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Review Article

Does dominance of crossing retinal ganglion cells make the eyes cross? The temporal retina in the origin of infantile esotropia – a neuroanatomical and evolutionary analysis

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ABSTRACT.

A closer look at the evolution of the eye and the brain provides a possible explanation for both the origin of infantile esotropia and its motor characteristics. In the course of evolution, the eyes have moved from a lateral to a frontal position. Consequently, the monocular visual fields started to overlap resulting in a binocular visual field. In lateral-eyed animals, the retinae project to the contralateral visual cortices only. These projections are also found in binocular mammals and birds with binocular visual fields but in addition there are uncrossed projections from the temporal retinae to the visual cortex. The partial chiasmal decussation and the corpus callosum provide the necessary structure that allows binocular vision to develop. Disruption of normal binocular development causes a loss of binocularity in the primary visual cortex and beyond. Beyond the primary visual cortex, the contralateral eye dominates while the temporal retinal signal appears to lose influence. Loss or absence of binocular vision in infantile esotropia may be caused by inadequate retinotopic matching between the nasal and temporal retinal signals like in albinism with an abnormal or asymmetric chiasmal decussation or agenesis of the corpus callosum. Dominance of the crossing retinal signal might also explain the motor characteristics of infantile esotropia (asymmetric OKN, latent nystagmus, DVD). A normal binocular cortical signal will predominate over the evolutionary older, originally non-binocular, retinal projections to the superior colliculi (CS) and the accessory optic system (AOS). A suppressed temporal retinal signal paves the way for the re-emergence of eye movements driven by one eye, as in lateral-eyed non-binocular animals.

Key words: chiasm – dissociated vertical divergence – infantile esotropia – strabismus – temporal retina

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Introduction

Mammals, birds and modern reptiles evolved from the Captorhinidae, or stem reptiles, over 300 million years (Carroll 1988). Many species are lateral-eyed, each eye viewing the ipsilateral visual field. The retina projects entirely to the contralateral side of the brain. In frontal-eyed, binocular species, like predatory birds and primates, the brain also receives input from the contralateral fields via uncrossed fibres. In humans, both nasal retinae are sufficient to view the entire visual field. Contrary to non-binocular species, the visual cortex of binocular species receives additional input from the temporal retinae.

Binocularity appears dependent on the partial decussation of the retinal ganglion cells at the chiasm, thus feeding one side of the brain with information from the nasal retina of the contralateral eye and from the temporal retina of the ipsilateral eye (Petros et al. 2008). Corresponding retinal fibres project to layer IV B of the primary visual cortex allowing to analyse disparity and promote fusion and stereopsis.

Fish, for instance, have laterally positioned eyes, and the retinal ganglion cell fibres crossover completely at the chiasm precluding the detection of disparity and therefore fusion and stereopsis. Nevertheless, incomplete decussation itself is not a prerequisite for binocular vision. Predatory, frontal-eyed birds also have completely decussating fibres at the chiasm but their temporal retinal fibres cross over a second time from the dorsal lateral geniculate nucleus and then project to the visual 'wulst' where binocular integration occurs (Husband & Shimizu 2001).

Leporé et al. (1992) demonstrated that other structures than the chiasm

may enable binocular vision in cats. Sectioning all crossing fibres at the midline of the chiasm did not appear to affect disparity detection to a great extent.

Binocular vision is also dependent on the corpus callosum, a structure found only in placental mammals. Its evolutionary origin is possibly related to the midline fusion of sensory cortical areas. Only mammals show a topographical organization of the sensory cortex (Aboitiz et al. 1992). In the central vertical meridian of the retina, decussating and non-decussating retinal fibres overlap (Fukuda et al. 1989). Signals from this narrow strip, representing the vertical centre, will only reach the contralateral visual cortex via the temporal retinal fibres and the corpus callosum. So, hemidecussation in the chiasm enables a direct comparison of the nasal and the temporal retinal input in the visual cortex while the corpus callosum adds the contralateral temporal signals from the central visual field (Aboitiz & Montiel 2003).

In binocular mammals, binocular vision probably results from the convergence and integration of three signals: (i) the ipsilateral temporal hemiretina, (ii) the contralateral nasal hemiretina and (iii) the central part around the vertical centre in the contralateral uncrossed retinal ganglion cell pathway relayed via the corpus callosum.

Sensory fusion probably results from the imposition of the callosal central vertical meridian onto the central vertical meridian relayed directly from the lateral geniculate body. The 'callosal visual field' appears to set the boundaries for the fusion range. In cats, the callosal visual field subserving fusional convergence subtends twice the angle of the field subserving divergence, similar to the fusional convergence/divergence ratio in humans (Quoc et al. 2011).

The chiasm and the corpus callosum are part of the retinal projections to the visual cortex (via the lateral geniculate bodies of the thalamus). The primary visual cortex projects into the temporal cortex ('ventral stream') and the parietal cortex ('dorsal stream'). The ventral stream is mainly parvocellular and associated with object recognition, while the dorsal stream is mainly magnocellular and involved in spatial awareness.

Apart from the visual cortex, the retina also projects to the superior colliculi and from the colliculi to the pulvinar thalami. Via the pulvinar, there is a pathway to the magnocellular system in the parietal cortex which could explain the phenomenon of blind sight.

In lateral-eyed birds, the pathway from the retina to the pulvinar is much more developed than the one to visual cortex via the lateral geniculate bodies. In predatory birds, the reverse applies (Husband & Shimizu 2001). It has been demonstrated that even in different primate taxa, an increase in convergence of the orbits correlates with an increase in visual brain structures, specifically the parvocellular system (Barton 2004). The degree of binocularity of a species determines the size of the brain, and an increase in binocular visual field correlates with an increase in the parvocellular system (part of the retino-geniculo-cortical projections).

There is a third pathway from the retina which projects to the terminal nuclei of the accessory optic system in the brain stem. This pathway facilitates the optokinetic reflex and supports the vestibular system in maintaining a stable view of the outside world. Lateral-eyed species usually demonstrate well-developed vestibulo-ocular and optokinetic reflexes. In binocular species, the cortically initiated smooth pursuit movements and vergence predominate (Mustari et al. 2008).

During the evolution, the laterofrontal shift of the eye position correlates with the increase of the parvocellular pathway from the retina to the visual cortex via the lateral geniculate nucleus (LGN). In addition, the corpus callosum emerges while the cortically initiated smooth pursuit movements start to predominate over the optokinetic reflexes. Neuroanatomically, this changing hierarchy is illustrated by the afferent projections of one of the nuclei of the accessory optic system: the nucleus of the optic tract (NOT). In lateral-eyed species, the NOT is reached from the contralateral retina. In binocular species, this pathway is supplemented by multiple binocular projections from the visual cortex (Hoffmann & Stone 1985; Hoffmann et al. 1992; Mustari et al. 2001).

Development of Cortical Binocularity in Infantile Esotropia

Both esotropia induced by prisms or surgery in the sensitive postnatal period and infantile esotropia change the binocular response of neurons in the primary visual cortex dramatically (Crawford & von Noorden 1980). After early surgically induced strabismus, neurons in the primary visual cortex, area 17, of kittens were found to be responsive to one eye only (Hubel & Wiesel 1965). An approximately equal representation of both eyes was found in both hemispheres. These results have often been confirmed, although a small bias of the non-operated eye in the ocular dominance columns sometimes occurred (Berman & Murphy 1982; Freeman & Tsumoto 1983; Sireteanu & Best 1992). Also most cortical neurons distal to area 17, the extrastriate cortex, could exclusively be triggered by one eye (Chino et al. 1988; Sireteanu & Best 1992). An equal representation of both eyes, however, is not found in the extrastriate cortex. The large majority of neurons in, for example, area 18 respond to the contralateral eye exclusively. In contrast to this huge contralateral dominance, only a slight dominance of the non-operated eye was found (Schroder et al. 2002). The ipsilateral signal, with an origin in the temporal retina, appears to lose competition between afferents distal to area 17. In electrophysiological studies, specifically cortical neurons representing the temporal retina were found to be unresponsive to a stimulus from the squinting eye (Kalil et al. 1984). In the early postnatal period, crossing nasal retinal afferents were found to be far less vulnerable than temporal uncrossed retinal afferents (Tumosa et al. 1982; Bisti & Carmignoto 1986). Hemiretinal suppression of only the temporal retina is demonstrated under binocular viewing conditions in squint (Joosse et al. 1999).

The corpus callosum appears to be of pivotal importance in the binocular destiny of cortical neurons. Sectioning crossing retinal ganglion cell neurons at the midline of the optic chiasm of strabismic cats restores responsiveness of cortical neurons to the squinting eye. The binocular response was restored

after sectioning all crossing retinal ganglion cells (Di Stefano & Gargini 2002). Apparently, in strabismus, the ipsilateral non-decussating projection from the temporal retina is suppressed.

Could–Maldevelopment of Fusion Pathways Cause Infantile Esotropia?

In 1903, Worth postulated a cerebral centre for binocular vision and fusion. Malfunctioning of this centre, he assumed, may cause strabismus. Much later, it was suggested that sensory features of infantile strabismus may result from defect motor pathways which preclude normal binocular sensory experience (Tychsen 1992; Wright et al. 1994; Tychsen & Burkhalter 1997). Interhemispherical connections in the corpus callosum, with a representation of the vertical meridian and its immediate surroundings, enable continuity of the visual field. Visual experience guides the postnatal development of the corpus callosum. Signals from this narrow strip, representing the vertical centre, will only reach the contralateral visual cortex via the temporal retinal fibres and the corpus callosum. Unilateral strabismus appeared to cause asymmetrical development of callosal connections (Quoc et al. 2011). This asymmetry possibly precludes the imposition of the central vertical meridian onto the 'central vertical', relayed directly from the lateral geniculate nucleus.

Several diseases are known to interfere with normal development of decussating and non-decussating projections or the interhemispherical connections of the corpus callosum.

Agenesis of the corpus callosum is likely to hinder normal binocular fusion. Indeed, in 46% of patients with only partial agenesis of the corpus callosum, strabismus was found (Goyal et al. 2010). In albinism, part of the temporal retina projects to the contralateral cortex. The border between crossed and uncrossed ganglion cell fibres appeared to have moved 6–14 degrees into the temporal retina (Hoffmann et al. 2003). Probably, this erroneous projection may cause strabismus. Both strabismus and projection errors of retinal ganglion cells at the optic chiasm also occur in Prader–Willi syndrome (Creel et al. 1986). Misrouting with crossing of temporal retinal ganglion cell fibres and monocular cerebral areas was described in a normally pigmented macaque (Sincich & Horton 2002).

Besides prominent misrouting in the chiasm, as in albinism or agenesis of the corpus callosum, more subtle misrouting may cause a mismatch between temporal and nasal signals or between the direct thalamic and the indirect corpus callosum signal. Also the vertical meridian of one retina may not coincide with the overlapping zone of the other eye. In a primate study, the retinal vertical meridian in one of three monkeys was found not to coincide with the fovea (Fukuda et al. 1989).

Therefore, strabismus appears to occur in diseases in which misrouting of pathways necessary for fusion is found. Misrouting that causes mismatch between pathways necessary for fusion possibly might, in itself, cause infantile esotropia.

Motor Aspects of Infantile Esotropia

Roelofs (1928) was the first to describe the co-occurrence of early onset strabismus, asymmetry of pursuit and optokinetic eye movements, latent nystagmus and dissociated vertical divergence. After Lang (1968) named it congenital strabismus syndrome, strabismus was often found not to occur immediately after birth. Nowadays, it may be called infantile esotropia or infantile strabismus syndrome (Kommerell 1988).

Until the age of 6 months, normal children will show better temporal to nasal tracking than nasal to temporal (Atkinson 1979). In infantile strabismus, this pursuit asymmetry is also detected after the age of 6 months and from this asymmetry latent nystagmus likely arises (Kommerell 1988).

Lateral-eyed species share the same optokinetic asymmetry. Optokinetic nystagmus, together with the vestibular-ocular reflex, is used to reduce blur associated with motion of the eyes and body. The temporal to nasal bias probably makes the stabilization mechanisms less sensitive to forward motion of the animal.

Binocular frontal-eyed animals have oculomotor pathways for smooth pursuit and vergence, besides optokinetic and vestibular pathways. Where optokinetic and vestibular eye movements are generated in the brainstem, smooth pursuit and vergence are initiated in the cerebral cortex. Lack of temporal retinal input into cortical orchestration of pursuit and optokinetic pathways likely explains the occurrence of latent nystagmus (Mustari & Fuchs 1990; Watanabe et al. 2005; Mustari et al. 2008). Lack of temporal retinal input into cortical orchestration of vergence pathways may explain the occurrence of dissociated vertical divergence (ten Tusscher & Rijn van 2010, 2011; ten Tusscher 2011, 2012).

Latent nystagmus

Latent nystagmus is a conjugate horizontal jerk nystagmus that becomes apparent when one eye is covered. The slow phase is directed towards the nose. The fast phase is directed towards the fixating eye.

Pathways that mediate the optokinetic reflex belong to the accessory optic system and terminal nuclei of the brainstem. The medial and lateral terminal nuclei mediate vertical optokinetic movements. Nuclei responsible for horizontal optokinetic eye movements are the dorsal terminal nucleus and the nucleus of the optic tract (NOT). The NOT, located in the pretectum, receives a direct projection from the contralateral eye. The right NOT responds to a moving stimulus from left to right only, while the left NOT only responds to a leftward directed stimulus.

In lateral-eyed animals, the eye projects to the contralateral NOT which responds to object movements to the side contralateral to the eye (temporal to nasal).

In binocular frontal-eyed animals, these same projections from the eyes to the NOT are dominated ten-fold by the parvocellular projection to the NOT (via the MT and MST in the parietal cortex). The cortical pathway towards the NOT has both an ipsilateral and contralateral division. Both become functional after birth, and in time, the optokinetic temporal-nasal bias disappears after birth (Mustari & Fuchs 1990; Hoffmann et al. 1992; Mustari et al. 2001, 2008).

In infantile strabismus, the functional projection from the ipsilateral

eye, via the visual cortex, to the brainstem nuclei declines (Watanabe et al. 2005). MT, MST and their projections to the NOT contain input mainly from the contralateral eye. Therefore, the NOT responds mainly to the contralateral eye which results in a nasally directed motion bias. If both eyes are fixating the motion bias of both eyes levels out. Covering one eye gives rise to a nasal drift of the fixating eye: latent nystagmus (Mustari & Fuchs 1990; Hoffmann et al. 1992; Mustari et al. 2001, 2008).

Dissociated vertical divergence

Dissociated vertical divergence (DVD) is also known as alternating hyperphoria or dissociated vertical deviation. Like in latent nystagmus, the eye movement becomes apparent after covering one eye. The eye behind the cover slowly moves upward. The more visually dominant the fixating eye is over the other eye, the more the non-dominant eye elevates. While elevating, the eye also extorts, and the other eye intorts. So, DVD combines vertical divergence (oppositely directed vertical eye movements) with torsional version (torsional eye movements of both eyes in the same direction). A similar combination of vertical divergence and torsional version occurs in the ocular tilt reaction. In the ocular tilt reaction, however, the elevating eye incyclorotates.

Enright (1990) showed that eye movements during disparity-induced vertical vergence are characterized by the identical co-occurrence of vertical divergence with torsional version and excyclorotation of the upward moving eye. Analysis of eye movements in DVD with scleral search coils showed a striking similarity between DVD and disparity-induced vergence (Rijn van et al. 1997). Therefore, DVD is likely a supranuclear disorder of vertical vergence pathways.

If the eyes move from one point to another and both saccadic and vergence input are called for, large amounts of vergence are realized by asymmetrical activation of both superior colliculi (Zhou & King 1998). It seems that the former concept of distinct saccade pathways for conjugate eye movements and separate vergence neurons no longer holds true and that both pathways likely are interdependent (Cullen & Horn van 2011). von Helmholtz (1962) concept of separate eye movement centres for both eyes individually best explains the findings during fast eye movements. The majority of neurons in the saccadic premotor circuitry appears to trigger the individual eye instead of a conjugate eye movement (Zhou & King 1998; Cullen & Horn van 2011).

The saccade/vergence/fixation pathway that projects from the cortex to the rostral pole of the superior colliculus, the corticotectal pathway, contains a two-dimensional motor map. Electrophysiological experiments in the superior colliculus of the monkey also revealed a two-dimensional motor map from which horizontal and vertical saccades are generated (Opstal van et al. 1991). Nuclei caudal to the superior colliculus have a three-dimensional motor map, with a torsional component. The rostral pole of the superior colliculus projects to the rostral interstitial nucleus of the MLF (riMLF) and the omnipause neurons. The riMLF contains burst neurons for vertical and torsional saccades. Besides input from the superior colliculus, the riMLF receives projections from omnipause neurons. Conjugate torsional eye movements are generated by the interstitial nucleus of Cajal (INC). The INC gets its input from the riMLF and vestibular nuclei (Leigh & Zee 2006). In cats, a direct projection from the superior colliculus to the INC was found (Altman & Carpenter 1961). Torsional version generated by the INC has an opposite direction on both sides of the brainstem: the right INC initiates clockwise torsion in both eyes, the left INC counterclockwise (Klier et al. 2007).

The two-dimensional cortical fixation/vergence/saccade signals must be adjusted to the three-dimensional vestibular coordinates of the brainstem. The INC receives both input from the two-dimensional corticotectal pathways and from the three-dimensional vestibular pathways (ten Tusscher & Rijn van 2011). Asymmetrical vergence stimuli may lead to asymmetrical activation of both INC's, giving rise to cycloversion.

In infantile strabismus, the functional projection from the ipsilateral eye, via the visual cortex, to the brainstem nuclei is suppressed. The corticotectal projection to the superior colliculus is dominated by crossing retinal ganglion cells of the contralateral eye.

The influence of the temporal retina in the pathway from the cortex to the NOT diminishes in infantile esotropia. These pathways converge with the same cortical neurons that project to the superior colliculus (Schoppmann & Hoffmann 1979). So, not only cortical pathways to the NOT, but also neurons to the superior colliculus are likely dominated by the contralateral eye. Hence, covering one eye results in asymmetrical activation of the cortex, INC's and omnipause neurons. Asymmetrical activation of the INC's will result in a conjugate torsional movement of the eyes. Asymmetrical activation of the omnipause neurons will result in vertical divergence (ten Tusscher & Rijn van 2010). In this hypothesis, we assume that activation of cortical vertical saccade/vergence neurons results in depression of the eye, while inhibition of the same neuron causes elevation. This assumption is supported by two studies: (i) downward-directed saccades were found to be larger and faster than upward directed saccades (Collewijn et al. 1988); (ii) during one of the stages of general anaesthesia, the eyes elevate. This stage appears to coincide with cortical deactivation (Power et al. 1998).

The same neuroanatomical hypothesis might also explain the occurrence of dissociated horizontal divergence (DHD). Instead of vertical omnipause neurons, horizontal omnipause neurons are triggered asymmetrically from the superior colliculi (ten Tusscher & Rijn van 2011).

Conclusion

In summary, the present neuroanatomical hypothesis of corticotectal lateralization explains all motor aspects of infantile strabismus. Latent nystagmus, DVD and DHD are dissociated eye movements: they occur during unequal visual input to the individual eyes. Due to dominance of the nasal retina, the more activated retina gives rise to dominance of the contralateral visual cortex. In turn, this dominance results in asymmetrical activation of corticotectal pathways that project to the superior colliculus (which explains the occurrence of both DVD and DHD) and NOT (which explains the occurrence of latent nystagmus).

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