The Neural Mechanism for Latent (Fusion Maldevelopment) Nystagmus

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Abstract: Latent nystagmus (LN) is the by-product of fusion maldevelopment in infancy. Because fusion maldevelopment—in the form of strabismus and amblyopia—is common, LN is a prevalent form of pathologic nystagmus encountered in clinical practice. It originates as an afferent visual pathway disorder. To unravel the mechanism for LN, we studied patients and nonhuman primates with maldeveloped fusion. These experiments have revealed that loss of binocular connections within striate cortex (area V1) in the first months of life is the necessary and sufficient cause of LN. The severity of LN increases systematically with longer durations of binocular decorrelation and greater losses of V1 connections. Decorrelation durations that exceed the equivalent of 2–3 months in human development result in an LN prevalence of 100%. No manipulation of brain stem motor pathways is required. The binocular maldevelopment originating in area V1 is passed on to downstream extrastriate regions of cerebral cortex that drive conjugate gaze, notably MSTd. Conjugate gaze is stable when MSTd neurons of the right and left cerebral hemispheres have balanced binocular activity. Fusion maldevelopment in infancy causes unbalanced monocular activity. If input from one eye dominates and the other is suppressed, MSTd in one hemisphere becomes more active. Acting through downstream projections to the ipsilateral nucleus of the optic tract, the eyes are driven conjugately to that side. The unbalanced MSTd drive is evident as the nasalward gaze-holding bias of LN when viewing with either eye.

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Supported by a Grant EY10214 (L.T.) from the National Institutes of Health, A Walt and Lilly Disney Award for Amblyopia Research from Research to Prevent Blindness (L.T.), Summer Student Research Scholarship from the University of Toronto Faculty of Medicine (M.R.), Grant MOP 67104 (A.W.) and a New Investigator Award (A.W.) from the Canadian Institutes of Health Research.

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Journal of Neuro-Ophthalmology 2010;30:276–283
doi: 10.1097/WNO.0b013e3181dfa9ca

Latent nystagmus (LN) is a common subtype of pathologic nystagmus observed in human and nonhuman primates (1). It is linked strongly to binocular maldevelopment in infancy, from either strabismus or deprivation of monocular spatial vision (amblyopia).

LN is characterized by a conjugate horizontal slow-phase drift of eye position that is directed nasalward with respect to the viewing eye (2,3). When viewing switches from eye to eye, the direction of the slow-phases reverses instantaneously: leftward when the right eye (RE) is fixating and rightward when the left eye (LE) is fixating (Fig. 1). The severity of the nystagmus (and its conspicuity during clinical examination) increases when one eye is covered, hence the term *latent*. When the nystagmus is evident with both eyes open, it is called manifest LN.

LN is distinguished easily during clinical examination from congenital nystagmus, also called the infantile nystagmus syndrome (INS), by the fact that LN has instantaneous reversal of direction with alternating fixation. By eye movement recording, it is distinguished also in waveform. The waveform of LN is always that of decreasing velocity and linear trajectory, whereas that of INS is of increasing velocity and pendular trajectory (2). Eye movement recordings or high magnification clinical inspection with a slit-lamp biomicroscope or ophthalmoscope frequently reveals a superimposed small torsional movement.

Seminal contributions to our understanding of the clinical features of LN have been made by Dell'Osso et al (2,4), who have also clarified the historical origins of LN's various terms. In 1872, Faucon (5) first described what we now appreciate as manifest LN. In 1912, Fromaget and Fromaget (6) introduced the term *nystagmus latent*. These early reports of LN were reviewed by Sorsby (7) in 1931.

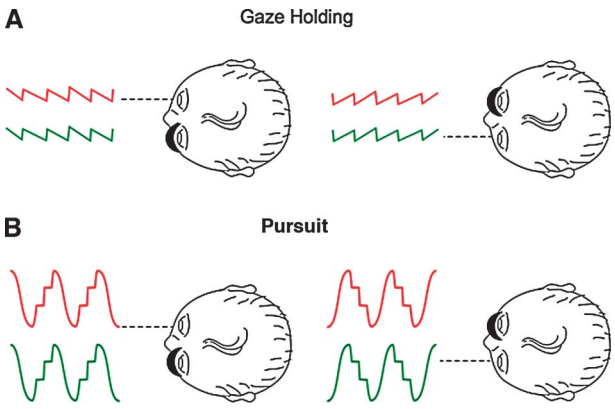

FIG. 1. Nasalward gaze asymmetries in strabismic human and monkey. **A**. Latent nystagmus in gaze holding. When the subject views with the right eye, both eyes have a nasalward slow-phase drift, followed by temporalward refoveating fast-phase microsaccades. The direction of the nystagmus reverses instantaneously when the left eye fixates so that the slow phase is nasalward with respect to the fixating eye. **B**. Pursuit. Horizontal smooth pursuit is asymmetric during monocular viewing. Pursuit is smooth (normal) when target motion is nasalward in the VF. Pursuit is cogwheel (low gain) when the target moves temporalward. The movements of the 2 eyes are conjugate, and the direction of the asymmetry reverses instantaneously with a change of fixating eye so that the direction of robust pursuit is always for nasalward motion in the visual field (likewise for OKN).

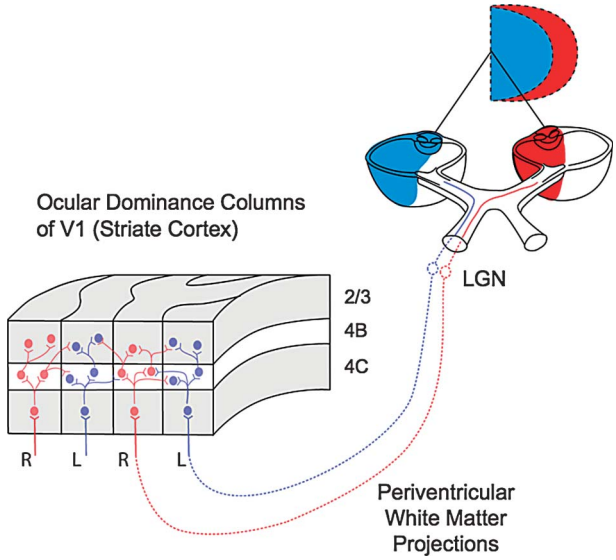

FIG. 2. Neuroanatomic basis for binocular vision. Monocular retinogeniculate projections from left eye (temporal retina, nasal visual hemifiled) and right eye (nasal retina, temporal hemifield) remain segregated up to and within the input layer of ocular dominance columns (ODCs) in V1, layer 4C (striate visual cortex). Binocular vision is made possible by horizontal connections between ODCs of opposite ocularity in upper layers 4B and 2/3 (as well as lower layers 5/6, not shown). RE inputs = red; LE inputs = blue.

The oxymoron *manifested latent* nystagmus was introduced by Kestenbaum (8) in 1947, who emphasized that LN is often observed in patients with strabismus when they view with both eyes open.

Although infantile esotropia is the leading association with LN, any disorder that perturbs development of binocular fusion in infancy, such as monocular or severe binocular deprivation, will produce LN and manifest LN (9,10). The National Institutes of Health Committee on Eye Movement and Strabismus classification (11) has therefore recommended that the terms LN/manifest LN be replaced by the etiologic descriptor *fusion maldevelopment nystagmus*.

DEVELOPMENT OF FUSION ELIMINATES NASALWARD VISUAL CORTEX BIASES

Behavioral studies have shown that the postnatal development of binocular sensory and motor functions in normal infant monkeys parallels that of normal infant humans but on a compressed time scale: one week of monkey development approximates 1 month of human (12–15). Binocular disparity sensitivity and binocular fusion are absent in human and monkey neonates. Stereopsis emerges abruptly in humans during the first 3–5 months of postnatal life (16–20) and in monkeys, during the first 3–5 weeks (14), achieving adult-like levels of sensitivity.

V1 horizontal axonal connections are key components of fusion development and maldevelopment (Fig. 2). Binocularity in primates begins with horizontal connections between V1 ocular dominance columns (ODCs) of opposite ocularity (21–23). These connections are immature in the first weeks of life, conveying crude weak binocular responses (24–26). Maturation of binocular connections requires correlated (synchronous) activity between right eye and left eye geniculostriate inputs (27,28). Decorrelation of inputs (Fig. 3), produced by binocular noncorrespondence, causes loss of horizontal connections over a period of days in V1 of kittens (27,29). The inference from our experimental results and clinical studies is that similar losses occur over a period of weeks in V1 of monkeys and over a period of months in V1 of children. Binocular decorrelation also promotes interocular suppression (Fig. 4) as a further hindrance to fusion (1).

In the first months of life in humans and weeks of life in monkeys, monocular motion visual evoked potentials reveal a nasotemporal asymmetry (30–33). Monocular preferential looking testing reveals greater perceptual sensitivity to nasalward motion (34). Monocular pursuit and optokinetic tracking reveal biases favoring nasalward target motion (12,35–38). These nasalward motion biases are pronounced before onset of sensorial fusion and stereopsis but systematically diminish thereafter. They are retained in subtle form in normal adult humans and can be unmasked using

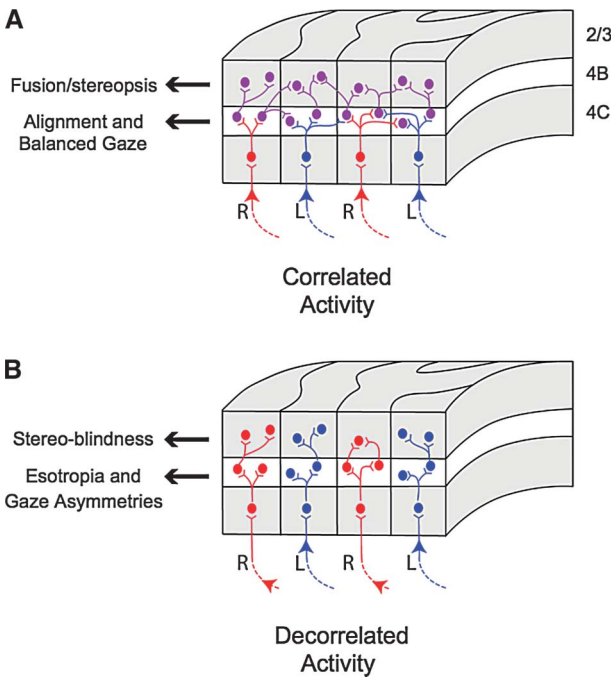

FIG. 3. Horizontal connections for binocular vision to layer 2–4B of V1 in normal (correlated activity) primates (**A**) and strabismic (decorrelated) primates (**B**). V1 of normal primates is characterized by equal numbers of monocular and binocular connections. In strabismic primates, the connections are predominantly monocular. RE inputs = red; LE = blue; binocular = violet.

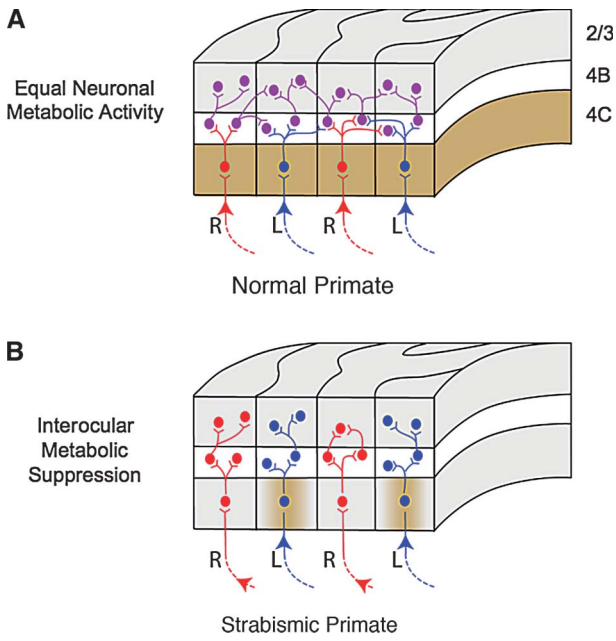

FIG. 4. Metabolic activity in neighboring ocular dominance columns (ODCs) within V1 of normal primates (**A**) and strabismic primates (**B**). In normal primates, layer 4C stains uniformly for the metabolic enzyme cytochrome oxidase (brown), indicating equal activity in right eye and left eye columns. In strabismic primates, a narrow monocular zone within the dominant ODCs (shown here as left eye) shows normal metabolic activity (brown), but ODCs belonging to the suppressed eye (shown as right eye) and binocular border zones between ODCs are pale, connoting abnormally low (suppressed) activity.

contrived monocular stimuli (39,40). If normal maturation of binocularity is impeded by eye misalignment or monocular deprivation, the nasalward biases persist and become pronounced (34,41–47). The nasalward gaze bias is the key feature of the fusion maldevelopment syndrome. Other common findings are loss of stereopsis, interocular suppression, strabismus, and smaller amplitude torsional/vertical oscillations of the eyes.

BINOCULAR DECORRELATION FROM VARIOUS CAUSES BEGINS THE LN CASCADE

Clinical studies of children (43) and adults (2,4,44,48) with LN have inspired a series of behavioral, physiological, and neuroanatomic studies in nonhuman primates (NHPs) who had LN associated with naturally occurring (22,23,49–55) or experimentally induced (1,10,56–65) infantile strabismus. The common finding of these experiments is that the prevalence and severity of LN correlate systematically with the age of onset and duration of binocular decorrelation in infancy.

The most common clinical cause of binocular decorrelation is strabismus, which in human infants is overwhelmingly esotropic (convergent) (66). Early onset esotropia exceeds exotropia by a ratio of 9:1. Esotropia is also the most common form of naturally occurring strabismus in NHPs (67,68). It may therefore be considered the paradigmatic form of strabismus in primates. However, any prolonged deprivation of normal binocular experience in early infancy can cause binocular decorrelation (e.g., monocular congenital cataract, uniocular high ametropia in hyperopia or myopia, uniocular neonatal vitreous hemorrhage, uniocular corneal clouding, dense bilateral cataracts). In NHP models, monocular deprivation (uniocular amblyopia) or severe binocular deprivation (bilateral amblyopia) (10,57,63) produced by eyelid suturing (the thin translucent eyelid of NHPs mimics a congenital cataract, allowing diffuse luminance to the retina but blocking spatial vision) is also used to generate LN. But an important fact to note is that loss of spatial vision is not required; the majority of human and NHP infants with strabismus alternate fixation initially and have no amblyopia (69). The necessary and sufficient factor is binocular decorrelation, not lack of sharp visual acuity.

Decorrelation durations that exceed the equivalent of 3 months in human infant development result in an LN prevalence of 100% (1,65,70). Perturbing these inputs from the first week of life causes LN, but delaying the perturbation to the time of onset of normal fusion and stereopsis (the equivalent of age 2–4 months in human) is equally effective (71). The severity of the resultant LN corresponds

to the severity of loss of binocular connections between ODCs of opposite ocularity in visual area V1 and the severity of interocular suppression (1,72). Area V1 feeds forward to extrastriate areas MT/MST known to be important for gaze holding and gaze tracking, such as smooth pursuit, optokinetic nystagmus (OKN), and the short-latency ocular following response (73–76).

MALDEVELOPMENT IN V1 IS PASSED ON TO MEDIAL TEMPORAL AND MEDIAL SUPERIOR TEMPORAL AREAS

Visual areas V1, V2 (prestriate cortex), medial temporal (MT), and medial superior temporal (MST) of the cerebral cortex are major components of the conjugate gaze pathway (77). Each of these areas in normal primates contains directionally selective binocular neurons (78–81). MST in each cerebral hemisphere encodes ipsiversive gaze (74,82–84). MST in turn projects downstream to the brain stem visuomotor nuclei that generate eye movements, including the nucleus of the optic tract (NOT), medial vestibular nucleus, and interconnected abducens and ocular motor nuclei (77,85). In primates, subcortical inputs to NOT may play a minor role (for reviews of the physiology of NOT and its role in LN see the work of Mustari and colleagues, as well as Hoffmann) (9,10,86). But the dominant pathway is from MST to brain stem. The dominant role of the cortical pathway, and the minimal role of a subcortical pathway, is reinforced by studies of children. Neuroimaging of visual cortex, combined with eye movement recordings, has shown absence of visually driven pursuit or OKN in cerebrally blind infants (87,88).

One mechanism for the gaze-holding asymmetry would be overrepresentation of nasalward neurons within visual areas V1 through MT in the immature/strabismic cortex. However, directional and binocular responses of neurons in V1, V2, and MT have been investigated in infant monkeys, as well as in monkeys with early onset strabismus, and no overrepresentation of neurons selective for nasalward motion has been found (26,61,89,90). Rather than overrepresentation of nasalward neurons, the mechanism appears to be lack of connectivity of and suppression of temporalward neurons. In strabismic animals, binocular (excitatory) responses are reduced and interocular suppression is increased (89–91). These physiological abnormalities have neuroanatomic correlates. In V1 of strabismic monkeys, binocular connections are deficient (22,23) and interocular metabolic activity is suppressed (53,92,93).

BINOCULAR DECORRELATION UNMASKS AN INNATE NASALWARD MONOCULAR BIAS

LN is always linked to abnormal binocular development in infancy. This important clinical observation motivated the studies of NHPs, which have provided the functional-structural correlations needed to explain the pathophysiology. The translational value of NHP studies cannot be overstated. The NHP studies have provided the pivotal facts necessary to explain one of the most common clinical ocular motor disorders. The NHP studies have also motivated repair of fusion earlier in infancy (94), thereby preventing LN or reducing its severity.

LN is caused by an afferent binocular visual pathway defect. The binocular defect unmasks a directional bias encoded in the cerebral gaze pathways. Normal binocular development (fusion) in the first months of life eliminates the directional bias; abnormal development (maldeveloped fusion) exaggerates the bias. If fusion goes unrepaired in infancy, the directional bias persists permanently throughout adult life (1,95).

A key implication emerging from the NHP studies is that the visual cortex in each cerebral hemisphere is wired innately for nasalward motion. The innate wiring is monocular. To generate temporalward gaze holding, signals must traverse binocular connections, unimpeded by interocular suppression. If normal binocularity fails to develop, the system remains predominantly monocular and asymmetric, incapable of driving temporalward gaze holding or robust temporalward pursuit/OKN (10,43,44,61,66,90). LN is an abnormal monocular bias added on to a normal ipsiversive hemispheric gaze bias.

HYPOTHETICAL SIGNAL FLOW FOR LN

Figure 5 illustrates the mechanism for LN, showing the circuit mediating gaze holding in primates and the role of binocular connections. Shaded structures indicate less active visual and motor neurons caused by occlusion of one eye or interocular suppression. The circuit on the right depicts the pathways and visuomotor component structures in a primate with LN.

The flow is from top to bottom, starting from the monocular visual field (VF) of the fixating (or viewing) RE. The nasal and temporal VFs in primates are unequal in area, with a bias favoring the larger temporal hemifield. Retinal ganglion cell fibers (RGC) from the nasal and temporal retinas decussate at the optic chiasm, synapse at the lateral geniculate nucleus (LGN), and project to alternating monocular RE and LE ODCs in V1. During development, RGCs from the nasal retina outnumber and establish connections earlier than those from the temporal retina. The LGN laminas corresponding to the nasal retina (laminas 1, 3, and 5) contain more neurons and develop earlier than those from the temporal hemiretina (laminas 2, 4, and 6). Within the LGN, the neurons remain monocular, with no binocular interlaminar interaction.

The monocular bias, favoring nasal hemiretinal inputs, is passed on to the ODCs of area V1. In each V1, ODCs representing the nasal hemiretina (temporal visual hemifield) occupy slightly more cortical territory than those

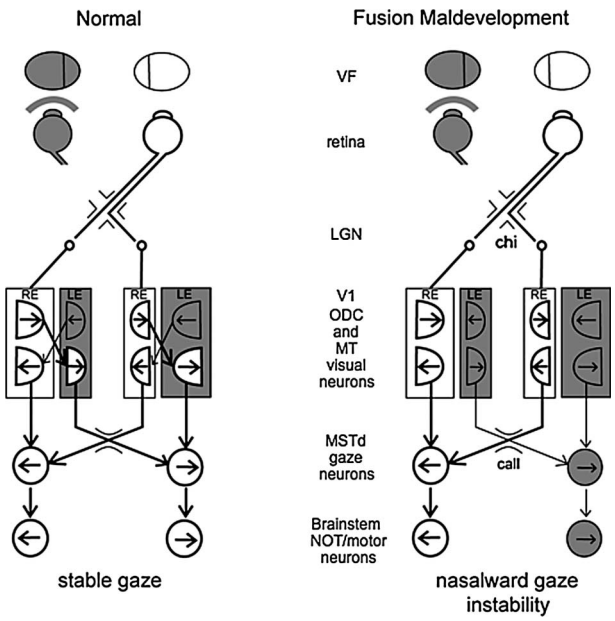

FIG. 5. Neural network diagrams showing visual signal flow for pursuit and gaze holding in strabismic and normal primates. A paucity of mature binocular connections explains behavioral asymmetries evident as asymmetric pursuit/optokinetic nystagmus and latent fixation nystagmus. In all primates, pursuit area neurons in each hemisphere encode ipsilaterally directed pursuit. Signal flow is initiated by a moving stimulus in the monocular visual field (VF), which evokes a response in visual area neurons V1 and MT. Each eye at birth has access, through innate monocular connections, to the pursuit area neurons in MSTd of the contralateral hemisphere. Access to pursuit neurons of the ipsilateral hemisphere requires mature binocular connections. In fusion maldevelopment (right column), retinal ganglion cell fibers from the nasal and temporal hemiretina (eye) decussate at the optic chiasm (chi), synapse at the lateral geniculate nucleus (LGN), and project to alternating rows of ODCs in V1 (visual area rectangles). In each V1, ODCs representing the nasal hemiretina (temporal visual hemifield) occupy slightly more cortical territory than those representing the temporal hemiretina (nasal hemifield), but each ODC contains neurons sensitive to nasally directed and temporally directed motion (half circles shaped like the matching hemifield; arrows indicate directional preference). Visual area neurons, including those beyond V1 in area MT, encoding nasally directed motion are wired innately—through monocular connections—to the pursuit area. In normal primates (left column), binocular connections are present, linking neurons with similar orientation/directional preferences within ODCs of opposite ocularity (diagonal lines between columns). When the subject views with the right eye, visual neurons preferring nasally directed motion project to the left hemisphere pursuit area and visual neurons preferring temporally directed motion project to the right hemisphere pursuit area. Temporally directed visual area neurons gain access to pursuit area neurons only through binocular connections. Call = corpus callosum. Bold lines = active neurons and neuronal projections.

representing the temporal hemiretinas (nasal hemifield), but each ODC contains neurons sensitive to nasalward (leftward) versus temporalward (rightward) visual motion. Receptive field neurons in V1 and MT are simplified here as half circles to match their corresponding hemifields. The arrows indicate the directional preference of the neurons. The visual area neurons (including those beyond V1 in area MT) are sensitive to both nasalward and temporalward motion (26,61,89), but only those encoding nasalward motion are wired innately through monocular connections to gaze (eye motion) neurons in the MST area (congregated in the dorsal-medial portion or MSTd). MSTd in each cerebral hemisphere encodes ipsiversive gaze (74,82–84), which is nasalward gaze in relation to the contralateral eye (leftward for MST in the left cerebral hemisphere and rightward for MST in the right hemisphere) (90).

The only difference between the LN primate's visual cortex and the normal primate's visual cortex is a paucity of binocular horizontal connections (23,72) (compounded by interocular suppression (53,92,93)). The paucity is depicted as a lack of diagonal RE ODC to LE ODC connections, absent in the LN cortex (right side of figure), and present in the normal cortex (left side of figure). In the cortex of normal primates, access to MSTd for temporalward gaze requires binocular connections to homoversive neurons within neighboring ODCs that have opposite ocularity (LE ODC neurons when viewing with the RE). The pathway from V1/MT to MSTd requires efferent projections through the splenium of the corpus callosum (96,97).

MSTd efferents project to the ipsilateral brain stem NOT (85,98) and to ipsiversive-related brain stem structures (medial vestibular nucleus, dorsolateral pontine nucleus, and ocular motor nuclei of cranial nerves 3 and 6).

RECONCILING CURRENT KNOWLEDGE WITH PREVIOUS LN HYPOTHESES IN HUMANS

Based on clinical observations and eye movement recordings in humans, several mechanisms have been proposed as the cause of LN. Ishikawa (99) thought that LN could be explained as a hyperactive stretch reflex of the medial rectus muscles, which drove the viewing eye nasalward. Although the muscular basis is untenable, he drew further attention to the linkage of LN with other nasalward visuomotor biases, notably infantile esotropia.

Dell'Osso et al (2,4) hypothesized that LN arose from a *confusion of egocentric direction* caused by strabismus. Patients with unilateral or alternating strabismus view at any given moment with one eye predominantly. The viewing eye is displaced laterally with respect to the midline of the head. This displacement is not present with binocular fusion. With fusion, the perceptual center (cyclopean eye) coincides with midline. The incongruity between the body midline and the laterally displaced monocular view was

believed to generate a neural command driving the viewing eye toward midline, that is, nasalward. By revising *confusion of egocentric direction* to *unbalanced, infantile, monocular interhemispheric MSTd drive*, the hypothesis of Dell'Osso et al (2,4) can be updated to fit well with current biology. Volitional manipulation of interhemispheric activity can also alter LN direction. Dell'Osso et al (100) reported a monocular patient with LN who could do so by imagining viewing through the lost eye (replaced by an ocular prosthesis).

The notion of unbalanced cerebral hemisphere activity as a cause of nystagmus was emphasized by Sharpe et al (101,102). and by Zee (103). They proposed an imbalance of pursuit *tone* to explain a linear conjugate slow-phase drift of the eyes toward the more active hemisphere in adult patients with unilateral parietooccipital damage and normal binocular vision. Although they did not extrapolate their hypotheses to include a mechanism for LN, their insights may be considered important contributions.

van Dalen (39) pointed out that a subtle form of LN can be evoked in normal adult humans when viewing monocularly by flashing light in a Ganzfeld at high temporal frequencies. A current interpretation would be that by eliminating all gaze-stabilizing and fusional cues, while simultaneously activating visual motion neurons, the Ganzfeld unmasks the vestiges of the infantile nasalward bias. Kommerell and Mehdorn (48) emphasized the association of LN with impairment of temporalward OKN under conditions of monocular viewing. The nasotemporal OKN asymmetry was postulated to cause LN through mechanisms that remained to be worked out. Tychsen and Lisberger (44) postulated a defect in nasotemporal motion sensitivity within extrastriate visual areas MT/MST as the cause of both LN and pursuit/OKN asymmetries in humans with maldeveloped fusion. The work in humans by each of these investigators motivated the NHP experiments reviewed here that have helped to reveal the biology of LN.

REFERENCES

1. **Tychsen L.** Causing and curing infantile eostropia in primates: the role of de-correlated binocular input (an American Ophthalmological Society Thesis). Trans Am Ophthalmol Soc. 2007;105:564–593.
2. **Dell'Osso LF,** Schmidt D, Daroff RB. Latent, manifest latent, and congenital nystagmus. Arch Ophthalmol. 1979; 97:1877–1885.
3. **Dell'Osso LF.** Congenital, latent and manifest latent nystagmus—similarities, differences and relation to strabismus. Jpn J Ophthalmol. 1985;29:351–368.
4. **Dell'Osso LF,** Traccis S, Abel LA. Strabismus: a necessary condition for latent and manifest latent nystagmus. Neuroophthalmology. 1983;3:247–257.
5. **Faucon A.** Nystagmus par insuffisance des droits externes. J Ophthal (Paris). 1872;1:223–229.
6. **Fromaget C,** Fromaget H. Nystagmus latent. Ann Oculis. 1912;147:344–352.
7. **Sorsby A.** Latent nystagmus. Br J Ophthalmol. 1931;15:1–8.
8. **Kestenbaum A.** Clinical Methods of Neuro-Ophthalmologic Examination, 2nd edition. New York, NY: Grune and Stratton, 1961.
9. **Tychsen L.** Binocular vision. In: Hart WM Jr., ed. Adler's Physiology of the Eye: Clinical Applications. 9th edition. St Louis, MO: CV Mosby, 1992:773–853.
10. **Tusa RJ,** Mustari MJ, Das VE, Boothe RG. Animal models for visual deprivation-induced strabismus and nystagmus. Ann NY Acad Sci. 2002;956:346–360.
11. **N.E.I./N.I.H. Committee.** A Classification of Eye Movement Abnormalities and Strabismus (CEMAS). Report of a National Eye Institute Sponsored Workshop. [Internet] Bethesda, MD: National Eye Institute, National Institute of Health; 2001. Available at: http://www.nei.nih.gov/news/statements/cemas.pdf.
12. **Atkinson J.** Development of optokinetic nystagmus in the human infant and monkey infant: an analogue to development in kittens. In: Freeman RD, ed. Developmental Neurobiology of Vision. New York, NY: Plenum, 1979:277–287.
13. **Boothe RG,** Dobson V, Teller DY. Postnatal development of vision in human and nonhuman primates. Ann Rev Neurosci. 1985;8:495–545.
14. **O'Dell C,** Boothe RG. The development of stereoacuity in infant rhesus monkeys. Vision Res. 1997;37:2675–2684.
15. **Brown RJ,** Wilson JR, Norcia AM, Boothe RG. Development of directional motion symmetry in the monocular visually evoked potential of infant monkeys. Vision Res. 1998;38: 1253–1263.
16. **Fox R,** Aslin RN, Shea SL, Dumais ST. Stereopsis in human infants. Science. 1980;207:323–324.
17. **Birch EE,** Gwiazda J, Held R. Stereoacuity development for crossed and uncrossed disparities in human infants. Vision Res. 1982;22:507–513.
18. **Birch EE,** Gwiazda J, Held R. The development of vergence does not account for the onset of stereopsis. Perception. 1983;12:331–336.
19. **Birch EE,** Shimojo S, Held R. Preferential-looking assessment of fusion and stereopsis in infants aged 1 to 6 months. Invest Ophthalmol Vis Sci. 1985;26:366–370.
20. **Gwiazda J,** Bauer J, Held R. Binocular function in human infants: correlation of stereoptic and fusion-rivalry discriminations. J Pediatr Ophthalmol Strabismus. 1989; 26:128–132.
21. **Hubel DH,** Wiesel TN. Ferrier lecture. Functional architecture of macaque monkey visual cortex. Proc R Soc Lond B Biol Sci. 1977;198:1–59.
22. **Tychsen L,** Burkhalter A. Neuroanatomic abnormalities of primary visual cortex in macaque monkeys with infantile esotropia: preliminary results. J Pediatr Ophthalmol Strabismus. 1995;32:323–328.
23. **Tychsen L,** Wong AM, Burkhalter A. Paucity of horizontal connections for binocular vision in V1 of naturally-strabismic macaques: cytochrome-oxidase compartment specificity. J Comp Neurol. 2004;474:261–275.
24. **Chino Y,** Smith EL, Hatta S, et al. Suppressive binocular interactions in the primary visual cortex (V1) of infant rhesus monkeys. Soc Neurosci Abstr. 1996;22(1):645.
25. **Chino YM,** Smith EL III, Hatta S, Cheng H. Postnatal development of binocular disparity sensitivity in neurons of the primate visual cortex. J Neurosci. 1997;17:296–307.
26. **Hatta S,** Kumagami T, Qian J, Thornton M, Smith EL 3rd, Chino YM. Nasotemporal directional bias of V1 neurons in young infant monkeys. Invest Ophthalmol Vis Sci. 1998; 39:2259–2267.
27. **Lowel S,** Singer W. Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. Science. 1992;255:209–212.
28. **Löwel S,** Engelmann R. Neuroanatomical and neurophysiological consequences of strabismus: changes in the structural and functional organization of the primary visual cortex in cats with alternating fixation and strabismic amblyopia. Strabismus. 2002;10:95–105.

29. **Trachtenberg JT,** Stryker MP. Rapid anatomical plasticity of horizontal connections in the developing visual cortex. J Neurosci. 2001;21:3476–3482.
30. **Norcia AM,** Garcia H, Humphry R, Holmes A, Hamer RD, Orel-Bixler D. Anomalous motion VEPs in infants and in infantile esotropia. Invest Ophthalmol Vis Sci. 1991;32: 436–439.
31. **Norcia AM.** Abnormal motion processing and binocularity: infantile esotropia as a model system for effects of early interruptions of binocularity. Eye. 1996;10:259–265.
32. **Brown RJ,** Norcia AM. A method for investigating binocular rivalry in real-time with the steady-state VEP. Vision Res. 1997;37:2401–2408.
33. **Birch EE,** Fawcett S, Stager D. Co-development of VEP motion response and binocular vision in normal infants and infantile esotropes. Invest Ophthalmol Vis Sci. 2000;41: 1719–1723.
34. **Bosworth RG,** Birch EE. Nasal-temporal asymmetries in motion sensitivity and motion VEPs in normal infants and patients with infantile esotropia. J AAPOS. 2003;38:61.
35. **Naegele JR,** Held R. The postnatal development of monocular optokinetic nystagmus in infants. Vision Res. 1982;22:341–346.
36. **Wattam-Bell J,** Braddick O, Atkinson J, Day J. Measures of infant binocularity in a group at risk for strabismus. Clin Vis Sci. 1987;1:327–336.
37. **Jacobs M,** Harris C, Taylor D. The development of eye movements in infancy. In: Lennerstrand G, ed. Update on Strabismus and Pediatric Ophthalmology. Proceedings of the Joint ISA and AAPO&S Meeting Vancouver, Canada June 19 to 23, 1994. Boca Raton, FL: CRC Press; 1994: 140–143.
38. **Tychsen L.** Critical periods for development of visual acuity, depth perception and eye tracking. In: Bailey DB Jr., Bruer JT, Symons FJ, Lichtman JW, eds. Critical Thinking About Critical Periods Baltimore, MD: Paul H. Brookes Publishing Co., 2001:67–80.
39. **van Dalen JTW.** Flash-induced nystagmus: its relation to latent nystagmus. Jpn J Ophthalmol. 1981;25:370–376.
40. **van Die G,** Collewijn H. Optokinetic nystagmus in man. Human Neurobiol. 1982;1:111–119.
41. **Schor CM,** Levi DM. Disturbances of small-field horizontal and vertical optokinetic nystagmus in amblyopia. Invest Ophthalmol Vis Sci. 1980;19:668–683.
42. **Maurer D,** Lewis TL, Brent HP. Peripheral vision and optokinetic nystagmus in children with unilateral congenital cataract. Behav Brain Res. 1983;10:151–161.
43. **Tychsen L,** Hurtig RR, Scott WE. Pursuit is impaired but the vestibulo-ocular reflex is normal in infantile strabismus. Arch Ophthalmol. 1985;103:536–539.
44. **Tychsen L,** Lisberger SG. Maldevelopment of visual motion processing in humans who had strabismus with onset in infancy. J Neurosci. 1986;6:2495–2508.
45. **Tychsen L,** Rastelli A, Steinman S, Steinman B. Biases of motion perception revealed by reversing gratings in humans who had infantile-onset strabismus. Dev Med Child Neurol. 1996;38:408–422.
46. **Westall CA,** Eizenman M, Kraft SP, Panton CM, Chatterjee S, Sigesmund D. Cortical binocularity and monocular optokinetic asymmetry in early-onset esotropia. Invest Ophthalmol Vis Sci. 1998;39:1352–1360.
47. **Fawcett SL,** Birch EE. Motion VEPs, stereopsis, and bifoveal fusion in children with strabismus. Invest Ophthalmol Vis Sci. 2000;41:411–416.
48. **Kommerell G,** Mehdorn E. Is an optokinetic defect the cause of congenital and latent nystagmus? In: Lennerstrand G, Zee DS, Keller EL, eds. Functional Basis of Ocular Motility Disorders. Oxford, United Kingdom: Pergamon Press, 1982:159–167.
49. **Matsumoto B,** MacDonald R, Tychsen L. Constellation of ocular motor findings in naturally-strabismic macaque: Animal model for human infantile strabismus. Invest Ophthalmol Vis Sci . 1991;32(Suppl):820.
50. **Tychsen L,** Leibole M, Drake D. Comparison of latent nystagmus and nasotemporal asymmetries of optokinetic nystagmus in adult humans and macaque monkeys who have infantile strabismus. Strabismus. 1996;4: 171–177.
51. **Tychsen L,** Boothe RG. Latent fixation nystagmus and nasotemporal asymmetries of motion visually-evoked potentials in naturally-strabismic primate. J Pediatr Ophthalmol Strabismus. 1996;33:148–152.
52. **Tychsen L,** Burkhalter A, Boothe R. [Functional and structural abnormalities of the visual cortex in early childhood strabismus]. Klin Monatsbl Augenheilkd. 1996; 208:18–22.
53. **Tychsen L,** Burkhalter A. Nasotemporal asymmetries in V1: ocular dominance columns of infant, adult, and strabismic macaque monkeys. J Comp Neurol. 1997;388: 32–46.
54. **Tychsen L,** Yildirim C, Anteby I, Boothe R, Burkhalter A. Macaque monkey as an ocular motor and neuroanatomic model of human infantile strabismus. In: Lennerstrand G, Ygge J, eds. Advances in Strabismus Research: Basic and Clinical Aspects. London, United Kingdom: Portland Press Ltd., 2000:103–119.
55. **Tychsen L,** Scott C. Maldevelopment of convergence eye movements in macaque monkeys with small and large-angle infantile esotropia. Invest Ophthalmol Vis Sci. 2003; 44:3358–3368.
56. **Bunin G,** Rivera G, Goode F, Hustu HO. Ocular relapse in the anterior chamber in childhood acute lymphoblastic leukemia. J Clin Oncol. 1987;5:299–303.
57. **Tusa RJ,** Repka MX, Smith CB, Herdman SJ. Early visual deprivation results in persistent strabismus and nystagmus in monkeys. Invest Ophthalmol Vis Sci. 1991; 32:134–141.
58. **Tychsen L,** Quick M, Boothe RG. Alternating monocular input from birth causes stereoblindness, motion processing asymmetries, and strabismus in infant macaque. Invest Ophthalmol Vis Sci. 1991;32(Suppl):1044.
59. Serious eye injuries associated with fireworks—United States, 1990–1994. MMWR Morb Mortal Wkly Rep. 1995; 44:449–452.
60. **Tychsen L,** Burkhalter A, Boothe RG. Neural mechanisms in infantile esotropia: what goes wrong? Am Orthopt J. 1996;46:18–28.
61. **Kiorpes L,** Walton PJ, O'Keefe LP, Movshon JA, Lisberger SG. Effects of early-onset artificial strabismus on pursuit eye movements and on neuronal responses in area MT of macaque monkeys. J Neurosci. 1996;16:6537–6553.
62. **Tychsen L,** Yildirim C, Foeller P. Effect of infantile strabismus on visuomotor development in squirrel monkey (*Saimiri sciureus*): optokinetic nystagmus, motion VEP and spatial sweep VEP. Invest Ophthalmol Vis Sci. 1999;40:S405.
63. **Tusa RJ,** Mustari MJ, Burrows AF, Fuchs AF. Gaze-stabilizing deficits and latent nystagmus in monkeys with brief, early-onset visual deprivation: eye movement recordings. J Neurophysiol. 2001;86:651–661.
64. **Angelucci A,** Levitt JB, Walton EJ, Hupe JM, Bullier J, Lund JS. Circuits for local and global signal integration in primary visual cortex. J Neurosci. 2002;22:8633–8646.
65. **Richards M,** Wong A, Foeller P, Bradley D, Tychsen L. Duration of binocular decorrelation predicts the severity of latent (fusion maldevelopment) nystagmus in strabismic macaque monkeys. Invest Ophthalmol Vis Sci. 2008;49: 1872–1878.
66. **Tychsen L.** Infantile esotropia: current neurophysiologic concepts. In: Rosenbaum AL, Santiago AP, eds. Clinical Strabismus Management: Principles and Surgical Techniques. Philadephia, PA: WB Saunders, 1999: 117–138.
67. **Kiorpes L,** Boothe RG. Naturally occurring strabismus in monkeys (*Macaca nemestrina*). Invest Ophthalmol Vis Sci. 1981;20:257–263.

68. **Kiorpes L,** Boothe RG, Carlson MR, Alfi D. Frequency of naturally occurring strabismus in monkeys. J Pedriatr Ophthalmol Strabismus. 1985;22:60–64.
69. **Panel AQoCCPO.** Amblyopia. Preferred practice patterns 1992:1–24.
70. **Wong AM,** Foeller P**,** Bradley D, Burkhalter A, Tychsen L. Early versus delayed repair of infantile strabismus in macaque monkeys: I. Ocular motor effects. J AAPOS. 2003;7:200–209.
71. **Foeller PE,** Bradley D, Tychsen L. Shorter vs longer durations of later-onset infantile strabismus in macaque monkeys. Invest Ophthalmol Vis Sci. 2008;49:1121.
72. **Tychsen L,** Richards M, Wong A, Foeller P, Burhkalter A, Narasimhan A, Demer J. Spectrum of infantile esotropia in primates: behavior, brains and orbits. J AAPOS. 2008;12: 375–380.
73. **Findley LJ,** Antczak FJ. Commentary: how to prepare and present a lecture. JAMA. 1985;253:246.
74. **Dürsteler MR,** Wurtz RH. Pursuit and optokinetic deficits following chemical lesions of cortical areas MT and MST. J Neurophysiol. 1988;60:940–965.
75. **Komatsu H,** Wurtz RH. Relation of cortical areas MT and MST to pursuit eye movements. I. Localization and visual properties of neurons. J Neurophysiol. 1988;60:580–603.
76. **Dennis M,** Spiegler BJ, Obonsawin Mc, Maria BL, Cowell C, Hoffman HJ, Hendrick EB, Humphreys RP, Bailey JD, Ehrlich RM. Brain tumors in children and adolescents—III. Effects of radiation and hormone status on intelligence and on working, associative and serial-order memory. Neuropsychologia. 1992;30:257–275.
77. **Tusa RJ,** Ungerleider LG. Fiber pathway of cortical areas mediating smooth pursuit eye movements in monkeys. Ann Neurol. 1988;23:174–183.
78. **Poggio GF,** Fischer B. Binocular interaction and depth sensitivity in striate and prestriate cortex of behaving rhesus monkey. J Neurophysiol. 1977;40:1392–1405.
79. **Albright TD,** Desimone R, Gross CG. Columnar organization of directionally selective cells in visual area MT of the macaque. J Neurophysiol. 1984;51:16–31.
80. **Orban GA,** Kennedy H, Buillier J. Velocity sensitivity and direction selectivity of neurons in area V1 and V2 of the monkey: influence of eccentricity. J Neurophysiol. 1986; 56:462–480.
81. **DeAngelis GC,** Groh JM, Newsome WT. Organization of disparity selectivity in macaque area MT. Soc Neurosci Abstr. 1996;22(1):644.
82. **Newsome WT,** Wurtz RH, Komatsu H. Relation of cortical areas MT and MST to pursuit eye movements. II. Differentiation of retinal from extraretinal inputs. J Neurophysiol. 1988;60:604–620.
83. **Komatsu H,** Wurtz RH. Relation of cortical areas MT and MST to pursuit eye movements. III. Interaction with full-field visual stimulation. J Neurophysiol. 1988;60: 621–644.
84. **Yamasaki DS,** Wurtz RH. Recovery of function after lesions in the superior temporal sulcus in the monkey. J Neurophysiol. 1991;66:651–673.
85. **Mustari MJ,** Fuchs AF, Kaneko CR, Robinson FR. Anatomical connections of the primate pretectal nucleus of the optic tract. J Comp Neurol. 1994;349:111–128.
86. **Hoffmann K-P,** Distler C. The optokinetic reflex in macaque monkeys with congenital strabismus. In: IV Symposium of the Bielschowsky society for the study of strabismus; 1992; Eye Clinic Heidelberg of the Ruprecht-Karls University. Germany: Aeolus Press; 1992. 46.
87. **Tychsen L.** Absence of subcortical pathway optokinetic eye movements in an infant with cortical blindness. Strabismus. 1996;4:11–14.
88. **Werth R.** Residual visual functions after loss of both cerebral hemispheres in infancy. Invest Ophthalmol Vis Sci. 2007;48:3098–3106.
89. **Watanabe I,** Bi H, Zhang B, Sakai E, Mori T, Harwerth RS, Smith EL 3rd, Chino YM. Directional bias of neurons in V1 and V2 of strabismic monkeys: temporal-to-nasal asymmetry? Invest Ophthalmol Vis Sci. 2005;46: 3899–3905.
90. **Mustari MJ,** Ono S, Vitorello KC. How disturbed visual processing early in life leads to disorders of gaze-holding and smooth pursuit. Prog Brain Res. 2008;171:487–495.
91. **Endo M,** Kaas JH, Jain N, Smith EL III, Chino Y. Binocular cross-orientation suppression in the primary visual cortex (V1) of infant rhesus monkeys. Invest Ophthalmol Vis Sci. 2000;41:4022–4031.
92. **Horton JC,** Hocking DR, Adams DL. Metabolic mapping of suppression scotomas in striate cortex of macaques with experimental strabismus. J Neurosci. 1999;19:7111–7129.
93. **Wong AM,** Burkhalter A, Tychsen L. Suppression of metabolic activity caused by infantile strabismus and strabismic amblyopia in striate visual cortex of macaque monkeys. J AAPOS. 2005;9:37–47.
94. **Tychsen L.** Can ophthalmologists repair the brain in infantile esotropia? Early surgery, stereopsis, monofixation syndrome, and the legacy of Marshall Parks. J AAPOS. 2005;9:510–521.
95. **Tychsen L.** Strabismus: the scientific basis. In: Taylor D, Hoyt CS, eds. Pediatric Ophthalmology and Strabismus, 3rd edition. Edinburgh, United Kingdom: Elsevier Saunders, 2005:836–848.
96. **Pasik T,** Pasik P. Optokinetic nystagmus: an unlearned response altered by section of chiasma and corpus callosum in monkeys. Nature. 1964;203:609–611.
97. **Hoffmann KP,** Distler C, Ilg U. Callosal and superior temporal sulcus contributions to receptive field properties in the macaque monkey's nucleus of the optic tract and dorsal terminal nucleus of the accessory optic tract. J Comp Neurol. 1992;321:150–162.
98. **Mustari MJ,** Fuchs AF. Discharge patterns of neurons in the pretectal nucleus of the optic tract (NOT) in the behaving primate. J Neurophysiol. 1990;64:77–90.
99. **Ishikawa S.** Latent nystagmus and its etiology. In: Reinecke RD, ed. Strabismus. Proceedings of the Third Meeting of the International Strabismological Association, May 10-12, 1978, Kyoto, Japan. New York, NY: Grune and Stratton; 1978:203–214.
100. **Dell'Osso LF,** Abel LA, Daroff RB. Latent/manifest latent nystagmus reversal using an ocular prosthesis: implications for vision and ocular dominance. Invest Ophthalmol Vis Sci. 1987;28:1873–1876.
101. **Sharpe JA,** Lo AW, Rabinovitch HE. Control of the saccadic and smooth pursuit systems after cerebral hemidecortication. Brain. 1979;102:387–403.
102. **Sharpe JA,** Lo AW. Voluntary and visual control of the vestibuloocular reflex after cerebral hemidecortication. Ann Neurol. 1981;10:164–172.
103. **Zee DS.** The ocular motor system. In: Lessell S, van Dalen JTW, eds. Neuro-ophthalmology. Amsterdam, the Netherlands: Excerpta Medica, 1980:137.