THE RELATIONSHIP BETWEEN INFANTILE STRABISMUS AND LATENT NYSTAGMUS

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SUMMARY

The so-called infantile strabismus syndrome consists, among other signs, of (1) strabismus, (2) a defect of pursuit and optokinetic tracking with particular involvement of temporally directed responses on monocular viewing, (3) latent nystagmus and (4) adduction preference of the fixating eye. The following causal relationship between these three phenomena is suggested. (1) Binocularity in the visual cortex is impaired, either as a primary defect or as a consequence of misalignment of the eyes. (2) The reduced binocularity prevents maturation of signal transmission from the visual cortex to the brainstem such that slip control is evident in poor pursuit and optokinetic responses, particularly to monocular, temporally directed stimuli. (3) The asymmetry of the pursuit and optokinetic systems is also evident in latent nystagmus which reflects a tonic preponderance, directed nasally with reference to the fixating eye. The directional preponderance drives the slow phases of latent nystagmus if the visual input is unbalanced in favour of one eye. Because of the maldeveloped slip control latent nystagmus is not inhibited by visual contours. When both eyes are open the better-functioning nasally directed pursuit and optokinetic control systems of the two eyes complement each other and largely prevent drifting of the eyes. The defect responsible for the abnormal motor control cannot be located between the retina and the visual cortex because perception of motion is only slightly impaired and a nasal-temporal asymmetry of the motion VEP, typically encountered in infantile strabismus, does not correlate quantitatively with the asymmetry of the motor control. Rather, the defect is located between the cortex and the brainstem. (4) Adduction preference of the fixating eye with a compensatory headturn is due to a gaze-evoked component added to the latent component of the nystagmus. The gaze-evoked component is a purposeful reaction that allows dampening of the nystagmus in adduction at the expense of an increase in abduction.

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The occurrence of early onset strabismus, nasal–temporal asymmetry in smooth tracking responses, latent nystagmus (LN) and adduction preference of the fixating eye are highly correlated.[1–11] Therefore, the combination of these phenomena (among others) has been defined by Lang[12] as a syndrome, the so-called congenital squint syndrome. Because strabismus is rarely present at birth and usually becomes manifest during the first 6 months of life, the term 'infantile strabismus syndrome' may be more appropriate.

Although a common cause for all three phenomena should be given consideration, a causal interdependence between them appears to be more likely. At a symposium of the German Ophthalmological Society in 1977, van Hof - van Duin[13,14] suggested that the reduced binocularity caused by strabismus could prevent maturation of the smooth tracking systems, in that the nasal–temporal asymmetry in pursuit and optokinetic responses, which is a normal feature in the first few months of life, remains as a permanent defect. We proposed at the same symposium that the nasal–temporal asymmetry of the pursuit and optokinetic systems results in LN.[15,16] The basic idea of this hypothesis is still valid. However, we now formulate the hypothesis with a slight modification, suggesting that only one of the two control mechanisms normally contributing to smooth pursuit remains poorly developed, namely the control of slip across the retina, whereas the control of position with respect to the fovea is intact. We further suggest that both asymmetry of the smooth tracking responses and LN are due to a maldevelopment of slip control.

Hypothesis

1. Binocularity in the visual cortex is impaired, either as a primary defect or as a consequence of misalignment of the eyes.

2. The reduced binocularity prevents maturation of signal transmission from the visual cortex to the brainstem such that slip control of the retinal image remains maldeveloped. The maldeveloped slip control is evident in poor pursuit and optokinetic responses, particularly to monocular, temporally directed stimuli.
3. The asymmetry of the pursuit and optokinetics systems is also evident in LN which reflects a tonic preponderance, directed nasally with reference to the fixating eye. Because of the maldeveloped slip control LN is not inhibited by visual contours.
4. Adduction preference of the fixating eye with a compensatory headturn is due to a gaze-evoked component added to the latent component of the nystagmus. The gaze-evoked component is a purposeful reaction that allows dampening of the nystagmus in adduction at the expense of an increase in abduction.

ASYMMETRY IN PURSUIT AND OPTOKINETIC RESPONSES

The asymmetry in pursuit and optokinetic responses is defined as a reduction of responses to monocular tracking stimuli directed to the temporal side, while the responses for nasally directed stimuli are normal or less reduced. Healthy infants show such an asymmetry,[17–21] but the asymmetry disappears by about 6 months of age if signs of normal binocularity appear.[17,19] In adults, a slight nasally directed preponderance is only observed if optokinetic stimulation is confined to the temporal hemifield; this asymmetry is counterbalanced by a temporally directed preponderace of the nasal hemifield.[22]

Van Hof - van Duin suggested that the reduced binocularity caused by strabismus could prevent maturation of the smooth tracking systems.[13,14] This hypothesis is supported by the persistence of nasal–temporal asymmetry in each eye in cats which had been deprived of binocular vision by unilateral lid suture early in life.[13,23] The crucial factor in producing asymmetry in pursuit and optokinetic responses appears to be the reduced binocularity rather than monocular or binocular deprivation. Amblyopia is not a prerequisite for the asymmetry.[24–28] Cats rendered exotropic, but not amblyopic, by early surgery, show reduced optokinetic responses, predominantly in the temporal direction.[29] In monkeys deprivation of binocular vision by alternating lid suture or bilateral lid suture immediately after birth results in a complete defect of the temporally directed smooth tracking systems.[30,31] In the monocularly deprived, i.e. amblyopic, monkey a nasal-temporal asymmetry is present when the deprived eye is stimulated, whereas stimulation of the non-deprived eye results in normal optokinetic responses.[32]

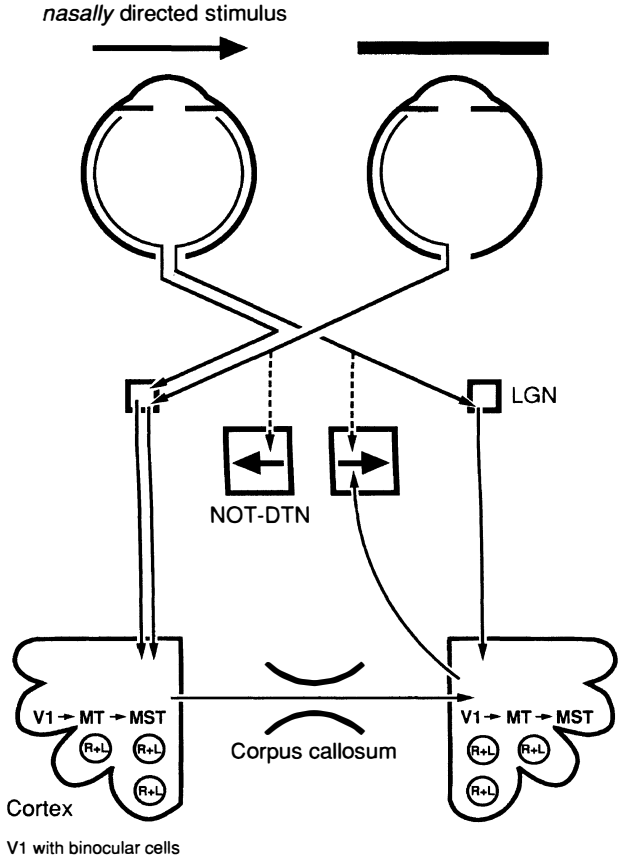
Neurophysiological Evidence

On the basis of microelectrode recordings in cat and monkey it has been suggested that the asymmetry in the optokinetic and pursuit systems is due to a maldevelopment of the cortical projection to the NOT–DTN (Fig. 1) The NOT–DTN is an important relay station of the optokinetic and also for the pursuit system that receives direct input from the contralateral eye and indirect input from both eyes via both occiptal lobes.[38–40] Lesions of the visual cortex dramatically reduce the optokinetic response to temporally directed motion under conditions of monocular viewing in the cat[38,41] and in the monkey.[42] Dark rearing of cats also results in asymmetry in the smooth tracking systems and may be equivalent to a surgical lesion of the visual cortex.[14,43] The relative preservation of responses to nasally directed motion is due to the direct subcortical projection from the retina to the contralateral NOT–DTN. This has been demonstrated in cat[38] and in monkey.[44] In the normal adult human, the subcortical projection alone seems to be insufficient to drive the NOT–DTN, as most critically blind patients do not show any optokinetic response.[45] But the relative preservation of responses to nasally directed stimuli in patients with incomplete bilateral occipital lobe destruction could be due to remnants of the subcortical projection to the NOT–DTN which might have been released from cortical control.[46]

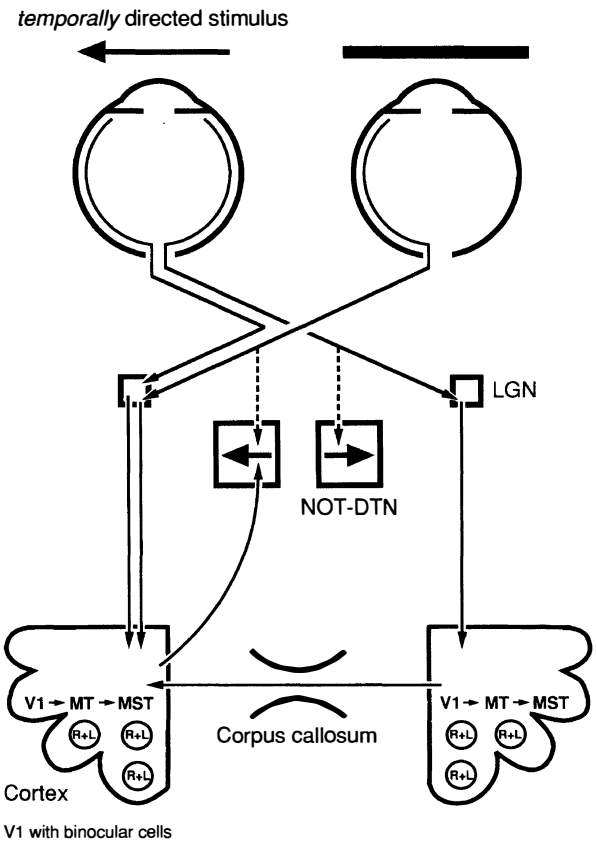
In primates NOT–DTN is not the only relay station for smooth tracking. The DLPN (dorsolateral pontine nucleus) is also very important, particularly for pursuit of small objects.[47] DLPN receives input from the visuomotor cortex (MT and MST corresponding to V5) and from the NOT–DTN.[34] It seems possible that maturation of the cortical input to NOT–DTN requires a gating input from the retina, but neurophysiological data to support this notion are still lacking.

Electrophysiological Evidence

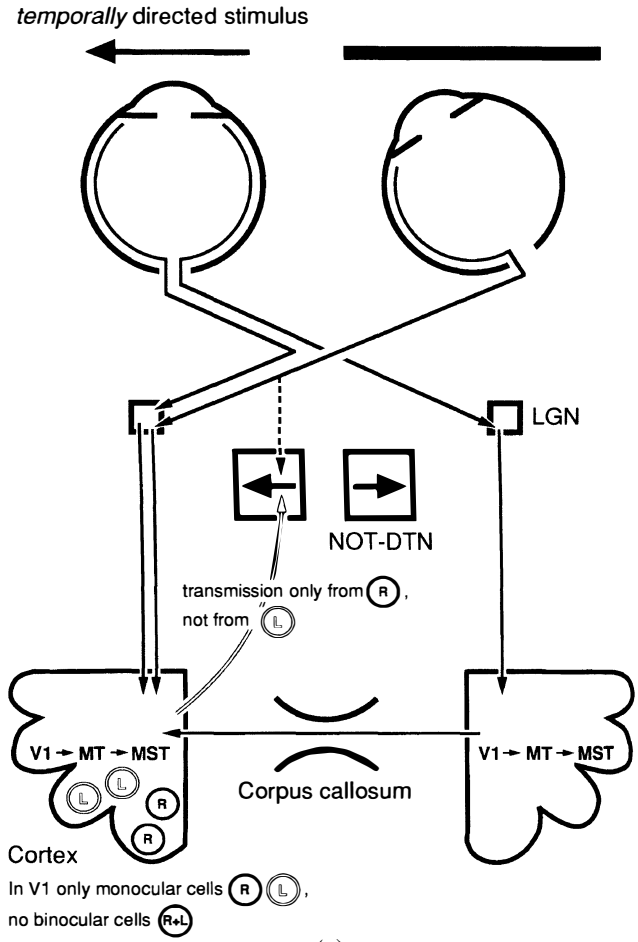
The hypothesis demonstrated in Fig. 1c states that the impairment of temporally directed tracking is due to a defect in the transmission of motion signals from the visual cortex to the brainstem, and does not imply a defect between the retina and the visual cortex. Norcia *et al.*[48] challenged this hypothesis because they found a nasal–temporal asymmetry of motion visual evoked potentials (motion VEP) in patients with infantile strabismus and suggested on these grounds that the optokinetic asymmetry might be due to a defect in the transmission of motion signals between the retina and the visual cortex. We performed a similar experiment in 20 patients with infantile esotropia, asymmetry of the monocular optokinetic nystagmus and LN.[49] Only 8 of the 20 patients showed a clear difference between the VEPs



(a)



(b)



(c)

Fig. 1. *Pathways of horizontal pursuit and optokinetic responses in the normal human (a and b) and in the case of infantile esotropia (c). The NOT (nucleus of the optic tract) and the DTN (dorsal terminal nucleus the accessory optic tract) are located in the pretectum lateral to the quadrigeminal plate. Stimulation of NOT-DTN evokes ipsilaterally directed pursuit and optokinetic responses (arrows). NOT-DTN receives subcortical and cortical input. In animals with little binocular vision, such as the rabbit, NOT-DTN is restricted to subcortical input from the contralateral eye. This is the reason why, in the rabbit, smooth tracking movements of both eyes directed to the right can be elicited only from the left eye, and vice versa. The subcortical pathway 'inherited' from the rabbit also exists in humans,[73] but, most likely, plays a role only the first 3 months of life. After this time the cortical pathway matures and provides a projection from each eye to both NOT-DTNs. (a) The projection from the left eye to the contralateral NOT-DTN which enables nasally directed smooth tracking. (b) The connection to the ipsilateral NOT-DTN which enables temporally directed smooth tracking.[33,34] (c) The situation in infantile esotropia according to the hypothesis of Hoffmann.[34-36] Temporally directed stimuli cannot be transmitted to the ipsilateral NOT-DTN. Maturation of this function would have required an early match (during the first 3 months of life) between the action potentials coming via cortex from the left eye and those coming through the 'inherited' subcortical pathway from the right eye.[36,37] This match was not established because binocular cells were lacking in the visual cortex.*

evoked by back and forth movements with a mirror-like asymmetry between the two eyes (phase shift 180° ± 20°). There was no significant correlation between the degree of VEP and optokinetic asymmetries. Therefore, we assume that the VEP asymmetry does not reflect the primary cause of the optokinetic asymmetry. We considered that the VEP asymmetry might in part be a consequence of LN typically released under monocular stimulation, and therefore looked for a model condition to test this possibility. Upbeat and downbeat nystagmus are ideal for this purpose since they are acquired, not inhibited by fixation, and combined with good binocular vision. In such patients we found a marked up-and-down asymmetry of the motion VEP, supporting our suspicion.[49] However, some asymmetry of the motion can be found in normal babies during the first few months of life and in patients with infantile strabismus who do not have LN.[48] This shows a genuine defect of signal transmission between the retina and the cortex, probably related to undeveloped binocularity, but this defect is probably too small account for the asymmetry of the eye movements.

Psychophysical Evidence

Several studies of patients with infantile strabismus show that motion perception is intact or only slightly impaired. We studied a patient with a nasal–temporal asymmetry so marked that temporally directed smooth tracking movements could not be elicited at all. This patient was nevertheless able accurately to estimate various velocities in that direction.[50] This result is compatible with a study conducted by Tychsen and Lisberger[26] who presented a nasally or temporally moving single target to patients with infantile strabismus whilst they were fixating a central stationary target. The ability to discriminate differences in velocity was normal when nasally and temporally directed motions were considered separately. Only when the patients compared target speed in the two directions did they judge temporally directed stimuli to be slightly slower than nasally directed. Tychsen and Lisberger regarded this perceptual asymmetry as an indication of a primary defect in the retino-cortical pathway, but an alternative interpretation is possible. Since it is likely that their patients had 'manifest LN' due to suppression of their squinting eye, as most patients with LN have,[1,51,52] they may have adapted to unidirectional slip of the retinal image in everyday life and therefore underestimated temporally directed motion. This idea is supported by recent work of Shallo-Hoffmann *et al.*[74]

Contrast sensitivity for perceived motion in strabismus patients with a nasal–temporal asymmetry of the optokinetic nystagmus has been found to be symmetrical.[24]

LATENT NYSTAGMUS

LN is defined as a jerk nystagmus whose rapid phases are directed to the side of the visually dominant eye. With the left eye occluded the slow phases are directed to the left and with the right eye occluded the slow phases are directed to the right. It has been suggested that the term 'latent nystagmus' should be reserved for waveforms with a linear or an exponentially decreasing velocity of the slow phase, whereas cases with an increasing velocity of the slow phase should be defined as 'congenital nystagmus with a latent component'.[52,53] Apparently, there is some overlap between congenital nystagmus and LN both in patients[54] and in experimental monkeys.[30,31]

The intensity of LN can vary spontaneously,[55] and during occlusion therapy for strabismic amblyopia LN can decrease considerably in a few days.[56] In darkness the drift bias of the eyes depends on whether the patient has been using his or her right or left eye for fixation prior to being in darkness.[57] Cognitive factors also modify the LN. For instance, the slow phases can be reversed if the patient alternately occludes his or her right and left eye in total darkness,[16,45,58–60] and some patients are able to manifest their LN at will in the presence of visual contours.[61]

We suggest that LN reflects a directional preponderance in the tonic neural activity of the pursuit and optokinetic systems. Because of the maldeveloped slip control, evident in poor smooth tracking responses, LN is not inhibited by visual contours.

This idea is based on an analogy with 'hemispheric' nystagmus. Patients with hemispheric lesions typically show an ipsilateral defect of pursuit and optokinetic responses[45] and a nystagmus with slow phases directed to the opposite side.[62] Similar to LN, hemispheric nystagmus is not inhibited by visual contours because slip control of the retinal image is not available. A unilateral lesion of the vestibular system also results in a directional preponderance, but the vestibular nystagmus is inhibited by visual contours if the pursuit and optokinetic control systems have remained intact.

The directional preponderance in the pursuit and optokinetic systems drives the slow phases of LN if the visual input is unbalanced in favour of one eye. Occlusion of one eye causes such an imbalance. When both eyes are open the better-functioning nasally directed smooth tracking systems of both eyes complement each other and largely prevent drifting of the eyes.

In support of our hypothesis Tychsen and Lisberger[26] found a high correlation between the intensity of LN and the magnitude of pursuit asymmetry,

although part of this correlation may have been due to a mere addition of the LN and the pursuit response.[63] Comparing LN with the asymmetry in full-field optokinetic nystagmus, a clear correlation is not obvious,[54,64,65] but it may well be that the asymmetry in pursuit of a small target and the optokinetic responses to small stimulus fields[24,59] are more relevant to LN than the responses to large stimulus fields. Besides, our hypothesis does not require a high correlation between the intensity of LN and the asymmetry of smooth tracking, and the finding that not only temporally, but also nasally directed tracking responses are reduced in some LN patients[54,64] is compatible with our hypothesis. Neither is the fact at variance with our hypothesis that normal infants show a nasal–temporal asymmetry of smooth tracking without having LN.[17–20] The spontaneous activity of NOT–DTN neurons in newborn kittens is very low and develops only very gradually.[36] Accordingly, we assume that the directional preponderance reflected in LN develops only gradually if the cortical input to NOT–DTN fails to mature.

LN patients are able to keep the fixating eye close to a moving target, even when monocularly tracking a target that moves in the temporal direction. How can this be achieved if slip control of the retinal image is not available? We suggest that LN patients track a moving target by controlling the position of the retinal image relative to the fovea. Normals employ two control variables when they pursue a moving target: the position of the retinal image in relation to the fovea[66,67] and the slip across the retina. Under artificial conditions such as an after image stabilised on the retina slightly away from the fovea, position control alone suffices to elicit smooth tracking.[66] In patients with congenital nystagmus the effectiveness of position control has been demonstrated.[68] In patients with LN the role of position control in tracking moving targets remains to be explored.

Qualifications

Although early deprivation of binocular visio appears to be an important pathogenetic factor of optokinetic asymmetry and LN, a lack of binocular vision is not an absolute determinant of LN and, conversely, the presence of binocular vision does not preclude LN absolutely. We have seen a patient with unilateral hypoplasia of the optic nerve who has congenital squint and very likely never had binocular vision. Nevertheless, the nasal–temporal asymmetry in the smooth tracking responses was very subtle and LN was absent on careful ophthalmoscopic examination. On the other hand we have seen exceptional patients with LN who had no overt strabismus on cover testing and had binocular vision with only slightly reduced stereopsis. These observations show that factors other than defective binocular vision play a role in the pathogenesis of LN. These factors can compensate or aggravate the condition.

Our hypothesis does not concern the question whether infantile strabismus is caused primarily by an inability to establish binocularity in the visual cortex or by a defect in motor fusion.[69] Both possibilities exist and may even overlap in the same patient.

GAZE-EVOKED COMPONENT OF THE NYSTAGMUS AND COMPENSATORY HEADTURN

In many patients with infantile strabismus the nystagmus increases when the fixating eye is abducted and decreases when it is adducted (Alexander's law or, in bioengineers' terms, 'the integrator is leaky'). To make use of the nystagmus minimum the patient adopts a compensatory headturn. The gaze-evoked component of the nystagmus may be regarded as a purposeful reaction in that it allows the patient to dampen his or her nystagmus by bringing the fixating eye in an adducted position. This advantage may be so important that the patient puts up with an increase in the nystagmus in abduction and a compensatory headturn. This, admittedly teleological idea is based on analogous findings in vestibular nystagmus, which also obeys Alexander's law.

ALTERNATIVE HYPOTHESES

Tychsen and Lisberger[26] suggested that LN might constitute a tonic drive which leads to convergent strabismus. This hypothesis appears unlikely since the nystagmic drift is conjugate and nasally directed only in the viewing eye, while the non-viewing eye drifts temporally. Moreover, asymmetry in the smooth tracking systems and LN also occur in patients who have had divergent strabismus from infancy (Roelofs[1] and our own experience).

Lang[70] suggested that LN may be due to a preponderance of the nasal half of the retina over the temporal half. However, this hypothesis fails to explain why there are slow drifts towards the allegedly preponderant half of the retina. One would rather expect rapid movements, in analogy to acquired field defects where the preserved area of the retina is acquired by saccades. Moreover, in some patients the whole waveform of the LN is executed with the target imaged on the temporal retina.[53] This finding cannot be reconciled with the idea that LN is driven by a preponderance of the nasal retina. Comparing the pupillary response to a light spot 5° in diameter, no significant difference between the nasal and temporal retina could be demonstrated in patients with LN.[71]

Dell'Osso *et al.*[52] advanced the hypothesis that switching the egocentric localisation from one esotropic eye to the other may cause the slow phases of the LN. This explanation appears unlikely because there are no other conditions, such as pastpointing in patients with an eye muscle palsy, where a change in egocentric localisation is associated with a slow drift of the eyes.

Whether or not proprioception plays a role in the pathogenesis of LN, as suggested by Ishikawa,[72] has remained speculative.

Key words: Strabismus, Latent nystagmus, Optokinetic nystagmus, Visual evoked potential (VEP).

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