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Individual set-point and gain of emmetropization in chickens

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ABSTRACT

During the developmental process of emmetropization evidence shows that visual feedback guides the eye as it approaches a refractive state close to zero, or slightly hyperopic. How this "set-point" is internally defined, in the presence of continuous shifts of the focal plane with different viewing distances and accommodation, remains unclear. Minimizing defocus blur over time should produce similar end-point refractions in different individuals. However, we found that individual chickens display considerable variability in their set-point refractive states, despite that they all had the same visual experience. This variability is not random since the refractions in both eyes were highly correlated – even though it is known that they can emmetropize independently. Furthermore, if chicks underwent a period of experimentally induced ametropia, they returned to their individual set-point refractions during recovery (correlation of the refractions before treatment versus after recovery: $n = 19$ chicks, 38 eyes, left eyes: slope 1.01, $R = 0.860$; right eyes: slope 0.85, $R = 0.610$, $p < 0.001$, linear regression). Also, the induced deprivation myopia was correlated in both eyes ($n = 18$ chicks, 36 eyes, $p < 0.01$, orthogonal regression). If chicks were treated with spectacle lenses, the compensatory changes in refraction were, on average, appropriate but individual chicks displayed variable responses. Again, the refractions of both eyes remained correlated (negative lenses, $n = 18$ chicks, 36 eyes, slope 0.89, $R = 0.504$, $p < 0.01$, positive lenses: $n = 21$ chicks, 42 eyes, slope 1.14, $R = 0.791$, $p < 0.001$). The amount of deprivation myopia that developed in two successive treatment cycles, with an intermittent period of recovery, was not correlated; only vitreous chamber growth was almost significantly correlated in both cycles ($n = 7$ chicks, 14 eyes; $p < 0.05$). The amounts of ametropia and vitreous chamber changes induced in two successive cycles of treatment, first with lenses and then with diffusers, were also not correlated, suggesting that the "gains of lens compensation" are different from those in deprivation myopia. In summary, (1) there appears to be an endogenous, possibly genetic, definition of the set-point of emmetropization in each individual, which is similar in both eyes, (2) visual conditions that induce ametropia produce variable changes in refractions, with high correlations between both eyes, (3) overall, the "gain of emmetropization" appears only weakly controlled by endogenous factors.

1. Introduction

Emmetropization refers to the developmental process that reduces neonatal refractive errors by coordinating postnatal eye growth. In humans, refractions are initially widely scattered at birth but are tuned to an "optimal value" over the first 6 years of life. At this age, inter-individual variability in refractive states is much less than would be expected from random combinations of the powers of cornea and lens, and eye length (e.g. Hirsch & Weymouth, 1991). Emmetropization is controlled by visual input (e.g. Wallman & Winawer, 2004) but also by genetic factors (e.g. human: Lopes, Andrew, Carbonaro, Spector, & Hammond, 2009; chicken: Chen et al., 2009).

Unresolved questions are whether the "optimal refraction" (in children mildly hyperopic, like +0.5D) represents a genetically determined "set-point". Furthermore, it is unclear how the eye can sense when this set-point is reached. Deriving the necessary information from visual experience is not trivial because the focal plane, relative to the photoreceptor plane, shifts continuously with viewing distance and accommodation tonus. A question directly relevant to human myopia development is why similar visual experience can trigger enhanced axial eye growth in some but not all individuals. One hypothesis is that the gain of the visually-guided feedback loop controlling eye growth is genetically determined, making some eyes more susceptible to myopia development when they are frequently exposed to short viewing distances. However, Mutti, Mitchell, Moeschberger, Jones, and Zadnik (2002) could not find evidence for an inheritance of the susceptibility to near work-induced myopia. Also the set-point might be a genetically determined variable in emmetropization.

These questions have been studied in animal models. Wallman, Adams, and Trachtman (1981) were the first to show that emmetropization occurs also in chickens. Inter-individual variability of

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refractive errors declined over the first 8 weeks post-hatching. The average refractive states changed from hyperopia to close to zero. They also observed that the susceptibility of the chicken eye to deprivation myopia declined with age, suggesting that the "gain of emmetropization" also declined also with age. However, Saltarelli, Wildsoet, Nickla, and Troilo (2004) found that less myopia development at an older age can be explained by optical scaling. If chicks are exposed to two equally long successive treatment cycles with diffusers, interrupted by a period of recovery, they develop significantly less myopia at 27 days of age than at 3 days of age. Saltarelli et al. (2004) found that the absolute changes in vitreous chamber depth were similar in both cycles, suggesting that optical scaling (Hofstetter, 1969) could explain the smaller optical effect in the second cycle. Saltarelli et al. (2004) also found that the magnitudes of vitreous chamber elongation were correlated in the first and second cycle for each individual, suggesting that the "gain of emmetropization" may indeed be individually set. That genes may control the gain of emmetropization is supported by studies showing that different strains of chickens develop different amounts of myopia with diffusers in front of their eyes (e.g. Guggenheim, Erichsen, Hocking, Wright, & Black, 2002), and that there are also significant differences in myopia between male and female chicks (Zhu, Lin, Stone, & Laties, 1995).

We studied the endogenous control of emmetropization in chickens, using the treatment paradigm of Saltarelli et al. (2004). In addition to a treatment with diffusers, the effects of spectacle lenses in individual chicks were compared to those of diffusers, and the responses of both eyes were separately analyzed. Both set-points and gain of emmetropization were analyzed.

2. Methods

2.1. Animals

In total, 46 male white leghorn chickens (*Gallus domesticus*) were used for this study. In addition, data originating from 11 chicks of the same ages, which were treated with negative lenses and 16 chicks of the same ages which were treated with positive lenses in the course of another experiment in the lab, were included (Fig. 1B and C). Experiments conformed to the ARVO Resolution on the Use of Animals in Ophthalmic and Vision Research and were approved by the University Commission for Animal Welfare (reference AK 03/09). Chickens were obtained from a local hatchery (company Weiss in Kirchberg, Germany) one day after hatching. They were raised in groups in large cages in the animal facilities of the institute at a 12-h light/12-h dark cycle. Room temperature was kept at 30 °C during the first week post-hatching and at 28 °C thereafter. To accustom the chickens to the human voice, a radio played during the light period. Water and food were supplied *ad libitum.*

2.2. Treatment paradigms

Chicks were bilaterally treated with diffusers made from frosted plastic foil (Schaeffel & Howland, 1991), or positive or negative lenses (powers +7D and −7D), starting at day 5 post-hatching. Since all diffusers were made from a large sheet of frosted plastic foil, they did not differ in their optical effects and the observed variability in induced deprivation myopia cannot be attributed to variability of the diffusers (Bartmann & Schaeffel, 1994). The distances of the lenses from the corneal apex (vertex distances) ranged between 2 and 3 mm. All treatments were binocular.

The chicks were split up into five groups. The first three groups went through two successive periods of treatment, interrupted by a recovery period as follows: the first group consisting of seven chicks was initially deprived of sharp vision, using diffusers for 5 days. Chicks were then allowed to recover for 5 days, and subsequently deprived again for another 5 days. Chicks in the second

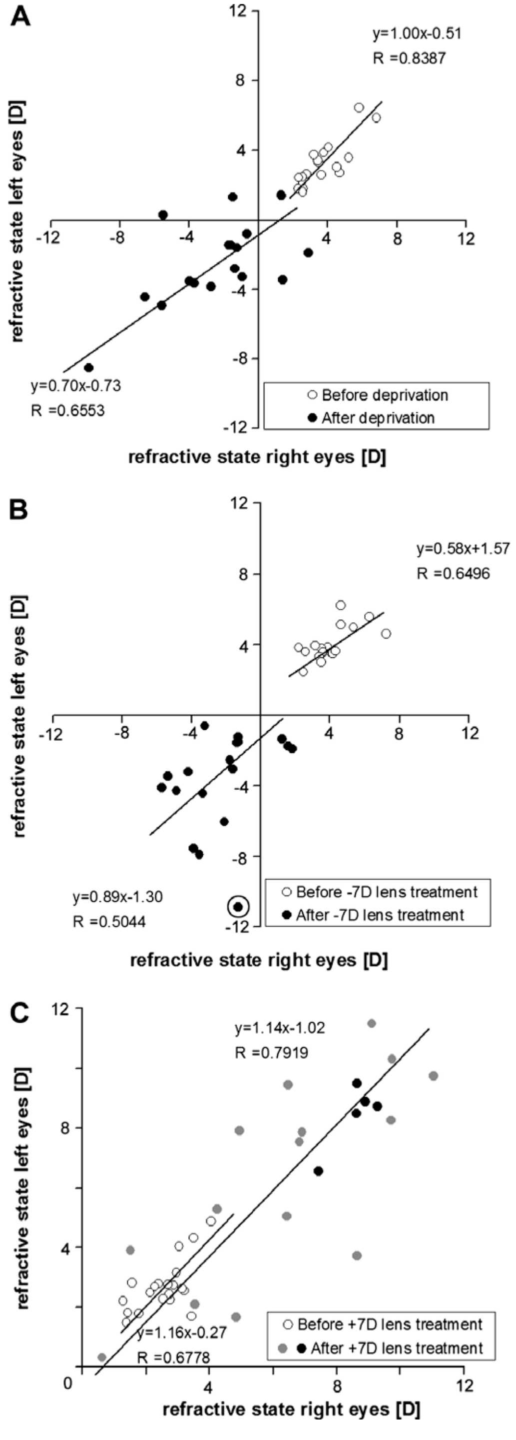

Fig. 1. Correlations between the refractions in both eyes before treatment (white circles) and after the treatment (black or grey filled circles) with (A) diffusers, (B) negative lenses, and (C) positive lenses. Orthogonal regressions were used: in all cases, the refractions in both eyes were correlated ($p < 0.01$ or better). In (B), the encircled data point was considered an outlier and was excluded from the regression analysis. In (C), further data from chicks of the same age and at the same time originating from other studies in the lab were also included and are denoted by grey circles.