6.

The fall-times of the hypothesized internal emmetropization signals for ocular length for both positive and negative lens wear in chicks. The large diamonds represent the relative change in ocular length (change in ocular length in the lens-wearing eye over the course of the experiment minus the change in the follow, untreated eye) following uninterrupted lens wear (hence, zero hour of darkness between episodes), and the small circles represent the relative change following particular treatment paradigms of various dark intervals. It is clear that the paradigm of having the dark interval of 24 hours between positive lens-wearing episodes still caused 50% of maximal ocular inhibition seen in continuous positive lens wear, and that only 0.4 hour of dark interval between negative lens-wearing episodes already caused the maximal ocular elongation seen in continuous negative lens wear to decline by

50%. Therefore, the fall-times (arrows) are approximately 24 and 0.4 hours for positive and negative lens wear, respectively. Adapted from Zhu and Wallman (Invest Ophthalmol Vis Sci., 2009;50:37–46).