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.

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In the August issue of the Archives, Dr Lawrence Tychsen wrote an accompanying editorial to my article on the accessory optic system (AOS) and its potential role in infantile strabismus. 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. 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. The finding of a normal vestibular ocular response is thought to rule out involvement of the vestibular system in infantile esotropia. The other dissociated movements that accompany infantile esotropia are then attributed to active vergence damping at the cortical level. 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. Accordingly, periventricular leukomalacia is considered a neurologic model for infantile esotropia.

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 Wiesel 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, 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.

Author Affiliations: Departments of Ophthalmology and Neurology, Mayo Clinic, Rochester, Minnesota.
Second, the conclusion that latent nystagmus arises from a cortical smooth pursuit defect ignores the evolutionary record. Latent nystagmus is driven by a normal monocular 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 nasalward 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 monocular 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 ocular reflex remains normal because labyrinth 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 dissociated vertical divergence and dissociated 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 definitive 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 esotropia that accompany latent nystagmus without invoking activation of these subcortical visual pathways that project to the vestibular nuclei.
tropia syndrome to be expressed. However, children with periven-
tricular leukomalacia have a different constellation of clinical find-
ings (including tonic downgaze, primary superior oblique overac-
tion, optic nerve hypoplasia, spontaneous conversion of esotropia to
exotropia) from those seen in infantile esotropia.39 Furthermore, peri-
ventricular leukomalacia is now rec-
ognized as a global injury to both
cortical and subcortical structures
(including the thalamus, basal gan-
glia, and cerebellum),60 making it a
poor model for infantile esotropia
caused by isolated injury to binocu-
lar cortical visual inputs.

Although dissociated eye move-
ments are an expression of subcor-
tical visual reflexes in lower ani-
mals, there is no question that the
human visual cortex is altered by in-
fantile esotropia3,5,8,41 and that cor-
tical suppression of one eye (brought
about by fixation, blurring, occlu-
sion, or volition) is a necessary
physiological condition to generate
dissociated eye movements in hu-
mans.38,42,43 After normal corticopre-
tectal connections become estab-
lished in primates, subcortical
retinopretectal projections may lose
their influence and be replaced by
cortical afferents,44 which would ex-
plain 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 down-
stream at the subcortical level.23 Be-
cause studies of infantile esotropia
have been largely limited to the cor-
tex, it is on the subcortical limb of the
operation that analysis should now
be focused. What is the line of evi-
dence showing that strabismus is gen-
erated in the basement of the brain?
The evidence can be summarized as
follows:33

1. Lateral-eyed animals have dis-
sociated binocular vision.
2. Lateral-eyed animals display a
constellation of subcortical visual re-
flexes that are driven by unbal-
anced visual input to the two eyes.
3. These subcortical reflexes are
visuovestibular in origin (meaning
that dissociated binocular visual in-
put is conveyed to the vestibular
nucleus and to the vestibulocerebel-
ulum, where luminance and optoki-
netic input are modulated).
4. Developmental disorders that
impair cortical development can al-
low primitive subcortical reflexes to
be expressed in humans.23
5. Humans have evolved from
lower animals and retain a vestibu-
locerebellum and an atavistic AOS.
6. Humans who have disso-
ciated binocular vision early in devel-
opment (most commonly, but not
exclusively, infantile esotropia) dis-
play a unique constellation of dis-
sociated eye movements.
7. Each of these dissociated eye
movements in humans conforms to
subcortical visual reflexes that are op-
erative in lateral-eyed animals, are
evoked by fluctuating binocular vi-
sual input, operate in one plane of vi-
sual space, and are driven by opto-
kinetic input or luminance disparity.
8. These dissociated eye move-
ments (latent nystagmus, primary
oblique muscle overaction, dissoci-
ated vertical divergence, disso-
ciated horizontal deviation) there-
fore seem to arise from subcortical
visual reflexes in lateral-eyed ani-
mals and are triggered in humans by
cortical suppression of one eye.
9. All of these dissociated eye
movements have a prominent tor-
sional component.
10. Human torsional eye move-
ments and other cyclovertical de-
viations such as skew deviation are
a signature of vestibular disease and
are conspicuously absent with les-
ions 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 binocu-
lar visual cortex. As the AOS modu-
lates full-field optokinetic move-
ments similar to the NOT and
operates in the canal-based coordi-
nate system, it emerges as an atrac-
tive candidate for generating these
atavistic torsional movements.1 In
the evolutionary sense, these are not
abnormal eye movements but are
normal eye movements that are re-
surgent. A comprehensive neuro-
anatomical model for infantile eso-
tropia must therefore incorporate the
cortico-mesencephalic-cerebellar
pathways (not brainstem),1 which
are known to provide a sensorimo-
tor circuit for the control and modu-
lation of eye movements in human
and nonhuman primates.22

For these reasons, we should con-
sider that the “cause” of infantile eso-
tropia lies not only upstairs in the
cerebral cortex but also downstairs
in the cerebellar cortex. In hu-
mans, neurologic lesions such as
midline cerebellar tumors48 and Chi-
ari malformations49 can also cause
acquired comitant esotropia. In the
rabbit, stimulation of the dorsal cap
of the inferior olive (which pro-
vides visual climbing fibers to the
cerebellar flocculus) inhibits reflex
contractions to the contralateral me-
dial rectus muscle and the ipsilat-
eral inferior oblique muscle.30,32 In
this context, bilateral floccular in-
hibition would provide one mecha-
nism whereby infantile esotropia and
bilateral inferior oblique overac-
ration could be generated without
“convergence.”

This body of evidence leads to the
conclusion that infantile esotropia
may also incorporate subcortical op-
tokinetic pathways such as the AOS.
As genetic studies provide molecu-
lar localization, we could find that
lesions anywhere along this ex-
panded roadmap may provide the
ocular motor derangements to de-
tail development of cortical binocu-
larity and give rise to infantile stra-
bismus. Depending on their
localization (visual cortex, AOS, cer-
ebellar flocculus), targeted neuro-
opharmacologic treatments may be-
come available.

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Correspondence: Michael C. Brod-
sky, MD, Departments of Ophthal-
mology and Neurology, Mayo Clinic,
200 First St SW, Rochester, MN
55905 (brodsky.michael@mayo.
edu).
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