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DURATION OF BINOCULAR DECORRELATION IN INFANCY PREDICTS THE SEVERITY OF NASOTEMPORAL PURSUIT ASYMMETRIES IN STRABISMIC MACAQUE MONKEYS

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Abstract—Purpose: Strabismus in human infants is linked strongly to nasotemporal asymmetries of smooth pursuit, but many features of this co-morbidity are unknown. The purpose of this study was to determine how the duration of early-onset strabismus (or timeliness of repair) affects the severity of pursuit asymmetries in a primate model.

Methods: Binocular image decorrelation was imposed on infant macaques by fitting them with prism goggles on day 1 of life. The goggles were removed after 3 weeks (*n*=2), 12 weeks (*n*=2) or 24 weeks (*n*=3), emulating surgical repair of strabismus in humans at 3, 12, and 24 months of age, respectively. Two control monkeys wore plano lenses. Several months after the goggles were removed, horizontal smooth pursuit was recorded using binocular search coils and a nasal-bias index (NBI) was calculated.

Results: Each animal in the 12- and 24-week groups developed a constant, alternating esotropic strabismus and a nasotemporal asymmetry of pursuit when viewing with either eye. Spatial vision was normal (no amblyopia). The 3-week duration monkeys were indistinguishable from control animals; they had normal eye alignment and symmetric pursuit. In the 12- and 24-week monkeys, the longer the duration of binocular decorrelation, the greater the pursuit asymmetry: for 15°/s target motion, the NBI in the 12-week and 24-week animals was 16× and 22× greater respectively, than that in the 3-week animals (ANOVA, *P*=0.03).

Conclusions: Binocular decorrelation in primates during an early period of fusion development causes permanent smooth pursuit asymmetries when the duration exceeds the equivalent of 3 months in human. These findings support the conclusion that early correction of infantile strabismus promotes normal development of cerebral gaze pathways.

Key words: visual development, ocular motor system, fusion, esotropia, visual cortex, brain repair.

Infantile (congenital) esotropia is a convergent misalignment of the visual axes with onset in the first 6–12 months of life (Costenbader, 1961; Taylor, 1972; von Noorden, 1988). It represents over 90% of all strabismus occurring in infancy, and ~40% of all pediatric strabismus (Graham, 1974; Lorenz, 2002). In addition to subnormal fusion and stereopsis, children and adults with infantile esotropia exhibit a defect of conjugate gaze, evident as asymmetric smooth pursuit (or optokinetic nystagmus (OKN)) (Tychsen et al., 1985; Tychsen and Lisberger, 1986a; Kommerell, 1987; Demer and von Noorden, 1988). The asymmetry is evident as a bias favoring nasalward target motion when viewing monocularly with either eye.

The appropriate age for surgical repair of infantile esotropia is controversial (Ing et al., 1966; Jampolsky, 1977; Parks, 1977). In North America, the average age of repair ranges from 10–18 months (von Noorden, 1996; Tychsen, 1999). Despite surgical repair at this age, deficits of binocular fusion persist permanently, including defective stereopsis, defective fusional vergence, and asymmetric pursuit (Tychsen et al., 1985; Tychsen and Lisberger, 1986a; Wright, 1996). Surgery before age 4–6 months ("early repair") has been advocated because of an enhanced probability of restoring stereopsis (Ing et al., 1966; Taylor, 1972; Ing, 1981, 1995b; Wright et al., 1994; Birch et al., 1995, 2000a). However, little detailed information is known regarding improvement in motor functions.

Behavioral studies have shown that the postnatal development of binocular sensory and motor functions in normal infant monkeys closely parallels that of normal infant humans, but on a compressed time scale (i.e. 1 week of monkey development is equivalent to 1 month of human) (Atkinson, 1979; Atkinson and Braddick, 1981; Boothe et al., 1985; O'Dell and Boothe, 1997). Infant monkeys with strabismus display the same constellation of perceptual and ocular motor abnormalities found in strabismic humans, including defective stereopsis, abnormal vergence, and gaze asymmetries (Kiorpes et al., 1996; Tychsen and Boothe, 1996; Tychsen et al., 1996, 2000; Tychsen and Scott, 2003). Thus, strabismic monkeys are an appropriate animal model for study of the human disorder.

We reported preliminary results describing early vs. delayed repair of esotropia in infant monkeys, using a model of optically-induced strabismus (Wong et al., 2003).

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Abbreviations: ANOVA, analysis of variance; MST, medial superior temporal; MT, medial temporal; NBI, nasal bias index; NOT, nucleus of the optic tract; OKN, optokinetic nystagmus; SSVEP, spatial sweep visually-evoked potential; V1, visual area 1 (striate cortex); V2, visual area 2 (pre-striate cortex).

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The "repair" (i.e. removal of prism goggles) was deliberately timed to mimic shorter (less than or equal to 3 months) vs. longer (12–24 months) durations of unrepaired esotropia in human infants. Early repair (shorter duration) was able to restore fusional vergence and stereopsis, whereas delayed repair (longer duration) caused permanent deficits. The purpose of the current study was to determine how the timing of repair influences the severity of pursuit asymmetries.

EXPERIMENTAL PROCEDURES

Animals and goggle-rearing groups

Nine normal infant rhesus monkeys (*Macaca mulatta*, seven male, two female) were used. They were born at the Yerkes Regional Primate Research Center in Atlanta, GA, and fitted with goggles on the first day of life. The fitting procedure, similar to the method described by Crawford et al. (1996), was not stressful to the monkeys and did not require anesthesia. Padded head straps held the goggle helmet firmly in place, preventing the infant from removing the apparatus. The lens holders unscrewed to allow thin plastic Fresnel prisms (Fresnel Prism & Lens, Eden Prairie, MN, USA) to be inserted and secured in place before each eye. The animals were observed during bottle feedings and periodically in the primate nursery to ensure that the goggles remained clear and in proper position. Normal play and interactions with other infant monkeys were not affected noticeably by the goggles. Once daily, the goggle helmet was removed for cleaning and, if necessary, adjustment. During these brief periods the animal was placed in a dark enclosure to prevent normal binocular experience.

The goggles created a combined horizontal and vertical optical strabismus to prevent fusion. As listed in Table 1, the experimental animals viewed through an 11.4° base-in prism in the right eye and an 11.4° base-down prism in the left eye. The two control animals (WE and AY) wore the same goggle apparatus but with plano lenses in place of prisms. The experimental animals wore the prism goggles for durations of 3 weeks, 12 weeks, or 24 weeks, corresponding to durations of unrepaired strabismus in human of 3, 12, and 24 months respectively. Once the defined period of goggle-rearing ended, the monkeys were transported to Washington University in St. Louis, MO, USA, where they were trained to perform visual fixation tasks without goggles using fruit juice as a positive feedback reward (Foeller and Tychsen, 2002).

Monocular visual acuity was measured using spatial sweep visually-evoked potentials (SSVEP) (Norcia and Tyler, 1985) without correction for refractive error. Attention to the grating stimulus display (viewing distance 1 m) for testing of visual acuity was ensured by rewarding the animals (a bolus of juice) for fixating the center of the display. Cycloplegic refractions revealed a refractive error $\leq +3.00$ spherical equivalents in each of the experimental and control animals. In the months before coil implantation, eye alignment was assessed using 35 mm photographs and video recordings (Hirschberg method) of each monkey (Quick and Boothe, 1992). All procedures were performed in compliance with the Association for Research in Vision and Ophthalmology resolution on the use of animals in research and were approved by the Washington University Animal Care and Use Committee. A minimal number of animals were used. General anesthesia and analgesics were employed for all surgeries. Awake recordings used only positive reinforcement and were not stressful for the animals.

Eye movement recording

Detailed descriptions of the surgical and recording methods have been published in previous reports; an abbreviated description is provided here (Foeller and Tychsen, 2002).

Using deep general inhalation anesthesia (supplemented by local infiltration and topical anesthesia), scleral search coils were implanted in both eyes and a custom-built, polycarbonate head-restraint-device was attached to the skull.

Table 1. Characteristics of the nine macaque monkeys used in the experiments

Animal/sex/age testing	Rearing conditions (RE prism; LE prism)	Eye alignment	Latent nystagmus	Pursuit/OKN asymmetry	DVD	Visual acuity SSVEP (cpd)	Refractive error (S.E.)
Control							
WE/M/1.5 y	3 Weeks plano lens (0°; 0°)	Orthophoric	No	No	No	RE: 22.85 LE: 20.50	+1.00 +1.00
AY/M/2 y	3 Months plano lens (0°; 0°)	Orthophoric	No	No	No	RE: 18.09 LE: 16.17	+1.75 +1.75
3 WK DURATION							
TE/M/1.5 y	3 Weeks prism (11.4° BI; 11.4° BD)	Orthophoric	No	No	No	RE: 19.85 LE: 21.40	+2.50 +2.00
SY/M/1.7 y	3 Weeks prism (11.4° BI; 11.4° BD)	Orthophoric	No	No	No	RE: 17.95 LE: 22.80	+1.75 +1.50
12 Wk duration							
YO/M/2 y	3 Months prism (11.4° BI; 11.4° BD)	ET: 16° RHT: 5°	Yes	Yes	Yes	RE: 21.10 LE: 19.06	+2.25 +2.37
GO/M/1.5 y	3 Months prism (11.4° BI; 11.4° BD)	ET: 8° LHT: 4°	Yes	Yes	Yes	RE: 8.25 LE: 10.64	+0.75 +1.25
24 Wk duration							
HA/F/2 y	6 Months prism (11.4° BI; 11.4° BD)	ET: 15° RHT: 4°	Yes	Yes	Yes	RE: 19.23 LE: 18.65	+1.50 +1.50
QN/F/2 y	6 Months prism (11.4° BI; 11.4° BD)	ET: 12° LHT: 4°	Yes	Yes	Yes	RE: 23.28 LE: 24.01	+2.00 +2.25
EY/M/1.5 y	6 Months prism (11.4° BI; 11.4° BD)	ET: 12°	Yes	Yes	Yes	RE: 8.91 LE: 7.66	−1.50 −2.00

Abbreviations: BI, base-in Fresnel prism; BD, base-down Fresnel prism; RE, right eye; LE, left eye; ET, esotropia; HT, hypertropia; DVD, dissociated vertical deviation; cpd, cycles per degree; S.E., spherical equivalent; spherical+50% any astigmatic error.