Observations on the relationship between anisometropia, amblyopia and strabismus

Earl L. Smith III [a,b,]*, Li-Fang Hung [a,b], Baskar Arumugam [a,b], Janice M. Wensveen [a], Yuzo M. Chino [a], Ronald S. Harwerth [a]

[a] College of Optometry, University of Houston, TX 77204, USA
[b] Brien Holden Vision Institute, Sydney, Australia

ARTICLE INFO

ABSTRACT

We investigated the potential causal relationships between anisometropia, amblyopia and strabismus, specifically to determine whether either amblyopia or strabismus interfered with emmetropization. We analyzed data from non-human primates that were relevant to the co-existence of anisometropia, amblyopia and strabismus in children. We relied on interocular comparisons of spatial vision and refractive development in animals reared with 1) monocular form deprivation; 2) anisometropia optically imposed by either contact lenses or spectacle lenses; 3) organic amblyopia produced by laser ablation of the fovea; and 4) strabismus that was either optically imposed with prisms or produced by either surgical or pharmacological manipulation of the extraocular muscles. Hyperopic anisometropia imposed early in life produced amblyopia in a dose-dependent manner. However, when potential methodological confounds were taken into account, there was no support for the hypothesis that the presence of amblyopia interferes with emmetropization or promotes hyperopia or that the degree of image degradation determines the direction of eye growth. To the contrary, there was strong evidence that amblyopic eyes were able to detect the presence of a refractive error and alter ocular growth to eliminate the ametropia. On the other hand, early onset strabismus, both optically and surgically imposed, disrupted the emmetropization process producing anisometropia. In surgical strabismus, the deviating eyes were typically more hyperopic than their fellow fixating eyes. The results show that early hyperopic anisometropia is a significant risk factor for amblyopia. Early esotropia can trigger the onset of both anisometropia and amblyopia. However, amblyopia, in isolation, does not pose a significant risk for the development of hyperopia or anisometropia.

1. Introduction

In both children and laboratory animals early abnormal visual experience can disrupt interocular alignment resulting in strabismus, interfere with sensory development producing amblyopia, and alter the course of emmetropization resulting in ametropias in one or both eyes (see Barrett, Bradley, and Candy (2013) for a recent detailed review). Given that each of these conditions can themselves alter visual experience, the presence of any one of these conditions in early childhood could potentially cause either or both of the other two conditions. In this respect, amblyopia is strongly associated with the presence of anisometropia and/or strabismus during early childhood (Abrahamsson, Fabian, Anderson, & Sjostrand, 1990; Aurell & Norrsell, 1990; Flom & Bedell, 1985; Ingram, Gill, & Lambert, 2003; Ingram, Lambert, & Gill, 2009; Levi, McKee, & Movshon, 2011), which suggests, but does not prove, that the co-occurrence of these conditions reflects a causal relationship.

Understanding the nature of any cause and effect relationships between strabismus, anisometropia, and amblyopia is critical for developing the most effective detection and management strategies for these early visual system abnormalities. These relationships are difficult to evaluate in children because the relative chronology of these conditions is not always obvious. This is especially true in patients with anisometropia and amblyopia because these conditions are often first detected long after either the anisometropia or amblyopia has developed (Shaw, Fielder, Minshull, & Rosenthal, 1988; Woodruff, Hiscox, Thompson, & Smith, 1994). In this effort, investigations involving laboratory animals, particularly non-human primates, are potentially valuable because it is

* Corresponding author at: University of Houston, College of Optometry, 4901 Calhoun Road, 505 J Armistead Bldg, Houston, TX 77204-2020, USA.
E-mail address: esmith@uh.edu (E.L. Smith III).

possible to induce specific conditions at known ages in subjects that are otherwise visually normal.

Unfortunately, extrapolating the existing animal data to the human condition is complicated by a number of issues. In particular, the earlier animal research focused primarily on the effects of visual experience on sensory (Boothe, Kiorpes, & Carlson, 1985; Harwerth, Smith III, Boltz, Crawford, & von Noorden, 1983; Kiorpes & Boothe, 1980; Kiorpes et al., 1987; Smith III, Harwerth, & Crawford, 1985; von Noorden, Dowling, & Ferguson, 1970) and oculomotor development (Quick, Tigges, Gammon, & Boothe, 1989; Tusa, Krepka, Smith, & Herdman, 1991). The potential effects of experimental manipulations on refractive development were often secondary aims. As a consequence, in many instances the data on refractive development were incomplete. For example, an animal's refractive status was often not assessed during or at the end of a given experimental rearing strategy. Instead the available refractive data were typically obtained later as a part of behavioral experiments relevant to amblyopia (Harwerth, Smith, Boltz, Crawford, & von Noorden, 1983; Smith III et al., 1985), which ignored the potential for recovery from induced ametropias (Qiao-Gridder, Hung, Kee, Ramamirtham, & Smith III, 2004; Smith III & Hung, 1999). In addition, in these early studies, little effort was given to determining the nature of any observed refractive errors (e.g., axial dimensions and corneal power). On the other hand, many of the early studies that focused on the effects of vision on refractive development rarely provided data on sensory or oculomotor development (Crewther, Nathan, Kiely, Brennan, & Crewther, 1988; Raviola & Wiesel, 1985). Moreover, the methods that have been employed to manipulate the visual experience of young animals have evolved as our understanding of potential confounding factors associated with these rearing strategies were discovered (Hung & Smith III, 1996; Whatham & Judge, 2001b). In a number of instances these potential confounding effects have been ignored and the "intriguing inconsistencies" (Barrett et al., 2013) between some early studies have obscured the nature of the relationships between anisometropia, amblyopia and strabismus.

The purpose of this investigation was to analyze the available data from non-human primates on the effects of visual manipulations on refractive development that are relevant to the relationships between anisometropia, amblyopia and strabismus. In particular, this analysis focuses on between-study inconsistencies in refractive development that appear related to methodological confounds that potentially masked causal relationships between anisometropia, amblyopia and strabismus. In addition, we present previously unpublished data, particularly on the effects of strabismus on refractive development.

2. Methods

2.1. Subjects

We have included previously published data from both New- (Marmosets, *Callithrix jacchus*) and Old-World primates. Results were available for four different species of macaques (stumptail macaques, *Macaca arctoides*; cynomolgus or crab-eating macaques, *Macaca fascicularis*; pigtailed macaques, *Macaca nemestrina*; and rhesus macaques, *Macaca mulatta*), with the majority of the data coming from pigtailed and rhesus monkeys. Although some early observations involving small numbers of monkeys suggested that there were qualitative differences in the phenomenon of form deprivation myopia between macaque species (e.g., the effects of muscarinic receptor blockers on the course of form-deprivation myopia) (Raviola & Wiesel, 1990), these potential differences have not been observed in more recent studies (Tigges et al., 1999). As a consequence, we have pooled data from all macaque species.

2.2. Rearing procedures

Our analysis, which relies primarily on interocular comparisons, focuses on animals that were subjected to unilateral interventions that were imposed relatively early in life and for which refractive error and/or axial length data were reported for both the treated and fellow untreated eyes. We included the results from studies involving monocular form deprivation produced by surgical eyelid closure, diffuser spectacles, diffuser contact lenses, and opaque ("black") contact lenses. Similarly, we included the results from animals reared with optically imposed anisometropia produced by either contact lenses or spectacle lenses. We excluded data from animals with experimentally induced aphakia because of potential confounds associated with surgically removing the crystalline lens.

Data from animals with experimentally induced strabismus were also analyzed. Ocular misalignments that were optically imposed using prisms or produced by either surgical or pharmacological manipulation of the extraocular muscles were included. However, animals that had undergone surgical procedures that involved tying the eye in an extreme deviated position were excluded (Harwerth et al., 1983; von Noorden & Dowling, 1970).

In our analysis, we have attempted to include all the relevant data from published English-language sources in which the refractive errors and rearing histories were available for individual animals and in which at least two or more animals were studied. In addition, we have included previously unpublished data from our laboratory and data from animals involved in our previous studies when relevant parameters were not included in our original publications. The rearing methods for surgical strabismus, optical strabismus, form deprivation and optically imposed anisometropia that were employed in our laboratory have been described in detail in previous publications. In brief, surgical esotropia was induced by shortening the medial rectus muscle combined with a tenotomy of the lateral rectus muscle (Bi et al., 2011; Harwerth, Smith III, Crawford, & von Noorden, 1997). These procedures, which were performed between 20 and 120 days of age (mean = 41 ± 24 days), produced a constant, unilateral esotropia of 10–20 degrees that was obvious immediately after the surgery. Strabismus was optically simulated by fitting 3–4 week-old rhesus monkeys with goggles that held 15 D prisms that were primarily oriented base-in in front of each eye (the prism in front of one eye was also rotated base-down by 15° to ensure that fusion was disrupted). The animals typically wore the prisms for durations of 4–12 weeks; subsequently the animals were allowed unrestricted vision (Harwerth et al., 1983; Smith, Chino, Cheng, Crawford, & Harwerth, 1997; Watanabe et al., 2005). Monocular form deprivation was produced by surgical eyelid closure using procedures first employed by von Noorden et al. (Harwerth et al., 1983; von Noorden & Dowling, 1970) or by rearing monkeys with a diffuser spectacle lens in front of one eye and a clear, zero-powered lens in front of the fellow eye. The diffuser spectacles consisted of a zero-powered carrier lens that was covered with a Bangerter Occlusion Foil (Smith III & Hung, 2000; Smith III, Hung, & Huang, 2012). We employed the "LP", "0.1" and "0.4" occlusion foils, which were specified by the manufacturer to reduce the visual acuities of human observers to light perception, ~20/200, and ~20/50, respectively. The animals wore the diffusers continuously from about 3 weeks of age, typically for periods ranging between 11 and 19 weeks. Both contact lens (Hung & Smith III, 1996; Smith III, Hung, & Harwerth, 1994) and spectacle lens rearing regimens (Hung, Crawford, & Smith III, 1995; Smith III & Hung, 1999; Smith III, Hung, & Harwerth, 1999; Smith III et al., 1985) have been employed to optically impose anisometropias. In both instances the treated eyes viewed through a powered single-vision lens (−3.0 to −10.0 D powers) and the fellow eyes were either untreated or viewed through a zero-powered control lens. These lens-rearing procedures were also ini-