An Expanded View of Infantile Esotropia

Bottoms Up!

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A recent editorial in the Archives assigned the primary pathogenesis of infantile esotropia to the visual cortex. This analysis addresses the limitations of this timeworn view and advances the perspective that infantile esotropia is a cortico-mesencephalic-cerebellar disorder wherein binocular cortical maldevelopment permits atavistic subcortical visual pathways to remain operational. This integrated neuroanatomical model predicts that primary neurodevelopmental disorders involving the accessory optic system or its connections to the cerebellum can also give rise to infantile esotropia.

Arch Ophthalmol. 2012;130(9):1199-1202

In the August issue of the Archives, Dr Lawrence Tychsen wrote an accompanying editorial1 to my article on the accessory optic system (AOS) and its potential role in infantile strabismus.2 I thank him for sharing his thoughts and taking an interest in this work and am pleased to have the opportunity to comment further on this subject.

Some believe that infantile esotropia is caused solely by abnormal binocular connections within the visual cortex. These connections include the primary visual cortex as well as higher cortical centers within the middle temporal area/medial superior temporal area that are involved in visual motion processing.2,4 According to this view, latent nystagmus is attributed to a cortical pursuit imbalance in the middle temporal area/medial superior temporal area with disinhibition of convergence leading to infantile esotropia.5 The finding of a normal vestibular ocular response is thought to rule out involvement of the vestibular system in infantile esotropia.2 The other dissociated movements that accompany infantile esotropia are then attributed to active vergence damping at the cortical level.2 This model requires that visually driven torsional eye movements be generated by the visual cortex and appears to be supported by the failure of decortication to reproduce dissociated eye movements.7 Accordingly, periventricular leukomalacia is considered a neurologic model for infantile esotropia.5

Because the visual cortex is readily accessible for study in monkeys, most of the investigational study of infantile esotropia has been focused on that area. Therefore, it is understandable that this general perspective is held by some investigators. What are the shortcomings of this perspective?

First, it attributes infantile esotropia to binocular alterations within the cerebral cortex that are secondary to binocular misalignment rather than causal. Hubel and Wiesel8 first showed that cutting extraocular muscles in kittens induces alternating strabismus and corollary changes within ocular dominance columns in the primary visual cortex. These changes were clearly the effect, rather than the cause, of infantile strabismus. In humans, no better evidence for this phenomenon can be found than in the work of Tychsen and coworkers,3,9 who have induced infantile esotropia in monkeys using base-out prisms and concluded that abnormal cortical binocular vision is the cause of infantile esotropia. Such experiments confirm that cortical binocular alterations following abnormal binocular visual experience can lead to infantile esotropia.

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Second, the conclusion that latent nystagmus arises from a cortical smooth pursuit defect ignores the evolutionary record. Latent nystagmus is driven by a normal monococular nasotemporal optokinetic asymmetry that fails to resolve in children with infantile esotropia. This nasal optokinetic preponderance manifests as latent nystagmus when fixation with either eye induces a tonic deviation of both eyes with nasolateral drift of the fixating eye. The question is whether this optokinetic asymmetry is generated at the cortical or the subcortical level, and there is experimental evidence that can be taken to support either conclusion.

What is clear is that the same monococular nasotemporal optokinetic asymmetry is present in lower vertebrates that do not possess a visual cortex. Hoffmann has shown in cats that development of binocular corticocortical pathways to the nucleus of the optic tract (NOT) and the dorsal terminal nucleus is necessary to cancel this asymmetry within the first year of life. So phylogenetically and ontogenetically, the monocular nasotemporal optokinetic asymmetry that drives latent nystagmus antedates development of the binocular visual cortex. The neuroanatomical substrate of this optokinetic asymmetry has been mapped to normal subcortical visual pathways that travel first from the retina to the contralateral NOT and dorsal terminal nucleus (a part of the AOS) in the pretectum and then via the cerebellar flocculus to the vestibular nuclei. These subcortical, visuovestibular pathways modulate optokinetic responses to whole-field movement (optic flow) in afoveate animals as opposed to cortical pursuit (a foveal function). Given that the monocular nasotemporal optokinetic asymmetry that generates latent nystagmus derives from a subcortical, afoveate, optokinetic pathway, a binocular defect in cortical (foveal) smooth pursuit cannot be the primary cause of latent nystagmus.

The proximate cause of latent nystagmus is that these subcortical optokinetic pathways remain operational. Since cortical pursuit pathways do not generate torsional eye movements, one simply cannot explain the large torsional movements that accompany latent nystagmus without invoking activation of these subcortical visual pathways that project to the vestibular nuclei. In this context, latent nystagmus conforms to a visuovestibular nystagmus that is ultimately driven by subcortical binocular visual input to the vestibular nuclei. Latent nystagmus also shows the phenomenon of velocity storage, which is unique to vestibular eye movements. As expected, the vestibular oculomotor reflex remains normal because labyrinthine input to the vestibular system is unaffected.

Optokinetic eye movements provide the pursuit system for lateral-eyed afoveate animals. In primates, the subcortical NOT has commissioned the cortex to provide integrated visual motion information from the 2 hemifields through the middle temporal area and medial superior temporal area. Efferent signals from the NOT and dorsal terminal nucleus may transmit velocity error information to the pursuit system. Pursuit and visuovestibular pathways remain functionally intermingled within the medial superior temporal area of the primate motion visual cortex. Therefore, it is not surprising that this visual motion asymmetry is represented at the cortical level, causing smooth pursuit to be coordinately impaired. So if one looks for cortical visual motion asymmetry in primates with latent nystagmus, one will find it and conclude that latent nystagmus must be cortical in origin.

Third, the notion that binocular cortical alterations unmask an innate convergence bias to produce infantile esotropia is problematic at several levels. Horwood has shown that normal infants display large, fleeting, convergence movements of the eyes during the first 4 months of life, which are indicative of an emerging vergence system. A greater frequency of these convergence movements between ages 2 and 4 months is predictive of normal binocular development and a lower likelihood of developing infantile esotropia. If infantile esotropia represents excessive convergence, why would normal infants display more excessive convergence movements than infants who are destined to develop infantile esotropia? It is also noteworthy that the prevalence of infantile esotropia increases during a period in which these convergence movements are disappearing in normal infants.

Jampolsky has emphasized the importance of distinguishing between convergence as an active binocular function and esotropia as a passive innervational output that is centrally driven by unequal visual input to the two eyes. Patients with accommodative esotropia show excessive convergence, while those with infantile esotropia do not. Misinterpreting infantile esotropia as a motor outcome of excessive convergence also supports the misconception that disassociated vertical divergence and disassociated horizontal deviation can be dismissed as excessive vergence damping of latent nystagmus, despite the fact that latent nystagmus is not present in some patients who have these other dissociated eye movements.

Fourth, the claim that early neurologic perturbation of cortical visual input is a high risk factor for the motor components of infantile strabismus is certainly correct, but the motor effects are due to a secondary involvement of lower motor circuits. Children with neurologic disease constitute the minority in those with findings that define infantile esotropia. There is no substantial evidence that injury to the developing cerebral cortex is necessary for infantile esotropia to develop. Indeed, the absence of neurologic disease is definitional for infantile esotropia. So while neurologic injury is a risk factor for the development of esotropia in infancy, it should not be inferred from this association that infantile esotropia is a “soft sign” of neurologic disease.

This leads to a concern about the use of periventricular leukomalacia as a neurologic model for infantile esotropia. It is true that this condition produces preterm injury to binocular visual input as evidenced by the bilateral focal white matter injury to the optic radiations that are visible on magnetic resonance imaging. It is also the case that periventricular leukomalacia is a neurologic disease that can cause elements of the infantile eso-
tropia syndrome to be expressed. However, children with periventricular leukomalacia have a different constellation of clinical findings (including tonic downgaze, primary superior oblique overaction, optic nerve hypoplasia, spontaneous conversion of esotropia to exotropia) from those seen in infants with esotropia.39 Furthermore, periventricular leukomalacia is now recognized as a global injury to both cortical and subcortical structures (including the thalamus, basal ganglia, and cerebellum),40 making it a poor model for infantile esotropia caused by isolated injury to binocular cortical visual inputs.

Although dissociated eye movements are an expression of subcortical visual reflexes in lower animals, there is no question that the human visual cortex is altered by infantile esotropia3-5,8,41 and that cortical suppression of one eye (brought about by fixation, blurring, occlusion, or volition) is a necessary physiological condition to generate dissociated eye movements in humans.38,42,43 After normal corticopretectal connections become established in primates, subcortical retinopretectal projections may lose their influence and be replaced by cortical afferents,44 which would explain the absence of dissociated eye movements in some7,15,45 but not all46 patients following “decortication.”

There is ample evidence that once cortical binocular vision is disrupted early in infancy, infantile esotropia and its dissociated eye movements are generated and operationalized downstream at the subcortical level.23 Because studies of infantile esotropia have been largely limited to the cortex, it is on the subcortical limb of the operation that analysis should now be focused. What is the line of evidence showing that strabismus is generated in the basement of the brain? The evidence can be summarized as follows23:

1. Lateral-eyed animals have dissociated binocular vision.
2. Lateral-eyed animals display a constellation of subcortical visual reflexes that are driven by unbalanced visual input to the two eyes.
3. These subcortical reflexes are visuovestibular in origin (meaning that dissociated binocular visual input is conveyed to the vestibular nucleus and to the vestibulocerebellum, where luminance and optokinetic input are modulated).
4. Developmental disorders that impair cortical development can allow primitive subcortical reflexes to be expressed in humans.23
5. Humans have evolved from lower animals and retain a vestibulocerebellum and an atavistic AOS.6 Humans who have dissociated binocular vision early in development (most commonly, but not exclusively, infantile esotropia) display a unique constellation of dissociated eye movements.
6. Each of these dissociated eye movements in humans conforms to subcortical visual reflexes that are operative in lateral-eyed animals, are evoked by fluctuating binocular visual input, operate in one plane of visual space, and are driven by optokinetic input or luminance disparity.8 These dissociated eye movements (latent nystagmus, primary oblique muscle overaction, dissociated vertical divergence, dissociated horizontal deviation) therefore seem to arise from subcortical visual reflexes in lateral-eyed animals and are triggered in humans by cortical suppression of one eye.
7. All of these dissociated eye movements have a prominent torsional component.
8. Human torsional eye movements and other cyclovertical deviations such as skew deviation are a signature of vestibular disease and are conspicuously absent with lesions at the level of the cerebral cortex.47

This evidence supports the view that dissociated eye movements are generated in the basement of the brain by primitive visual pathways that are modulated by the binocular visual cortex. As the AOS modulates full-field optokinetic movements similar to the NOT and operates in the canal-based coordinate system, it emerges as an attractive candidate for generating these atavistic torsional movements.3 In the evolutionary sense, these are not abnormal eye movements but are normal eye movements that are resurgent. A comprehensive neuroanatomical model for infantile esotropia must therefore incorporate the cortico-mesencephalic-cerebellar pathways (not brainstem),1 which are known to provide a sensorimotor circuit for the control and modulation of eye movements in human and nonhuman primates.22

For these reasons, we should consider that the “cause” of infantile esotropia lies not only upstairs in the cerebral cortex but also downstairs in the cerebellar cortex. In humans, neurologic lesions such as midline cerebellar tumors48 and Chiari malformations49 can also cause acquired comitant esotropia. In the rabbit, stimulation of the dorsal cap of the inferior olive (which provides visual climbing fibers to the cerebellar flocculus) inhibits reflex contractions to the contralateral medial rectus muscle and the ipsilateral inferior oblique muscle.50-52 In this context, bilateral floccular inhibition would provide one mechanism whereby infantile esotropia and bilateral inferior oblique overaction could be generated without “convergence.”

This body of evidence leads to the conclusion that infantile esotropia may also incorporate subcortical optokinetic pathways such as the AOS. As genetic studies provide molecular localization, we could find that lesions anywhere along this expanded roadmap may provide the ocular motor derangements to detail development of cortical binocularity and give rise to infantile strabismus. Depending on their localization (visual cortex, AOS, cerebellar flocculus), targeted neuropharmacologic treatments may become available.

Submitted for Publication: May 8, 2012; final revision received May 8, 2012; accepted May 18, 2012.
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Financial Disclosure: None reported.
Funding/Support: This work was supported in part by a grant from Research to Prevent Blindness.
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