Essential Infantile Esotropia: Potential Pathogenetic Role of Extended Subcortical Neuroplasticity

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Essential infantile esotropia is generated by prenuclear visual pathways that increase esotonus and gradually drive the eyes into a convergent position. Contrary to the prevailing notion that infantile esotropia reflects a primary disturbance within the visual cortex, accumulating evidence suggests that infantile esotropia is generated by lower subcortical centers that subserve nasalward optokinesis. These phylogenetically older visuo-vestibular pathways include the nucleus of the optic tract, accessory optic system, inferior olive, cerebellar flocculus, and vestibular nucleus. In humans, the subcortical visual system is normally turned off after the first few months of infancy but retains its function in children who develop infantile esotropia. Mutations or other perturbations that prolong subcortical neuroplasticity may therefore lead to a persistent simultaneous nasalward optokinetic imbalance in both eyes to generate infantile esotropia. Deficits in cortical motion processing and monocular nasotemporal asymmetry to foveated optokinetic targets are likely the effect, rather than the cause, of infantile esotropia.

Keywords: infantile esotropia, binocular misalignment, optokinetic motion, visual cortex

"Nature herself must be our advisor. The path she chalks must be our walk. For as long as we confer with our own eyes, and make ascent from lesser things to greater, we shall at last be received into her closet of secrets." 1

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ssential infantile esotropia (EIE) is a binocular misalignment characterized by a fixed crossing of the eyes within the first 6 months of life (Fig. 1). 2 It is occasionally present at birth, but more often manifests as a progressive naso-temporal deviation of both eyes. 3 EIE presents in the absence of additional neurological disease and is therefore isolated to the sensorimotor visual system within the brain. Most cases are nonhereditary and have no defined genetic etiology. 4

Figure 1 shows an infant with infantile esotropia. What is so amazing about this condition is that both eyes are held in an adducted position even though the child can abduct each eye fully, so this condition has to be prenuclear in origin. But under nondepolarizing paralyzing general anesthesia, the eyes assume a fairly normal position, 7 signifying that EIE has to be caused by increased baseline innervation (or tonus) to the medial rectus and inferior oblique muscles in the awake state.

It is considered axiomatic in neurology that movements are innervated by the cortex, whereas individual muscles are innervated by subcortical centers. The fact that individual extraocular muscles are hyperinnervated in EIE suggests that its prenuclear innervation must therefore be subcortical in origin. Its prominent association with binocular torsion, which is conspicuously absent in isolated lesions involving the visual cortex, provides further evidence that EIE is generated within the subcortical prenuclear ocular motor pathways. 5

WHY DOES ESSENTIAL INFANTILE ESOTROPIA DEVELOP?

The fundamental evolutionary clue to the neurology of EIE lies in the finding of monocular nasotemporal asymmetry (MNTA) to horizontal optokinetic stimuli. Patients with infantile esotropia show brisk nasalward optokinetic responses and absent temporalward optokinetic responses. 7-10 Even after surgical realignment of the eyes, MNTA persists throughout life, providing a “footprint in the snow” of resolved infantile esotropia. This horizontal optokinetic asymmetry is operative in most lateral-eyed afoveate animals and used for the detection of full-field optokinetic flow. 11-14 It is modulated by the nucleus of the optic tract (NOT) and the dorsal terminal nucleus of the accessory optic system (DTN-AOS) within the midbrain. 13,14 These centers generate visuo-vestibular eye movements by sending visual motion signals through the vestibulocerebellum to the vestibular nucleus, which rotates the eyes at the appropriate speed and direction to minimize retinal slip. 15-18

Both phylogenetically and ontogenetically, MNTA antedates development of the binocular visual cortex. 5,11,12 In lateral-eyed animals, MNTA may help to prevent temporalward optokinetic stimuli from pinning the eyes back as the animal is moving forward. 13,14,15 However, another unrecognized evolutionary advantage conferred by this reflex derives from the fact that the nose and mouth are always “nasal” to the eyes, necessitating accurate nasalward optokinetic tracking as the animal turns toward potential food substances seen by either eye. During this turning movement, the opposite eye is subjected to a temporalward full-field optokinetic stimulus that may be of different velocity (when objects in its field of vision are situated at a different distance). Having the eye with nasalward optokinetic input generate the response for both eyes allows the animal to accurately track the world it is turning...
The persistence of MNTA in EIE represents an atavism (from the Latin *atavus*, "ancestor"); signifying the reappearance of an ancestral trait that has been lost through evolutionary change in previous generations. It is therefore significant that EIE so often develops during the time when the subcortical motion pathways are normally turned off. This time course is often taken as evidence that EIE must be cortical in origin, but it could also signify that EIE represents a state of extended subcortical plasticity. What is the evidence in favor of the latter mechanism?

**NEUROANATOMY OF ESSENTIAL INFANTILE ESOTROPIA**

How does MNTA relate to the development of EIE? Figure 2, from an article by Behrens and associates, shows the neuroanatomy of MNTA. The subcortical motion pathways (demarcated by a red oval) are normally operative in the early months of human infancy. In investigating EIE, we have put our magnifying glass on secondary aberrations within the motion pathways of the visual cortex (demarcated by a green oval); however, the innervational changes that actually cause the eyes to turn in are generated within the subcortical motion pathways. In Figure 2, the left eye is receiving nasalward optokinetic input, which crosses through the chiasm to the right NOT and DTN-AOS. These structures respond to rightward optokinetic input (nasalward for the left eye), and project their output signal to the dorsal cap of the inferior olive, which acts as a comparator of motor commands from the cerebral cortex and brainstem nuclei and feedback from receptors via the spinal cord, visual system, and vestibular organs. The inferior olive relays gated information to the cerebellar flocculus, which processes visuo-vestibular input. The cerebellar flocculus then sends its output signal to the vestibular nucleus, which integrates visual motion input from the eyes with head motion input from the labyrinth. The vestibular nucleus provides a prenuclear signal to the oculomotor nuclei, which innervate the appropriate extraocular muscles to minimize retinal slip.

Beginning at 2 to 3 months of age, binocular cells from the visual cortex, which are bidirectionally sensitive to horizontal optokinetic motion, begin to establish connections to the NOT-DTN, allowing foveal pursuit to override the monocular subcortical optokinetic bias. By 6 months of age, monocular horizontal responses to optokinetic stimuli become symmetrical. According to the Hoffmann hypothesis, when the development of cortical binocular vision is preempted, only the crossed nasal fibers from the left eye have the necessary rightward visual motion sensitivity to project through the right visual cortex (middle temporal/medial superior temporal [MT/ MST]) and connect to the right NOT-DTN to form one unified system and run visual motion responses monocularly. Hebbian mechanisms require the monocular horizontal motion sensitivity of foveal pursuit (a cortical function) to be paradoxically dictated by the preexisting subcortical substrate of the NOT-DTN. Thus, uncrossed monocular fibers from the right temporal retina, which are selectively sensitive to leftward motion, cannot establish connections to the right NOT-DTN.

Because cortical motion pathways must feed into this preexisting subcortical directional bias, you end up with a secondary cortical pursuit motion asymmetry and foveal pursuit asymmetry to optokinetic stimuli that we see every
day in clinic when we spin the optokinetic drum nasally and temporally. Once monocular cortical pursuit connections become established, the subcortical motion pathways can be driven by nasalward foveal pursuit pathways within the visual cortex (mainly MT but also MST), allowing cortical suppression of one eye to signal binocular visual imbalance and thereby trigger subcortical visual reflexes.

Within the comparative biology literature, it is striking that each of the unique eye movements described in infantile esotropia, be it latent nystagmus, dissociated vertical deviation, or oblique muscle overaction, have precise analogs in lower lateral-eyed animals, and the subcortical neuroanatomical pathways for all of these movements are well-established. For example, MNTA underlies the clinical phenomenon of latent nystagmus in humans. The expression of these atavisms suggests that this subcortical visual motion circuitry is integral to the pathogenesis of EIE. In fact, a defining feature of EIE is the persistence of subcortical visual reflexes with signature torsional rotations of the eyes. In EIE, the older subcortical visual system runs the show, which explains why its neuroanatomy is so rarely included in neuro-ophthalmology textbooks. To understand it, we must shine our flashlight into the basement of the brain where old subcortical visual reflexes that are put to sleep in early infancy get reactivated.

**ROLE OF SUBCORTICAL OCULAR MOTOR PLASTICITY IN ESSENTIAL INFANTILE ESOTROPIA**

In humans, this subcortical optokinetic system is operational within the first few months of life. Thus, MNTA is expressed within the first several months of life of human infancy. Symmetrical optokinetic responses develop as normal cortical binocular vision matures. Because subcortical motion pathways normally shut down as cortical motion pathways develop, one could question whether the persistence of subcortical reflexes could be a secondary consequence of a primary cortical binocular maldevelopment. Although this is assumed by many to be the most likely cause of EIE, there is evidence that the subcortical pathways do not normally remain active in the absence of cortical binocular vision. Infants with homonymous hemianopia due to early unilateral hemispherectomy only retain MNTA to full-field optokinetic input during its normal critical period. This is something unique about EIE that allows these subcortical visual motion pathways to remain operational. Either a mutation in the subcortical pathways could enhance their neuroplasticity and preserve their function throughout life, or secondary remodeling of the visual cortex could serve to actively perpetuate their function.

Although corticofugal output has been recently shown to influence subcortical plasticity in the mature mammalian visual motor system, it remains unseen that a primary defect in cortical binocularity exists in EIE. Indeed, it is difficult to envision how a Worthian mechanism (such as congenital absence of bifoveal fusion) could cause EIE to develop when the emergence of monofixation syndrome in children with EIE who undergo successful strabismus surgery is considered to be a “stable sensorimotor situation” due to the preservation of robust peripheral fusion. The stability of the postoperative alignment, despite the absence of bifoveal fusion, suggests that, even if this cortical defect were innate, it is unlikely to be the primary driver of the EIE. The finding of primary monofixation syndrome in many children who never develop EIE further supports this conclusion.

If EIE represents a state of enhanced subcortical neuroplasticity, could simultaneous subcortical optokinetic input to both nasal retinas drive the eyes into an esotropic position? In lateral-eyed animals, the answer is yes. Under real-world conditions, a lateral-eyed animal only rarely receives simultaneous nasoward optokinetic flow when it moves backward in space, but in the laboratory, disconjugate full-field optokinetic input to both eyes can generate esotropia (nasalward optokinesis) or exotropia (temporalward optokinesis). This phenomenon has been demonstrated in rabbits, and more recently in zebrafish (Supplementary Video). So binocular nasalward optokinetic input definitely has the potential to drive the eyes into an esotropic position.

Although binocular MNTA has been speculated to cause EIE at the level of the visual cortex, the nasal retina of the esodeviated eye is cortically suppressed (Fig. 3), so the two eyes cannot generate simultaneous cortical optokinetic responses. But at the subcortical level, there is no interocular suppression, so both eyes can be pulled in simultaneously, just like in fish and in rabbits. The fact that the amplitude of EIE does not increase when either eye fixates shows that this subcortical nasalward drive is not related to foveal fixation but generated by simultaneous full-field viewing with both eyes. The beauty of this mechanism is that this subcortical optokinetic system can remain operational despite cortical suppression of the esodeviating eye.

**CONCLUSIONS**

EIE conforms to a state of extended subcortical neuroplasticity in which subcortical visual pathways fail to shut down within the third month of life, allowing an early subcortical nasalward optokinetic bias to simultaneously drive the eyes into an esotropic position. Cortical motion pathways secondarily reconfigure themselves to this monocular subcortical template. So, what we call “Chavessian” esotropia (i.e., esotropia secondary to a motor impedance of binocular fusion) may...
actually correspond to a genetic mutation or perturbation that extends subcortical neuroplasticity. Accordingly, EIE may represent a default to an older ocular motor control system that retains its neuroplasticity and continues to be expressed. The supreme irony of this mechanism is that, as the visual cortex becomes monocular, the subcortical binocular system becomes binocular, meaning that both nasal retinas are activated simultaneously at the subcortical level to drive the eyes inward.

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References


SUPPLEMENTARY MATERIAL