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Decorrelation of Cerebral Visual Inputs as the Sufficient Cause of Infantile Esotropia

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ABSTRACT

Background and Purpose: Human infants at greatest risk for esotropia are those who suffer cerebral insults that could decorrelate signals from the two eyes during an early critical period of binocular, visuomotor development. The authors reared normal infant monkeys under conditions of binocular decorrelation to determine if this alone was sufficient to cause esotropia, and associated behavioral as well as neuroanatomic deficits.

Methods: Binocular decorrelation was imposed using prism-goggles for durations of 3–24 weeks (control monkeys wore plano goggles), emulating unrepaired strabismus of durations 3 months to 2 years in human infants. Behavioral recordings were obtained, followed by neuroanatomic analysis of ocular dominance columns and binocular, horizontal connections in the striate visual cortex (area V1).

Results: Concomitant, constant esotropia developed in each monkey exposed to decorrelation for a duration of 6–24 weeks. The severity of ocular motor signs (esotropia angle; dissociated vertical deviation; latent nystagmus; pursuit/optokinetic tracking asymmetry; fusional vergence deficits), and the loss of V1 binocular connections increased as a function of decorrelation duration. Stereopsis was deficient and motion visually evoked potentials were asymmetric. Monkeys exposed to decorrelation for 3 weeks showed transient esotropia, but regained normal alignment, visuomotor behaviors, and binocular V1 connections.

Conclusions: Binocular decorrelation is a sufficient cause of infantile esotropia when imposed during a critical period of visuomotor development. The systematic relationship between severity of visuomotor signs and severity of V1 connectivity deficits provides a neuroanatomic mechanism for these signs. Restoration of binocular fusion and V1 connections after short durations of decorrelation helps explain the benefits of early strabismus repair in humans.

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INTRODUCTION

Strabismus (pathologic misalignment of the visual axes) is an important public-health problem, depriving approximately 4–5% of children of the lifelong advantages bestowed by normal binocular vision.[1–3] The leading form of developmental strabismus is concomitant (nonparalytic) esotropia, which has a bimodal, age-of-onset distribution.[3,4] The largest peak—comprising approximately 40% of all strabismus—occurs by age 12 months in children who are predominantly emmetropic (the age 3–4 years, later-onset group is predominantly hyperopic). Nonaccommodative, early-onset esotropia may be considered the paradigmatic form of strabismus in primates, as it is also the most frequent type of natural strabismus observed in monkeys.[5,6]

Infantile Strabismus Is a Visual Brain Disorder, Not an Eye Muscle Disorder

Several lines of evidence support the conclusion that infantile (concomitant) esotropia is a cerebral disorder. Concomitant esotropia exhibits none of the paralytic-fibrotic features of extraocular muscle palsy or the congenital cranial (brainstem) dysinnervation disorders (CCDD).[7–10] Studies of the extraocular muscles, orbital connective tissues, and brainstem circuitry in humans and nonhuman primates with concomitant esotropia have revealed no causal anomalies.[11–13] The striate cortex (area V1) is the first locus in the CNS for binocularity,[14,15] and binocular connections in V1 are important for generating the disparity signals that guide eye alignment.[11,12,16–20] In infants who suffer minimal perinatal encephalopathy (MPE) due to preterm delivery or other perinatal morbidities, the prevalence of infantile esotropia is 20-100 times higher than that in normal infants,[21–30] with no evidence of decline. A common anatomic feature of MPE is mild damage to the posterior optic radiations,[31–33] composing the visual inputs into V1. Clinical studies[30,34] have shown recently that the infantile esotropia syndrome in children with MPE is indistinguishable from that in normal infants, and strabismic MPE infants, like normal infants, may be capable of fusion acquisition with earlier correction. These findings imply that infantile esotropia in both normal and MPE infants is caused by a variety of subtle, intrinsic or extrinsic insults that impede binocular V1 development in the first months of life.

Gaps in Our Knowledge

Major stumbling blocks in our treatment of infantile esotropia are a lack of knowledge of the overlapping critical periods for stereoscopic, ocular motor, and motion processing maldevelopment, and the degree of functional repair achieved if the eyes are realigned earlier.[35,36] We can realign the eyes of strabismic children at a few months of age.[37–39] But does operating earlier substantially improve visuomotor outcomes, and correlatively, the development of visual cortex circuitry?

The appropriate age to operate for infantile esotropia is controversial.[40–42] Screening guidelines, pediatrician referral patterns, and surgeon preferences sum together to make surgical correction before age 10 months the exception. Stereopsis is restored in 40–50% of infants operated upon at age 10–18 months, though seldom

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to normal threshold levels.[43,44] Motion VEP asymmetries tend to be reduced in infants operated on before age 18 months.[45–48] Reports of infants who have had earlier surgery are limited, but the stereopsis and motion VEP outcomes of these children when tested at older ages tend to be better than those in the delayed-surgery groups.[37,38,41] The effects on gaze behaviors are unknown.

Studies of infant monkeys have documented that the development of stereopsis, pursuit/OKN, and motion VEPs closely parallel that of human infants, but on a compressed time scale (an approximate 1:4 ratio).[49–52] One week of monkey visual development is equivalent to one month of human. Thus, strabismus correction in monkeys at age 3–24 weeks is the equivalent of correction in children at age 3 months ("early") to age 24 months ("delayed," 2 years). The experiments described in summary fashion here were designed to fill gaps in our knowledge regarding timeliness of correction and functional/structural visuomotor repair. Detailed accounts of the methods have been published previously.[53]

METHODS AND RESULTS

Binocular Decorrelation that Begins at Birth and Endures More than 3 Weeks Causes Permanent Esotropia

Normal infant monkeys were fitted with prism goggles on the first day of life. The goggles caused chronic binocular decorrelation (noncorrespondence) for periods of 3, 6, 9, 12, and 24 weeks. Each animal who wore the goggles for a duration exceeding 3 weeks developed esotropic strabismus, which did not reduce over subsequent recording periods that extended to approximately age 75 weeks. The angle of the strabismus related to the duration of decorrelation. The smallest angles (2–4°) were recorded in the 6-week monkeys and the largest (10–13°) in the 24-week monkeys. Binocular search coil eye movement recording and automated cover testing showed that even smaller-angle strabismus persisted, replicating the findings in the subset of human infants who have small, constant angles of infantile esotropia.[54] As in children with infantile esotropia,[55–57] the horizontal misalignment was accompanied by dissociated vertical deviation (clinical DVD). Eye rotations and saccadic velocities showed no evidence of myopathy or cranial nerve dysfunction, replicating the behavior in humans with concomitant esotropia.[39,58]

It is important to note that the strabismus could not be explained as adaptation of the vergence pathways to prism (prism-adaptation).[59,60] Each monkey was fitted with a base-in horizontal prism over one eye. If the monkeys had prism-adapted, they would have developed a divergent strabismus. But they developed convergent strabismus. The implication is that the natural default of the immature, unstable vergence system of human and monkey is nasalward/esotropic.

Esotropic Monkeys, Like Esotropic Human Infants, Do Not Have Significant Strabismic Amblyopia

A virtue of the rearing paradigm is that deprivation of monocular spatial vision was avoided, as in natural esotropia. The majority of human infantile esotropes lack strabismic amblyopia in the first months of life; amblyopia may develop subsequently in a subset of patients who do not alternate fixation between the eyes and who have prolonged, uncorrected strabismus.[43,61,62] The strabismic monkeys tended to alternate fixation, though the majority showed idiosyncratic fixation preferences, as in humans. *SSVEP* (spatial sweep visual evoked potential) recordings of visual acuity showed absence of significant amblyopia (defined as an interocular acuity differ-

ence > 0.25 octaves). Strabismic monkeys tended to have the same range of refractive error (< +3.0 spherical equivalent) as control animals.

Esotropic Monkeys, Like Human Infantile Esotropes, Do Not Have Extraocular Muscle, Orbital Pulley, or Muscle Innervation Anomalies

Detailed analysis of paraffin-embedded sections (10 microns) through whole orbits (on average 1000/orbit) in strabismic animals revealed no abnormalities of horizontal rectus muscle anatomy (orbital and global layer), muscle fiber-type composition, cross-sectional area, posterior-to-anterior muscle trajectories, pulley connective tissue location, connective tissue composition, or innervation density.[12] The orbital anatomy of the artificially strabismic animals was indistinguishable from that of naturally esotropic and normal macaque monkeys. We found no evidence of anomalies of the small (vestigial), accessory lateral rectus muscle. Saccadic velocities and amplitudes were normal. These findings reinforce the conclusion that concomitant infantile strabismus is a brain disease not an eye muscle disease.

Pursuit, OKN, and Motion VEP Asymmetries

Pursuit asymmetry is evident as a bias favoring nasalward target motion under conditions of monocular viewing. The behavior serves as an indicator for early maldevelopment of binocular gaze pathways, and is present in > 90% of children who have infantile strabismus.[11,39,47,63] The asymmetry was present in each monkey subjected to decorrelation for 6–24 weeks, the equivalent of 6–24 months of uncorrected strabismus in children. The asymmetry was absent in all monkeys exposed to decorrelation for only 3 weeks. These results lead to the conclusion that the cerebral pursuit pathways maldevelop when the duration of binocular decorrelation exceeds approximately 6 weeks. Responses to temporalward target motion were on average 20–70% as strong as responses to nasalward motion. The largest asymmetries were recorded in animals exposed to decorrelation for 24 weeks. Pursuit was recorded in multiple sessions to approximately age 75 weeks. No recovery was evident, verifying that the deficit was permanent (as observed in human adults who have infantile strabismus).[64,65] Similar asymmetries were evident for horizontal OKN evoked by large-field stripe stimuli and motion VEPs elicited by horizontally oscillating gratings.

Latent Fixation (Fusion Maldevelopment) Nystagmus

The control and 3-week monkeys had stable fixation when viewing monocularly or binocularly. The 6–24 week monkeys showed latent nystagmus, most pronounced in the 24-week animals. The nystagmus was evident as nasalward slow-phase drifts, with respect to the fixating eye, interrupted by temporalward fast phase jerks. The wave-form of the slow-phase—decreasing or linear velocity—conformed to standard latent nystagmus criteria.[66] The nystagmus persisted, but was less pronounced, when viewing with both eyes uncovered—i.e., manifest-latent nystagmus. The largest mean velocity, 2.0°/sec, was recorded during monocular viewing in the 24-week monkeys. Nystagmus velocity during binocular viewing was 26–51% slower. Nystagmus intensity (the product of frequency and amplitude) increased systematically with increasing duration of decorrelation.

Impaired Disparity Vergence

Fusional vergence in normal monkeys and humans has been divided into two

components that subserve different binocular functions.[66,67] Short-latency (50–80 msec) vergence is driven by small disparities, typically 2.5° or less. It is facilitated by a prior saccade, and its chief function may be to correct the small vergence errors that occur at the end of conjugate saccades.[68] Longer-latency (150–250 msec) vergence responds to larger disparities (up to approximately 10°) during fixation and is boosted by accommodative (blur) cues. Both components of the vergence response were studied.

The stimulus used to evoke short-latency vergence was a large correlated-dot pattern displayed on a video monitor, viewed through liquid-crystal shutter goggles. By varying the horizontal offset of the dot patterns viewed by each eye, binocular disparity was produced devoid of monocular cues. The control and 3-week monkeys had appropriate convergent and divergent velocity deflections at latencies approximately 60–80 msec. In contrast, the 6–24 week animals displayed erratic vergence-velocity baselines and no convincing disparity responses.

Impaired Random-Dot Stereopsis

Stereopsis thresholds for random-dot stimuli were tested over a disparity range ± 5°, measured by recording eye movements in an automated, staircase preferential-looking paradigm. The stimulus display allowed measurement of stereopsis to ± 0.1° (360 arc sec). Control and 3-week duration monkeys displayed stereo-sensitivity (i.e., a minimum of 70% correct) over the entire range tested, with responses falling to chance level only for interleaved, zero-disparity, catch trials. The 6–24 week monkeys were stereo-blind. Optically realigning the eyes with Fresnel prism did not improve performance at even the largest disparities. The results showed general concordance between stereo-sensitivity and disparity-vergence performance.

Connectivity Deficits in Area V1

The anterograde tracer biotinylated dextrran amine (BDA) was used to label horizontal axonal projections between ocular dominance columns (ODCs) in V1. Connections to neighboring ODCs were quantified by counts of labeled synaptic boutons and pyramidal neuron bodies (somata) in ODCs of same and opposite-ocularity to that of the injected ODC. ODC ocularity was determined by transport [^{3}H]proline from one eye.[69,70] Normal adult, control, and 3-week monkeys had similar distributions of labeled boutons and somata in same- and opposite-eye ODCs.

The 6–24 week monkeys had 20–73% of the normal number of horizontal connections between ODCs of opposite ocularity. The duration of the decorrelation was related to the reduction in the number of binocular connections. Monkeys in the 24-week duration group had fewer binocular connections than monkeys in the 9–12 week group. The binocular deficit in 24-week monkey was comparable to that in monkeys with uncorrected natural esotropia. The results provide the first evidence in primates for defective neuroanatomic connectivity in V1 as a consequence of increasing durations of binocular decorrelation. The results also provide correspondence between visuomotor behaviors and V1 anatomy. The defect of connectivity in layers 2/3 and 4B indicate maldevelopment of neurons known to mediate the earliest stages of disparity sensitivity and motion processing for ocular motor control.

Interocular Suppression of ODC Metabolic Activity in V1

Abnormal metabolic activity, as revealed by CO (cytochrome oxidase) histochemistry,[69,70] was evident in area V1 of the strabismic monkeys. The abnormality was apparent as alternating rows of darker and lighter staining ODCs at the input layer

of primary cortex, lamina 4C.[14,71] Thin dark ODC stripes in layer 4C alternated with wider, pale stripes.[72] The centers of the dark stripes were 400–500 microns apart, or the normal width separating the centers of ODCs. The dark stripes corresponded to ODCs that stained intensely for CO (higher premortem metabolic activity), and the pale stripes to rows of ODCs that stained poorly (lower activity). In normal primates, layer 4C stains homogeneously and ODC stripes are not visible.[70,73] To make layer 4C ODCs visible using CO, a normal monkey must have one eye deafferented.[74–76]

ODC suppression in the strabismic animals was regional, detected variably in swaths of opercular or calcarine V1. In calcarine V1, ODCs driven by the temporal hemi-retina (ipsilateral eye) tended to be suppressed, implying that they are at a developmental disadvantage. The metabolic abnormality was confined to the binocular visual cortex; it was not a subcortical, brainstem pathology. ODC suppression was never observed in monocular regions—i.e., the optic disc representation or the monocular crescent. CO-labeling of the lateral geniculate nuclei (LGN) showed no evidence of inter-laminar (right vs. left eye) inequalities.

DISCUSSION AND CONCLUSIONS

Functional Impairments of Infantile Strabismus

The infantile esotropia syndrome in humans is a constellation of sensorimotor signs.[39,77] These include defective stereopsis, poor horizontal fusional vergence, and abnormal vertical vergence expressed as dissociated vertical deviation (DVD). Gaze asymmetries are other major behavioral indicators, manifested as nasalward biases of fixation (latent nystagmus), optokinetic tracking, smooth pursuit, ocular following, and motion visually evoked potentials.[39,78–80] A good animal model should possess all of these signs. Comprehensive behavioral testing was performed to detect (and quantify) these signs in strabismic monkeys. Each of the behavioral indicators is present and each increases in severity as a function of decorrelation duration. An advantage of using primates and operant-conditioning trials is the large number of measurements obtainable for each behavior in each animal. Behavioral measurements of this range and quality cannot be obtained in studies of children.

Structural Impairments of V1 (Striate Visual Cortex) in Infantile Strabismus

Monkeys who have natural or experimentally induced strabismus have striking structural and metabolic abnormalities in V1. The major structural deficit is a paucity of horizontal connections between ODCs of opposite-ocularity, and a strong preference for connections to ODCs of the same ocularity.[53,74,81–83] The defect of binocular connectivity is apparent in layer 4B and in CO inter-patch compartments of layers 2/3. A systematic functional-structural relationship exists. The most severe defects of horizontal connections are observed in the animals with the most severe behavioral impairments.[53] The metabolic defect is suppression of cytochrome oxidase (CO) activity in ODCs of opposite-ocularity, which may extend across opercular and calcarine V1 of both hemispheres or appear as a suppression scotoma in one retinotopic region.[72,75,84]

Primate Decorrelation as an Experimental Model for Infantile Esotropia

Maturation of binocular fusion requires correlated activity between right and left eye inputs to V1.[85–92] Before maturation of fusion, the vergence[93–96] and conjugate

gaze pathways[52,97–99] of normal infants show transient nasalward biases. Infants with perturbed V1 inputs have the highest clinical risk of developing nasalward strabismus and persistent nasalward gaze biases.[31–33] These observations led us to propose a cerebral mechanism. Infantile esotropia could be caused by impeding correlated binocular input to V1 in the first weeks of life, leading downstream, immature motor pathways to decompensate in the direction of innate (nasalward) biases. The hypothesis was tested by rearing neonatal monkeys under conditions that exposed them to periods of sensorial decorrelation, but left their eye muscles, motor pathways, and monocular spatial vision intact. A secondary goal was to determine whether the duration of binocular decorrelation predicted the severity of visuomotor maldevelopment (or the probability of recovery to normal function). The intervals of decorrelation were designed to emulate shorter vs. longer durations of uncorrected strabismus in children, with the aim of contributing behavioral and neuroanatomic information that could help clarify the harm done by delayed treatment.[37,41,42,77,100,101] The results of these experiments confirm that decorrelation is a sufficient cause of the infantile esotropia syndrome, and the severity of each syndrome component increases as a function of decorrelation duration. Restoration of binocular fusion and V1 connections, after short durations of decorrelation, helps explain the benefits of early strabismus repair in humans.

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