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Nature of the refractive errors in rhesus monkeys (*Macaca mulatta*) with experimentally induced ametropias

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ABSTRACT

We analyzed the contribution of individual ocular components to vision-induced ametropias in 210 rhesus monkeys. The primary contribution to refractive-error development came from vitreous chamber depth; a minor contribution from corneal power was also detected. However, there was no systematic relationship between refractive error and anterior chamber depth or between refractive error and any crystalline lens parameter. Our results are in good agreement with previous studies in humans, suggesting that the refractive errors commonly observed in humans are created by vision-dependent mechanisms that are similar to those operating in monkeys. This concordance emphasizes the applicability of rhesus monkeys in refractive-error studies.

1. Introduction

In a simplistic sense, the primary biometric variables that potentially contribute to the eye's refractive status are the refracting powers of the cornea and crystalline lens and the axial dimensions of the anterior chamber, lens and vitreous chamber. To understand the contributions of these variables to ocular refraction, a substantial number of primarily cross-sectional studies have examined the dimensions and distributions of these ocular components in populations of emmetropic and ametropic eyes, the interrelations between these ocular components in emmetropic and ametropic eyes, and the correlations between individual ocular components and refractive error (Bullimore, Gilmartin, & Royston, 1992; Fledelius, 1988, 1995; Goss, Cox, Herrin-Lawson, Nielsen, & Dolton, 1990; Grosvenor & Scott, 1991, 1993; Jensen, 1991; Larsen, 1971a, 1971b, 1971c, 1971d; Mayer, Hansen, Moore, Kim, & Fulton, 2001; McBrien & Millodot, 1987; Mutti et al., 2005; Sorsby, Benjamin, Davey, Sheridan, & Tanner, 1957; Sorsby, Benjamin, Sheridan, Stone, & Leary, 1961; Sorsby, Leary, & Fraser, 1966; Stenstrom, 1948; Zadnik et al., 2003). For example, correlation analyses have shown that the primary ocular components that influence refractive error are interdependent and that during early development these components grow in a coordinated manner to move the eye toward emmetropia (Carroll, 1981, 1982; Hirsch, 1947; Hirsch & Weymouth, 1947; Stenstrom, 1948; van Alphen, 1961). In other words, compensatory alterations in related parameters occur to promote emmetropia. In particular, the concept of the inflatable globe evolved from these studies and the notion that aspects of emmetropization are passive consequences of eye growth (Hofstetter, 1969; Koretz, Rogot, & Kaufman, 1995; Mutti et al., 1998; Wallman & Adams, 1987), specifically that increases in axial length during early development are counterbalanced by concomitant decreases in corneal power, lens thickness and lens power. These studies have also provided insights into the nature of refractive errors, in essence, how ametropic eyes, in particular myopic eyes, differ from emmetropic eyes. The results from these investigations have demonstrated the relative importance of individual ocular components in determining the eye's refraction and provided insights into the mechanisms that are associated with the development of common refractive errors.

It has been consistently shown that elongation of the vitreous chamber contributes to myopia (Wildsoet, 1998). However, each of the major ocular components has been shown to potentially contribute to myopic refractions. The degree of influence for a given component is somewhat dependent on the analysis methods and possibly the age of the sample studied (Wildsoet, 1998). For instance, in his classic study, Stenstrom (1948), using correlation analyses, showed that refraction was significantly correlated with corneal radius ($r = +0.18$), anterior chamber depth ($r = -0.34$), and especially axial length ($r = -0.76$); therefore, he concluded that axial length had the greatest influence on ocular refraction and that most myopia was axial in nature. Using Stenstrom's data and partial correlation analyses, Hirsch and Weymouth (1947)

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reported that axial length accounted for 47% of the variance in refractive error, while corneal power and anterior chamber depth were responsible for 24% and 7% of the variability of refraction, respectively. van Alphen (1961) reanalyzed Stenstrom's data using partial correlation coefficients and factor analysis and described the myopic eye as one with a longer than normal axial length and/or a more powerful cornea with a flatter crystalline lens. More recent investigations employing analyses based on structural models (Scott & Grosvenor, 1993) or quantitative analyses of growth curves (Jones et al., 2005) for individual ocular components have shown that in comparison to emmetropic eyes, myopic eyes have higher corneal powers, higher lens powers, and greater anterior and vitreous chamber depths.

Longitudinal studies of the changes in ocular components that occur during the onset and/or progression of myopia have emphasized the contribution of vitreous chamber elongation to myopic refractions (Fledelius, 1988; Grosvenor & Scott, 1993; Gwiazda et al., 2003; Jensen, 1991; Mutti et al., 2005). In both juveniles (Fledelius, 1988; Grosvenor & Scott, 1993; Gwiazda et al., 2003; Jensen, 1991) and adults (Grosvenor & Scott, 1993; McBrien & Adams, 1997), the onset and progression of myopia are strongly correlated with increases in axial length and, specifically, vitreous chamber depth. There is little or no evidence that increases in either corneal power (Fledelius, 1988; Goss & Erickson, 1987; Grosvenor & Scott, 1993; Jensen, 1991; McBrien & Adams, 1997; Parssinen, 1993) or lens power (Bullimore et al., 1992; Grosvenor & Scott, 1991; Jensen, 1991; Larsen, 1971c; McBrien & Adams, 1997; McBrien & Millodot, 1987) contribute to myopic progression. However, the growth curves for the anterior chamber and corneal power for myopic children are different in shape than those for emmetropic children (Jones et al., 2005).

There are a number of parallels between the structural characteristics of refractive errors in humans and those in animals with experimentally induced ametropias. In particular, in a wide variety of animal species, experimentally induced refractive errors are associated with alterations in vitreous chamber depth and axial length. For example, myopia produced by form deprivation or optical defocus is associated with vitreous chamber elongation in chicks (Schaeffel, Glasser, & Howland, 1988; Wallman & Adams, 1987; Wildsoet & Wallman, 1995), tree shrews (Marsh-Tootle & Norton, 1989; McBrien & Norton, 1992; Norton, Siegwart, & Amedo, 2006), guinea pigs (Howlett & McFadden, 2006; Jiang et al., 2009), marmosets (Graham & Judge, 1999; Troilo & Judge, 1993), and macaques (Greene, 1990; Hung, Crawford, & Smith, 1995; Qiao-Grider, Hung, Kee, Ramamirtham, & Smith, 2004; Smith, Bradley, Fernandes, & Boothe, 1999a; Smith, Harwerth, Crawford, & von Noorden, 1987; Smith & Hung, 2000; Smith, Hung, Kee, & Qiao, 2002a; Tigges, Tigges, Fernandes, Eggers, & Gammon, 1990; Wiesel & Raviola, 1977). However, the associations between experimental refractive errors and other ocular component changes are less consistent between species and, in some cases, between studies. For example, experimental myopia has been associated with increases in corneal power in guinea pigs (Howlett & McFadden, 2006). When form deprivation myopia is produced by lid closure, decreases in corneal power have been reported for chicks (Troilo, Li, Glasser, & Howland, 1995), marmosets (Troilo & Judge, 1993), and tree shrews (Marsh-Tootle & Norton, 1989; McBrien & Norton, 1992; Norton et al., 2006). However, when spectacle lenses are employed to produce myopia, corneal power is not affected in macaques (Hung et al., 1995; Smith & Hung, 1999; Smith, Hung, & Harwerth, 1994), chicks (Irving, Callender, & Sivak, 1995), marmosets (Graham & Judge, 1999) or tree shrews (Norton et al., 2006), which suggests that lid closure can have confounding mechanical effects on the cornea. Experimental myopia is associated with increases in anterior chamber depth in guinea pigs (Howlett & McFadden, 2006) and decreases in anterior chamber depth in tree shrews (Marsh-Tootle & Norton, 1989; McBrien & Norton, 1992; Norton et al., 2006). However, anterior chamber alterations have not been consistently observed in chicks (Schaeffel et al., 1988; Wallman & Adams, 1987; Wildsoet & Wallman, 1995), marmosets (Troilo & Judge, 1993) or macaques (Smith & Hung, 1999). Increases and decreases in crystalline lens thickness have been observed, respectively, in guinea pigs (Howlett & McFadden, 2006) and tree shrews with experimental myopia (Marsh-Tootle & Norton, 1989; McBrien & Norton, 1992; Norton et al., 2006; Siegwart & Norton, 1998), but no consistent changes in lens thickness have been found in chicks (Irving et al., 1995; Troilo et al., 1995), marmosets (Graham & Judge, 1999; Troilo & Judge, 1993) or macaques (Greene, 1990; Hung et al., 1995; Tigges et al., 1990; Wiesel & Raviola, 1977). However, experimental myopia does increase the variability of lens power in chickens with experimental myopia (Priolo, Sivak, Kuszak, & Irving, 2000).

Examining the nature of refractive errors in animals with experimentally induced refractive errors, particularly vision-induced ametropias, is important because it is a critical step in determining the applicability of animal data to the human condition. Moreover, if ocular development in these animals is similar to that of humans, the results from these animal investigations can identify which ocular components are affected by alterations in visual experience and, thus, provide the foundation for understanding the effects of visual experience on refractive development in humans. Refractive development and the optical organization of macaque eyes are very similar to those of humans (Bradley, Fernandes, Lynn, Tigges, & Boothe, 1999; Greene, 1990; Qiao-Grider, Hung, Kee, Ramamirtham, & Smith, 2007b). However, previous studies of the nature of experimental refractive errors in macaques have employed limited numbers of subjects and have not measured all of the key ocular components. The purpose of this study was to determine the structural features of experimentally induced refractive errors in a large number of infant rhesus monkeys.

2. Materials and methods

2.1. Subjects

Data are presented for 210 infant rhesus monkeys (*Macaca mulatta*). The subject population included most of the animals that we used in previous studies of the effects of visual experience on refractive development and for which we had complete biometric data (Hung & Smith, 1996; Hung, Wallman, & Smith, 2000; Hung et al., 1995; Kee, Hung, Qiao, Habib, & Smith, 2002; Kee, Hung, Qiao, & Smith, 2003; Kee, Hung, Qiao-Grider, Ramamirtham, & Smith, 2005; Kee, Hung, Qiao-Grider, Roorda, & Smith, 2004; Kee et al., 2007; Qiao-Grider, Hung, Kee, Ramamirtham, & Smith, 2007a; Qiao-Grider et al., 2004, 2007b; Ramamirtham et al., 2006, 2007; Smith, 1998a, 1998b; Smith, Bradley, Fernandes, Hung, & Boothe, 2001; Smith & Hung, 1999, 2000; Smith, Hung, Kee, Qiao-Grider, & Ramamirtham, 2003; Smith, Kee, Ramamirtham, Qiao-Grider, & Hung, 2005; Smith et al., 1994, 2007, 1999, 2002a; Smith, Hung, & Harwerth, 2000). The animals were obtained at 2–3 weeks of age and housed in our primate nursery that was maintained on a 12-h light/12-h dark lighting cycle. Animals reared under continuous lighting conditions were excluded from our analyses because evidence from chickens indicate that continuous light can produce alterations in the ocular components of the eye that are very different from those produced by form deprivation or optical defocus and that may be secondary to alterations in intraocular pressure (Lauber, 1987; Lauber & McGinnis, 1966; Li, Troilo, Glasser, & Howland, 1995). Our rearing and experimental procedures were reviewed and approved by the University of Houston's Institutional Animal Care and Use Committee and were