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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.

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 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 (Fig. 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", Fig. 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

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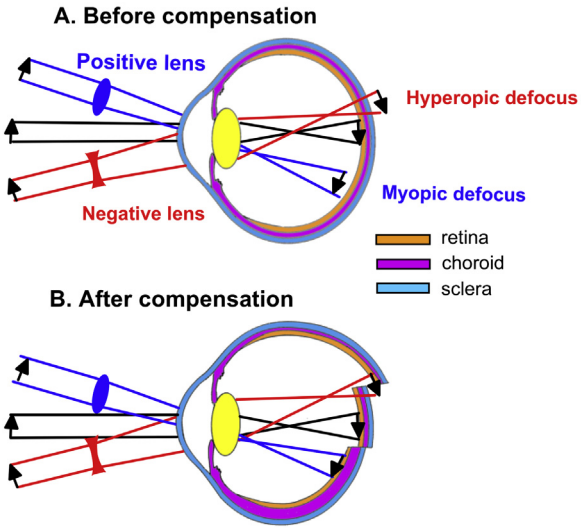

Fig. 1. Schematics of ocular compensation for defocus of opposite signs. (A) shows an emmetropic eye with a schematic representation of the myopic and hyperopic defocus produced by wearing a positive and negative spectacle lens, respectively. (B) shows ocular compensation: The eye reduces axial length 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 form Wallman and Winawer (Neuron, 2004; 43:447–68).

(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, 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.

1. 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 toward 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 (Fig. 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.

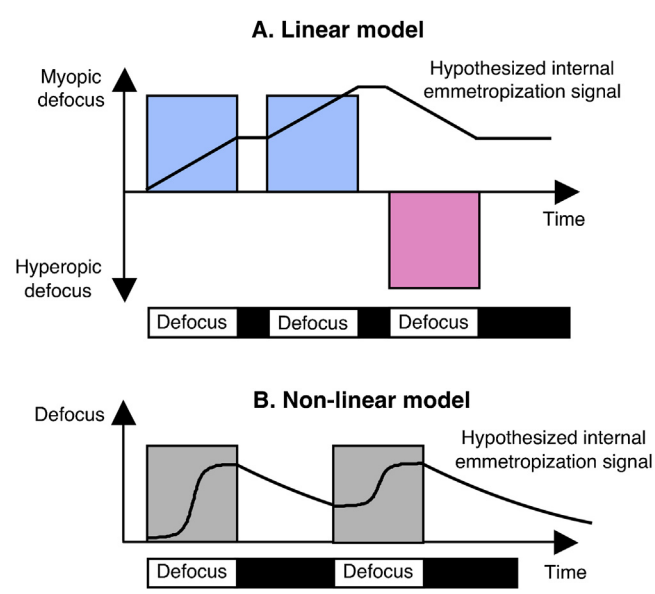

Fig. 2. Schematics for the linear model (A) and one type of the non-linear model (B) for the hypothesized internal emmetropization signal. The linear model (A) proposes that the signal is linearly related to the duration of defocus, and that signals produced by defocus of opposite signs cancel out each 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, 2009b; 50:37–46), with permission from the Association for Research in Vision and Ophthalmology ©ARVO.