

Perspective: Can eye movements contribute to emmetropization?

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During development, the eye tunes its size to its optics so that distant objects are in focus, a state known as emmetropia. Although multiple factors contribute to this process, a strong influence appears to be exerted by the visual input signals entering the eye. Much research has been dedicated to the possible roles of specific features of the retinal image, such as the magnitude of blur. However, in humans and other species, the input to the retina is not an image, but a spatiotemporal flow of luminance. Small eye movements occur incessantly during natural fixation, continually transforming the spatial scene into temporal modulations on the retina. An emerging body of evidence suggests that this space–time reformatting is crucial to many aspects of visual processing, including sensitivity to fine spatial detail. The resulting temporal modulations depend not only on ocular dynamics, but also on the optics and shape of the eye, and the spatial statistics of the visual scene. Here we examine the characteristics of these signals and suggest that they may play a role in emmetropization. A direct consequence of this viewpoint is that abnormal oculomotor behavior may contribute to the development of myopia and hyperopia.

The process of emmetropization

Emmetropization, the coordination of the eye's optical and geometrical properties, is one of the most fascinating aspects of visual development. Early in life, the length of the human eye typically does not match the degree of refraction produced by the cornea and lens, resulting in a defocused image on the retina. During the course of several years, physical changes

occur in the eye, particularly in its length, to ensure that the retina is placed at the focal distance determined by the optics when examining distant objects. This process is, unfortunately, not exempt from errors. Hyperopia and myopia, the consequences of a retina that is positioned, respectively, in front of or behind the eye's focal length, are common conditions. Myopia, in particular, currently affects more than 75% of the population in some countries (Saw, Katz, Schein, Chew, & Chan, 1996; Morgan et al., 2017) and is associated with severe adverse consequences, including an increased risk for retinal detachment (Gohil et al., 2015).

Multiple factors are known to play a role in emmetropization, including the structure of the environment (Morgan & Rose, 2005; Sherwin et al., 2012; Wu, Tsai, Wu, Yang, & Kuo, 2013), the characteristics of the light (Rucker, Britton, Spatcher, & Hanowsky, 2015), and even the amount of exercise (Jacobsen, Jenson, & Goldschmidt, 2008; Thykjaer, Lundberg, & Grauslund, 2016). It is also known that the visual input to the retina plays a fundamental role, as evidenced by a vast body of work showing that emmetropic eyes actively change size to compensate for the insertion of lenses (Wildsoet, 1997; Tran, Chiu, Tian, & Wildsoet, 2008). Given this strong influence, a major focus of research has been on the possible roles of spatial cues, such as the optical quality of the retinal image and the magnitude/sign of blur (Figure 1A; Wallman & Winawer, 2004). Yet correction of optical blur per se is not always sufficient to stop eye growth (Aller & Wildsoet, 2013), and in humans the eye often continues to elongate even when the image has been optically corrected.

Citation: Rucci, M., & Victor, J. D. (2018). Perspective: Can eye movements contribute to emmetropization? *Journal of Vision*, 18(7):10, 1–6, <https://doi.org/10.1167/18.7.10>.



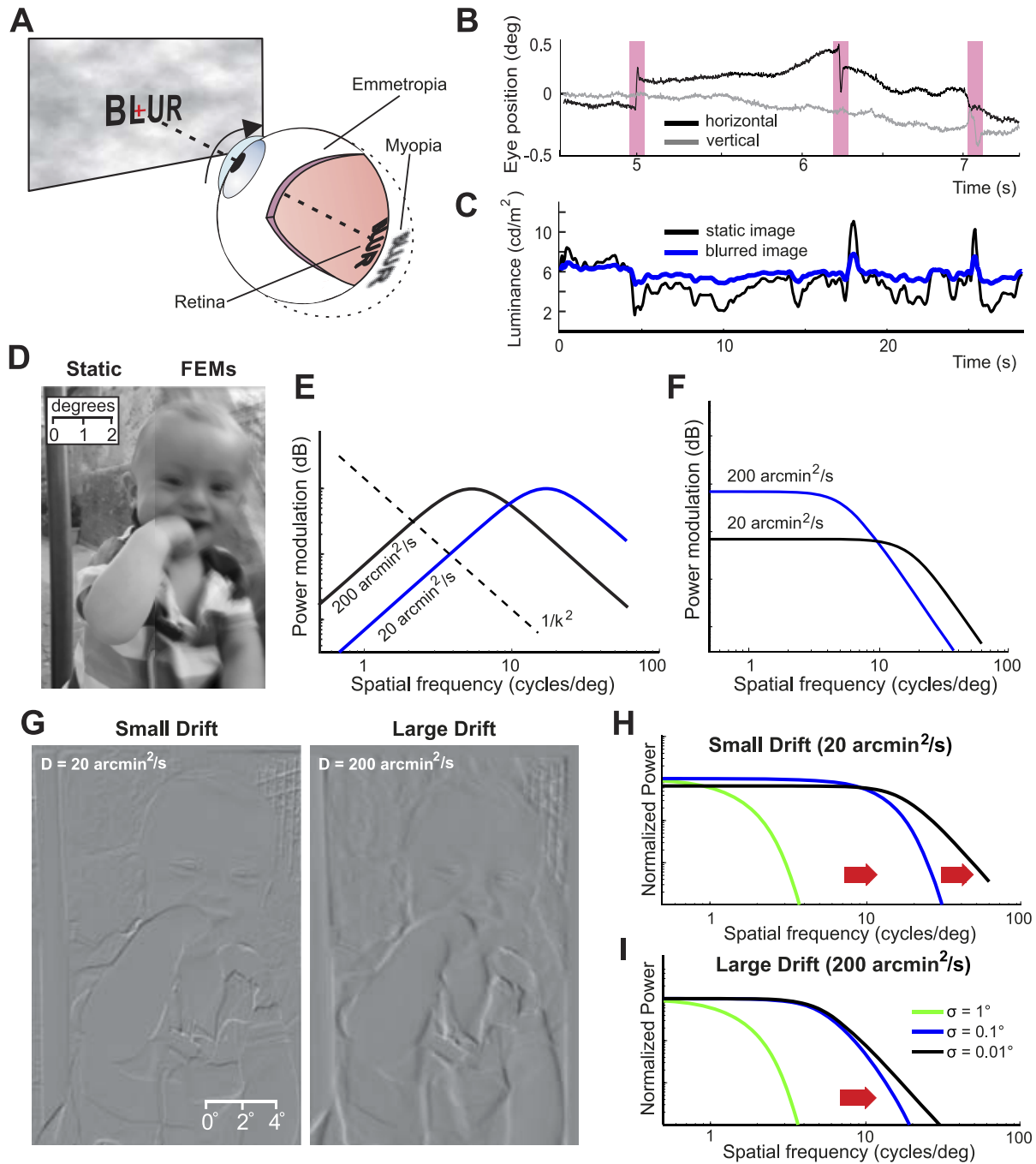


Figure 1. Emmetropization and eye movements. (A) During development, the eye grows to match the optical properties of the eye, focusing the image on the retina. Eyes longer and shorter than the focal length will result in myopia (dashed circle) and hyperopia, respectively. (B) Eye movements are always present: small saccades (microsaccades; magenta bars) separate periods of incessant jitter (ocular drift) even when attempting to maintain fixation on a single point. (C) Fixational eye movements continually modulate the luminance signals experienced by retinal receptors. (D) Image blur caused by acquiring an image with a camera moved in a way that replicates eye drift and a temporal integration of 100 ms. (E) Amplitude of the luminance modulations resulting from a Brownian model of eye jitter, a model that captures important features of ocular drift. At each individual temporal frequency ω (here 10 Hz), power increases with spatial frequency up to the critical frequency $k_c = \sqrt{\frac{\omega}{D}}$ where D is the diffusion constant of the motion. In the range below k_c the drift amplification counterbalances the spectral density of natural images (dashed line). Data are shown for two D values at the two ends of the range so far measured in humans (20 and 200 arcmin^2/s). (F) This effect equalizes temporal power on the retina (i.e., whitens the input spectrum) during viewing of natural scenes. Note that the extent of whitening depends on the amount of eye jitter. (G) Snapshots of the temporal modulations given by ocular drift in the range of sensitivity of retinal ganglion cells. The two panels refer to the different D values. Fixational modulations are blurred when drift is enlarged. (H–I) Changes in the input spectra during emmetropization. Each panel shows the temporal powers resulting from images with three different degrees of blurring (σ). Different panels show results for different amounts of drift. As the image becomes sharper on the retina, the range of frequency equalization extends with small drift (H), but remains limited with large eye movements (I).

Research on emmetropization and myopia has traditionally regarded the input to the retina as an image and, consequently, primarily focused on its spatial properties. However, emerging evidence from the parallel field of neural encoding suggests that a purely spatial view may be incomplete. The visual system appears to encode fine spatial information via a *spatio-temporal strategy* rather than a *purely spatial one*, a strategy that makes use of the temporal luminance modulations resulting from eye movements and their interactions with the characteristics of the natural world. The oculomotor space–time reformatting of retinal input signals also offers cues of defocus, which broaden the arena of possible emmetropization mechanisms. Although these oculomotor cues are present, little is currently known about their functional importance. The goal of this Perspective is to raise awareness about their occurrence, in order to stimulate interactions between myopia and oculomotor researchers to jointly investigate the testable predictions that these strategies generate.

Why consider eye movements?

The eyes are never at rest. Small eye movements—known as fixational eye movements (FEMs)—occur incessantly in the periods in between macroscopic relocations of gaze, alternating intervals of seemingly random trajectories (here referred to as ocular drifts) with small saccades (microsaccades; Kowler, 2011; Rucci & Poletti, 2015; Figure 1B). Although humans are not aware of them, these movements are relatively large on the retina: FEMs displace the stimulus by many receptors, yielding motion signals that would be clearly visible had they originated from movement of objects in the scene.

The incessant motion of the retinal image heavily constrains the range of mechanisms by which the visual system may detect blur. Its presence implies that, unless specifically tuned to handle FEMs, processes with relatively slow dynamics (like the responses of retinal ganglion cells) would mistakenly signal blur even with a perfectly focused retinal image. This happens because in a moving eye, loss of fine spatial information does not necessarily imply defocus: blur can occur not only in space, but also in time, much in the same way that a shaky hand holding a camera may yield a blurred picture even when the image is perfectly focused by the lens (Figure 1D).

So how can the visual system detect blur and regulate emmetropization in a moving eye? Unless one postulates the existence of mechanisms with much faster dynamics than those of retinal responses, dealing with the consequences of the physiological motion of

the retinal image becomes unavoidable. Thus, the process of emmetropization and the neural mechanisms for establishing fine spatial representations face similar challenges: how do retinal ganglion cells, with their relatively slow dynamics, transmit high-acuity information despite the presence of FEMs?

Unlike a camera, it has long been proposed that the retina is not adversely affected by FEMs, but uses these movements as part of a temporal encoding strategy for representing fine-scale spatial information (Marshall & Talbot, 1942; Ahissar & Arieli, 2001; Rucci & Victor, 2015). This proposal relies on the observation that FEMs alter the visual input signals impinging onto the retina in fundamental ways: by transforming spatial patterns of luminance into temporal modulations to retinal receptors, FEMs effectively reformat spatial information in the joint space–time domain. Supporting this idea, it is now known that the physiological jitter of the retinal image enhances—rather than degrades—high spatial frequency vision during natural post-saccadic fixation (Rucci, Iovin, Poletti, & Santini, 2007; Boi, Poletti, & Rucci, 2017; Ratnam, Domdei, Harmening, & Roor-da, 2017) and that the resulting temporal modulations are tuned to the characteristics of the natural world (Kuang, Poletti, Victor, & Rucci, 2012). The process of emmetropization could also utilize these modulations.

Oculomotor cues to blur

Blur information is manifest in luminance modulations delivered by eye movements to retinal receptors (Figure 1C). This happens because the temporal statistics of these modulations depend on the interaction between the spatial characteristics of the stimulus and the dynamics of eye movements. During fixation, when visual information is acquired, the amplitude of the modulation delivered by ocular drift varies with spatial frequency (Figure 1E): at each individual temporal frequency, it increases with the spatial frequency of the stimulus up to a critical frequency k_c and then declines above k_c . The critical frequency k_c increases as a function of temporal frequency and decreases with the amount of image motion on the retina (see Figure 1 caption).

Below the critical spatial frequency k_c , this amplification combines with the spatial characteristics of the natural world in a striking manner. In natural scenes, contrast is not evenly distributed across spectral components, but declines approximately proportionally to the square of the spatial frequency (Field, 1987). Remarkably, ocular drift amplifies contrast in exactly the opposite way. It enhances the frequency compo-

nents that possess less power in natural scenes, thus delivering fixational modulations that, during viewing of natural scenes, contain approximately equal amplitudes across a broad spatial frequency range (Figure 1F). That is, a form of matching exists between the characteristics of natural scenes and those of normal eye movements, which results in a very specific input reformatting during normal fixation: ocular drift transforms natural scenes with a spectral density that is heavily biased to low spatial frequencies into luminance fluctuations with equalized spatial power at nonzero temporal frequencies.

This redistribution of power is affected by lack of focus in several ways, each of which could potentially be used for emmetropization. Since blur causes the visual input to the retina to deviate from its natural statistics, both the amount of temporal power at high spatial frequencies and the “whitening” range in which the drift’s power amplification counterbalances the spectral distribution of natural scenes will be reduced. The specific effects will vary with temporal frequency, as they depend on whether blur is restricted above k_c , or also exerts its effects below. Thus, the visual system could estimate defocus by examining the amplitudes of temporal modulations and their distributions within specific spatial frequency bands and/or by comparing them across bands. This could be achieved, for example, by monitoring the responses of retinal ganglion cells, or possibly by mechanisms independent from those responsible for perception. It is important to realize that these cues are intrinsically grounded in the temporal domain: in principle, they could signal lack of focus even at an isolated point on the retina. They will also vary in strength as the eye approaches emmetropization: they will become less severe as the sharpness of the retinal image improves, but increase again, if the eye continues to grow after reaching emmetropia (Figure 1H).

In addition to the amount of blur, the statistics of fixational modulations also depend on the shape of the eye. This observation has interesting implications regarding how drift could inform about the direction of eye growth. A frequently asked question in the literature is how the visual system determines whether blur results from hyperopia or myopia, given that a snapshot of the retinal image at any given time does not provide information about the sign of blur (Schaeffel & Wildsoet, 2013). This information, however, may be present in the spatiotemporal signals to the retina: the linear velocity of the image on the retina changes with eye length, and real eyes deviate from a purely spherical geometry, as neither the center of eye rotation, nor the local center of curvature of the retinal surface, coincide with the optical nodal points. Thus, eccentricity-dependent asymmetries are likely to

arise due to structural differences between short and long eyes.

Possible consequences of using eye movements to detect blur

The statistics of fixational luminance modulations depend critically on how the eye moves. As mentioned above, below the critical spatial frequency k_c , larger drifts deliver stronger modulations to the retina, but this increment in power comes at the expenses of a reduction in the range of equalization (Figure 1F). That is, a trade-off exists between the amount of temporal power delivered to the retina and the extent of the spatial whitening: a stronger signal can only be obtained at the expense of a decrement in resolution. Figure 1G provides an intuitive understanding of how the amount of drift affects fixational modulations within the temporal range of sensitivity of retinal ganglion cells. Note that, because of the reduced range of whitening, luminance modulations signal information at a coarser scale when the diffusion constant of drift increases. Thus, even with a perfectly focused retinal image, the output signals leaving the retina will convey little information at high spatial frequencies (i.e., they will be blurred) if the eye jitters too much during fixation.

This dependence of fixational modulation on drift characteristics implies that abnormal eye movements may alter the temporal signals used by the visual system as cue to blur, potentially stimulating unnecessary eye growth. As an illustrative example, Figure 1I portrays a hypothetical scenario in which the emmetropization process is perturbed by a 10-fold change in jitter, which is within the range of individual differences that have been observed. As mentioned, a larger eye jitter increases temporal modulations within a band of low spatial frequencies, decreases modulations in the high spatial frequency range (beyond k_c), and reduces the range of whitening. During emmetropization, as the length of the eye changes, fixational modulations will undergo dynamic changes like those described for normal eye movements (Figure 1H). However, because of the larger amount of drift, both the whitening range and the temporal power at high spatial frequencies will remain below normal levels, even when the eye has reached emmetropia. Furthermore, since the characteristics of retinal motion resulting from abnormally large eye drift may be qualitatively similar to those present in a hyperopic eye, they may elicit eye growth even in an emmetropic eye. Similar considerations also apply to abnormally small eye drift, and the trade-off between the amount of power and the extent of whitening that it elicits.

The need for an interdisciplinary effort

The previous observations suggest new mechanisms that may be relevant to emmetropization. Rather than being regulated by purely spatial factors, such as the degree of blur in the retinal image, emmetropization might also be controlled by temporal signals. Modulations in the input signals to the retina are always present because of incessant eye movements, and these changes already appear to play a critical role in the way the visual system encodes fine spatial details. The eye may use similar strategies for emmetropization.

Fixational modulations of luminance depend, in a complex manner, on the statistics of natural environments, the optical and structural properties of the eye, and the observer's motor activity. Given the tuning of eye jitter to natural world statistics, this approach could lead to an explanation for the beneficial effects of outdoor exposure and exercise in myopia. Even with normal FEMs, the statistics of natural scenes are critical to balancing temporal power across spatial frequencies. Moreover, changes in emmetropization with the spectral distribution of visual stimulation have been reported (Hess, Schmid, Dumoulin, Field, & Brinkworth, 2006; Tran et al., 2008). These observations suggest that, spectral differences between urban and natural scenes (Torralba & Oliva, 2003), together with the recent intensification of urbanization, may play a role in the increasing prevalence of myopia. Furthermore, much evidence indicates that eye movements at this scale are, in fact, adaptable and controllable (Aytekin, Victor, & Rucci, 2014; Rucci & Poletti, 2015), and exercise may help tuning the amount of eye jitter (its effective diffusion constant) without altering its qualitative structure.

The mechanisms responsible for detecting the cues described here do not need to operate uniformly across the entire spatial frequency spectrum, but may privilege certain ranges of spatial frequencies (e.g., intermediate or high). Since these cues occur throughout the retina, they are consistent with findings that stimulation of the visual periphery is sufficient to elicit changes in eye length (Smith, Kee, Ramamirtham, Qiao-Grider, & Hung, 2005). These same mechanisms may also be responsible for ametropia in pathological conditions in which fixational eye movements are manifestly abnormal, such as congenital nystagmus (Weiss & Kelly, 2007; Dunn et al., 2014).

At present, because of the technical challenges inherent in reliably measuring small eye movements and the consequent intrusions that subjects have to endure in these experiments, most data on the detailed dynamics of FEMs come from adult emmetropic observers. Little is known about the characteristics of

FEMs during development and/or in populations affected by myopia or hyperopia. Future research will need to fill this gap in current knowledge. We believe that the multidisciplinary considerations presented in this article make a clear case for myopia experts, oculomotor researchers, and experts on neural encoding to join their forces and bring their diverse sets of expertise into a unified effort to unveil the spectrum of emmetropization mechanisms.

Keywords: myopia, hyperopia, ocular drift, microsaccade, saccade, retina, ganglion cell, visual acuity

Acknowledgments

This work was supported by National Institutes of Health Grants EY18363 and EY07977, and National Science Foundation Grants 1457238 and 1420212. We thank Rania Ezzo for her help with the figures of this paper.

Commercial relationships: none.

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