There are many types of spontaneous pathological nystagmus with a plethora of classifications, labels and waveforms. Although this can be daunting, nystagmus is a complicated, yet important, sign. Nystagmus has a wide range of associations – from acute neurological disorders to non-progressive visual impairment. Even a ‘little bit’ of nystagmus must be taken seriously, and there is considerable room for error. This article focuses on one of the most common types of nystagmus: latent nystagmus.

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**Learning objective**
Be able to identify and manage children at risk of developing an anomaly of binocular vision, with specific reference to latent nystagmus (Group 8.1.5.)

**About the author**
After studying physics and optics at Imperial College London, Chris Harris obtained his PhD from City University of New York, where he studied the development of human eye movements. In 1989 he set up an eye movement laboratory in Great Ormond Street Hospital, London, carrying out research into abnormal oculomotor development. In 2000, he was appointed professor of neuroscience at Plymouth University. He has published over 100 papers in the area and continues research into visual and motor development. He is honorary visiting professor at the School of Optometry and Vision Sciences at Cardiff University, where he collaborates on studies of nystagmus. He is scientific adviser to Nystagmus Network and co-edited its recent book on nystagmus. He teaches many aspects of vision and eye movements including visual perception on the new Plymouth University Optometry Programme.

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Of the many types of nystagmus, there are two types of developmental nystagmus: 1) infantile nystagmus syndrome (formerly known as congenital nystagmus); and 2) latent nystagmus (also known as fusional maldevelopment nystagmus syndrome). These developmental types of nystagmus have an onset in early infancy and cannot be acquired later. They are due to poorly understood anomalous visual development, often associated with sensory defects, and are extremely refractory to treatment. They contrast with the many other non-developmental types of nystagmus (also known as acquired nystagmus), which are usually secondary to neurological lesions. It is, however, important to recognise that nystagmus in infancy is not automatically infantile nystagmus syndrome or latent nystagmus, since infants can present with the other types of nystagmus due to brain malformations or peri- and post-natal brain damage.

**Latent nystagmus**

Latent nystagmus is typically associated with uniocular neonatal visual defects, particularly infantile (early-onset) esotropia, whereas infantile nystagmus syndrome is typically associated with visual defects in both eyes. However, some infants can exhibit both of these types of nystagmus, which can lead to confusion in diagnosis.

True latent nystagmus is a conjugate jerk horizontal nystagmus that emerges only with monocular occlusion. The slow phase is decelerating or linear and usually beats towards the side of the viewing eye, increasing in intensity with abduction, and decreasing or vanishing in adduction (Figure 1). Thus, latent nystagmus is peculiar and unique in as much as eye movements are normal when both eyes are viewing. Consequently, latent nystagmus is asymptomatic. However, in patients with unequal vision (usually from amblyopia), the nystagmus is manifest with both eyes open, and is called by the oxymoron ‘manifest latent nystagmus’. Some have argued that latent nystagmus is always manifest when eye movements are actually recorded.

Waveforms are typically decelerating, sometimes with a torsional component. In most cases, the nystagmus beats towards the non-amblyopic eye, but this may be overridden by eye dominance. In some cases, the direction of beats may be switched at will, depending on which eye the patient intends to look with, and might reverse in the dark. Most patients with manifest latent nystagmus do not perceive the world as oscillating (oscillopsia) in spite of the incessant retinal image motion. Affected individuals often adopt large head turns to reduce the nystagmus by bringing the viewing eye into full adduction.

The incidence of latent nystagmus is high. About 1% of infants develop infantile esotropia and at least half of these exhibit latent nystagmus. So, conservatively, more than 1:200 infants are expected to develop latent nystagmus, making it by far the most common type of nystagmus. Intriguingly, in a nystagmus survey based in Leicestershire, Sarvananthan et al. reported a prevalence of only 1:16,000. This discrepancy might be because many individuals are asymptomatic, or the nystagmus is either not recorded or considered incidental to esotropia, or mistaken for infantile nystagmus syndrome.

**Infantile esotropia syndrome and monocular OKN asymmetry**

Lang recognised that in children with congenital strabismus there was a strong association of latent nystagmus (57%), dissociated vertical deviation (DVD) (92%), excyclorotation of the non-fixing eye (65%), abnormal head posture (AHP) (70%), and cerebral damage (probably including prematurity) (15%). He also noted that, among patients with latent nystagmus, 99% had congenital strabismus, with orthotropia being extremely rare. He called these associations the congenital strabismus syndrome, which is now known as infantile esotropia syndrome (IES). Cerebral damage is common but no longer considered a cardinal feature. However, IES now includes persistent monocular optokinetic nystagmus (OKN) and smooth pursuit asymmetries, which turns out to be fundamental to our current understanding of IES and latent nystagmus.

It has been shown that the cardinal features of IES are correlated – that is the latent nystagmus intensity (intensity = amplitude x frequency), angle of squint, and degree of monocular OKN asymmetry all tend to be positively correlated with each other. Similar correlations occur in naturally strabismic monkeys. However, identifying a causal mechanism has been elusive. Brodsky’s view is that the cause is subcortical (‘downstairs’), unmasked by cortical maldevelopment.
The pretectal nucleus of the optic tract, by the eye experiencing temporal to nasal optic ocular reflex at low frequencies, and this is driven required to supplement the rotational vestibular system of movement. During head rotation, OKN is temporalward and away from the direction of movement. The asymmetry prevents the eyes being driven in laterally eyed animals. Monocular asymmetry allows laterally eyed animals to handle optic flow during self-motion. In forward motion, both eyes experience nasal to temporal optic flow and image motion is processed in striate and extra-striate cortex.

The ‘downstairs’ atavistic model

Brodsky’s atavistic model is based on the idea that monocular OKN asymmetry reflects a phylogenetically old subcortical system seen in laterally eyed animals. Monocular asymmetry allows laterally eyed animals to handle optic flow during self-motion. In forward motion, both eyes experience nasal to temporal optic flow and the asymmetry prevents the eyes being driven temporally and away from the direction of movement. During head rotation, OKN is required to supplement the rotational vestibular ocular reflex at low frequencies, and this is driven by the eye experiencing temporal to nasal optic flow. The pretectal nucleus of the optic tract, allied to the accessory optic system, provides the neural substrate for the asymmetry in laterally eyed animals (Figure 2a), in which stimulation of the nucleus of the optic tracts elicits OKN with slow phases to the side of the nucleus. The argument is that the neonate is endowed with this phylogenetically old subcortical fully crossed system, but it is superseded during postnatal development by the uncrossed neocortical system (Figure 2b). Brodsky posits that interruption of cortical development effectively unmasks the subcortical system which then persists with monocular asymmetry and nystagmus.

According to this model, the subcortical system is essentially a vestibular-driven system supplemented by the OKN at low frequencies. Consequently, if Brodsky is correct, the OKN should have a slow build-up with a time-constant similar to the vestibular system. However, there is no report that infant OKN has slow build-up. Rapid build-up is the norm, implying that it is not a simple primitive subcortical response. Even in an infant with delayed visual maturation who does not respond to visual objects, OKN is present with prolonged monocular asymmetry but still has a rapid build-up. Latent nystagmus has a very short latency and cannot be attributed to the slow-build-up system. Slow build-up OKN does exist in humans, but it is masked by the smooth pursuit/fast OKN system and only revealed following cerebellar floccular lesions. Thus, contrary to expectation, it seems that the putative subcortical pathway is unmasked, not by cortical lesions, but by failure of the subcortical eye position neural integrator (see later).

Evidence also shows that the cortex has a functional role in young infants. Infants born with absent cerebral function do not exhibit any OKN. Large cortical lesions dramatically affect OKN. In a rare case, focal seizures in the MT/MST area generated slow eye movements in the ipsiversive direction (epileptic nystagmus) from the age of 10 days, clearly showing functioning connectivity between cortex and the brainstem oculomotor centres from an early age.

The ‘upstairs’ cortical model

Tychsen has proposed that monocular OKN asymmetry is embedded in the neonatal cortex because of innate monocular connectivity in V1, MT, and MST (Figure 3). In this model, the crossed pathway from the nasal hemi-retina to the contralateral visual cortex has access to the contralateral MST, which is capable of driving eye movements in the temporal to nasal direction of the viewing eye. Post-natally, binocular connections develop in V1 (leading eventually to stereopsis), and this binocularity also allows nasal to temporal motion sensitivity to develop, which is relayed to the opposite MST via the corpus callosum. Lack of binocular development therefore prevents the nasal to temporal OKN from developing, leading to a temporal to nasal bias. Tychsen further argues that this bias is potentially strabismogenic but binocular fusion prevents esodeviations becoming manifest. If fusion is maldeveloped, esodeviations become manifest (esotropia) and the velocity bias leads to latent nystagmus.

Figure 2 The atavistic model of OKN based on the phylogenetically old lateral eyed system: (A) becoming superseded by frontal-eyed system; (B) with cortical control. Abbreviations: NOT – nucleus of the optic tract; VN – vestibular nucleus; VI – abducens nucleus; III – oculomotor nucleus; hc – horizontal semi-circular canal; MR – medial rectus; LR – lateral rectus; MLF – medial longitudinal fasciculus; χ – chiasm; VCX – visual cortex. Modified and reproduced from Brodsky with permission from Nystagmus Network

Figure 3 Cortical model based on Tychsen. Monocular OKN asymmetry is due to innate monocular connections (black connections). Later developing binocular connections (red arrows). Failure of binocularity and lack of fusion leads to latent nystagmus. Abbreviations: V1 – striate cortex; MT – medial temporal; MST – medial superior temporal; cc – corpus callosum. Modified and reproduced from Tychsen et al with permission
Alexander's law and the neural integrator

A feature of latent nystagmus is that it increases in intensity with abduction of the viewing eye and it is minimal in full adduction. This explains the extreme AHP often observed by patients with manifest latent nystagmus. The important point here is that the nystagmus depends on eye position (in head), and Brodsky has argued that this obeys Alexander’s law whereby spontaneous horizontal vestibular nystagmus (usually due to acute vestibular tone asymmetry) increases in intensity when the eyes move into the beat direction of the nystagmus. The reason for Alexander’s law is non-trivial because one would expect a vestibular signal to drive the eyes (that is, slow phases) at constant velocity in all eye positions. Clearly, some eye position signal is needed to explain Alexander’s law. Robinson et al23 argued that Alexander’s law is an adaptive response by the eye position neural integrator to reduce retinal slip at a given gaze direction (at the price of increased retinal slip in the opposite direction). The neural integrator integrates velocity commands to generate a tonic signal to counteract the viscoelastic forces which would otherwise pull the eye back to the primary position. The neural integrator is under adaptive control via the cerebellar flocculus/paraflocculus, which is itself driven by retinal slip signals emanating from the nucleus of the optic tract via the inferior olive. Thus, the model23 by Robinson et al makes sense in the context of acute vestibular nystagmus, where the pathological retinal slip is reduced adaptively by the neural integrator to reduce image motion.

The problem is that patients with ‘true’ latent nystagmus do not experience retinal slip when viewing with both eyes (or it is quite minimal). In fact, the neural integrator presumably works very well when both eyes have equal vision, and hence there is no adaptive drive to alter the neural integrator’s function. It is only when vision is unequal that latent nystagmus is seen, and therefore Alexander’s law does not provide an explanation. However, the neural integrator may still be crucial in latent nystagmus, because it receives input from cortical motion centres. Thus, lack of uncrossed MST inputs may lead to a monocular failure of integrator function.

Clinical testing

Testing for latent nystagmus should be a routine part of eye examinations. Because of its prevalence, and its associations with visual impairment and cerebral damage, it is also important to investigate for other visuomotor abnormalities, as latent nystagmus is seldom (if ever) idiopathic.

In a patient without clinically manifest nystagmus, occlusion (for example the cover test) will reveal a horizontal nystagmus which beats in the direction of the uncovered eye (and reverses on alternating occlusion). Under monocular viewing, the nystagmus intensity will increase with abduction and decrease, possibly to extinction, in full adduction. The nystagmus is conjugate, which can be confirmed by surreptitiously viewing the covered eye. Eye movement recording, if available, reveals a decelerating waveform. Note that with both eyes viewing, the nystagmus may become manifest in far eccentric gaze beating in the direction of gaze. Presumably, this is due to partial occlusion of the adducting eye by the nasal bridge and should not be confused with end-point or gaze-evoked nystagmus.

With clinically manifest nystagmus, the same procedure is carried out. However, the issue is whether only manifest latent nystagmus

(hence the term fusion maldevelopment nystagmus).

The role of stereopsis is critical for Tychsen’s model, but there is no evidence for a relationship between the development of stereopsis and OKN symmetry.26 Crucially, Shawkat et al showed that infants who were blind in one eye from birth (that is with no possibility of stereopsis or fusion) had no monocular OKN asymmetry, no strabismus, and no latent nystagmus, whereas a comparable group with neonatal unilateral cataracts demonstrated IES, as expected. Therefore, lack of binocularity, per se, cannot be the cause of latent nystagmus.

It appears that inter-ocular rivalry is essential for IES and latent nystagmus, and it is plausible that rivalrous binocular motion could be the culprit, rather than a failure of position symmetry.10 Crucially, Shawkat et al24 showed the culprit, rather than a failure of position that rivalrous binocular motion could be for IES and latent nystagmus, and it is plausible the cause of latent nystagmus.

Sensitivity.25 When each eye has no nasal to nasal to temporal as well as temporal to nasal sensitivity.

To motion in both eyes, and generally requires symmetry.10 Crucially, Shawkat et al24 showed the cause of latent nystagmus.

Figure 4. This wedge depends on vergence angle and is maximised by high-angle esodeviations, implying that esotropia may be an ‘adaptive’ developmental response. In any case, nasal to temporal sensitivity, motion-in-depth can only be resolved for objects which have motion vectors in the temporal to nasal direction for both eyes, as shown by the green ‘wedge’ in Figure 4. This wedge depends on vergence angle and is maximised by high-angle esodeviations, implying that esotropia may be an ‘adaptive’ developmental response. In any case, nasal to temporal sensitivity, motion-in-depth and vergence angle are inextricably linked. They depend not on Tychsen’s pathway, but probably via uniocular projections to area V5 (human MST/MT), where sensitivity to interocular velocity differences has recently been identified.27

It is also not clear whether monkey is a good model of human development. Monkeys, including macaque, have an accessory lateral rectus muscle in parallel with the lateral rectus. This weak muscle has been ignored by the oculomotor community as a vestigial retractor bulbii. However, Boothe et al28 have proposed that the accessory lateral rectus might render monkeys resistant to esodeviations; indeed, naturally strabismic monkeys have a smaller or absent accessory lateral rectus. They further argue that the absence of the accessory lateral rectus in humans could explain the high incidence of human esodeviations.

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is present due to unequal vision (usually amblyopia), or whether there is an additional nystagmus, usually infantile nystagmus syndrome. If the nystagmus has a null point in full adduction (that is, it disappears), then it is likely that the nystagmus is simply manifest latent nystagmus. If the patient is cooperative, VA should be measured monocularly with the viewing eye in full adduction (that is, the patient viewing at the null point), as this will yield the underlying VA in each eye, and reveal any amblyopia un-contaminated by the nystagmus. If the null point is far from full adduction, then infantile nystagmus syndrome or other nystagmus should be suspected.

Infantile nystagmus syndrome should always be suspected in a patient with a known association, for example albinism, aniridia or retinal dystrophy, since it is extremely unlikely that only manifest latent nystagmus is present. For example, the vast majority of albinos (ocular or oculocutaneous) have infantile nystagmus syndrome and many also have latent nystagmus, but this should be labelled as ‘infantile nystagmus syndrome with a latent component’, not manifest latent nystagmus.

Management
Once fully developed, latent nystagmus appears to be irreversible. The main management strategy, therefore, has been early intervention to pre-empt or reduce the nystagmus through good neonatal care, where signs of visual problems can be detected early without lengthy referral delays. The visual outcomes of early removal of neonatal cataracts have been extensively studied, although the effects on latent nystagmus have not always been measured. For unilateral dense cataracts, Birch & Stager30 analysed the effects of early surgical intervention with good compliance to follow-up care. They concluded that intervention ‘dose’ of deprivation, is important. However, caution is needed because post-operative care is complex and aphakia may be an inadvertent switch from deprivational to anisometropic amblyogenesis. The effect of early surgery for strabismus on latent nystagmus is unclear, as most studies on early surgery have not included nystagmus as an outcome. However, Zubcov et al34 have reported that early surgery may be beneficial by reducing manifest latent nystagmus to asymptotic latent nystagmus. Latent nystagmus also has implications for occlusion therapy since it will become manifest or more intense with occlusion of the ‘good’ eye. An alternative approach is to penalise the ‘good’ eye but still maintaining some binocularity, such as with atropine, thereby reducing the effect manifest latent nystagmus.35–37

Conclusion: an evo-devo perspective
From an evolutionary-developmental (evo-devo) perspective, latent nystagmus is a remarkably clear example of developmental plasticity. It cannot be acquired later in life, and only occurs following abnormal environmental exposure very early in life. There is no cure or undoing of the anomalous wiring of the brain. The only available tactic is to modify the visual environment as early as possible (surgery, occlusion therapy) in the hope of at least partially reversing the anomalous development and equalising vision and rendering the latent nystagmus less manifest. However, very early diagnosis is paramount. Latent nystagmus seems inextricably linked to infantile exotropia, development of motion sensitivity and binocularity. But stereopsis (or its lack) cannot be the explanation (or at least not the sole cause). The development of fusion and interocular velocity differences seem more likely candidates, but remain to be explored.

Figure 4 Illustration of the temporal to nasal (t-n) wedge for motion-in-depth mediated by inter-ocular velocity differences. Any velocity vector towards the eyes must fall within the green wedge to be resolved by the t-n responses of both eyes. Outside this wedge one or both eyes experience nasal to temporal (n-t) stimulation, and the velocity vector cannot be resolved if n-t sensitivity is absent. The larger the vergence angle, the thicker the wedge, which would be maximised by very large angle isopteria before six weeks had a good VA outcome, but progressively poorer outcomes the later the intervention. However, there was no mention of nystagmus in their study. Abadi and colleagues31 showed that surgery even at three weeks did not prevent nystagmus (both manifest latent nystagmus and infantile nystagmus syndrome) from developing, implying a very early critical period. For bilateral cataracts, the latent period for good VA outcome appears to be longer, up to about 10 weeks,32 but again the Abadi study showed that surgery at four weeks did not prevent nystagmus. A more recent study by Young et al35 also concluded that early surgery does not prevent nystagmus. The likelihood of nystagmus decreases with milder cataracts, consistent with the notion that the overall ‘dose’ of deprivation, is important. However,