# Timing of surgery for infantile esotropia: sensory and motor outcomes

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**ABSTRACT • RÉSUMÉ**

Infantile esotropia is a common ophthalmic disorder in childhood. It is often accompanied by profound maldevelopment of stereopsis, motion processing, and eye movements, despite successful surgical realignment of the eyes. The proper timing of surgery has been debated for decades. There is growing evidence from clinical and animal studies that surgery during the early critical periods enhances sensory and ocular motor development. The Congenital Esotropia Observational Study has defined a clinical profile of infants who will benefit most from early surgery, and several other studies have shown that early surgery does not lead to adverse long-term effects. Clinicians now should consider offering early surgery to patients with large-angle, constant infantile esotropia at or before 10 months of age.

L'ésotropie infantile est une maladie ophtalmique courante chez les enfants. Elle s'accompagne souvent d'un développement anormal profond de la vision stéréoscopique, de la motilité et des mouvements oculaires, malgré la réussite du réalignement chirurgical des yeux. Le débat sur le moment opportun de pratiquer la chirurgie se poursuit cependant depuis des décennies. Les études cliniques sur les animaux présentent de plus en plus de données probantes démontrant que la chirurgie pratiquée dès le début des périodes critiques améliore le développement sensoriel et oculomoteur. L'étude fondée sur l'observation de l'ésotropie congénitale définit un profile clinique des enfants qui bénéficient le plus d'une chirurgie précoce et plusieurs autres études démontrent que la chirurgie précoce n'a pas d'effets indésirables à long terme. Les cliniciens devraient maintenant songer à offrir la chirurgie précoce pour les patients qui ont une ésotropie infantile constante à angle ouvert, à l'âge de 10 mois ou avant.

Infantile esotropia is a nasalward eye misalignment that begins in the first 6 months of life. It affects 1 in every 100 to 500 persons.[1,2] Infantile esotropia is characteristically large in magnitude (>20 prism diopters [PD]) and cosmetically conspicuous. While there is uniform agreement among pediatric ophthalmologists that a large-angle, constant infantile esotropia requires surgical correction, the proper timing of surgery has been debated for decades.[3,4] In North America, the typical age at surgery ranges from 11 to 18 months, and in many parts of Western Europe, surgery is delayed until 2 to 4 years of age.[5] Despite successful surgical realignment of the eyes, a number of sensory-motor deficits often persist into adulthood.[6,7] They include abnormal stereopsis,[8,9] latent fixation nystagmus,[10–12] dissociated vertical deviation,[12,13] abnormal eye movements (e.g., nasotemporal asymmetries of optokinetic nystagmus [OKN][14–16] and smooth pursuit,[12,17] and abnormal vergence[18–20]), as well as abnormal visual motion processing[7,21–23] and global motion perception.[24–27]

In the last decade, advances in pediatric anesthesia and surgical techniques have made it possible to realign the eyes of strabismic infants at weeks or months of age.[28,29] The rationale for early surgery stems from research in animals showing that the earlier within the critical periods the eyes are aligned, the more likely it is that normal binocular vision will develop.[30–32] Indeed, a number of clinical studies have shown that the sensory and ocular motor outcomes of children who had early surgery are substantially better than those who were repaired at the current standard age of surgery (referred to as surgery from 11 to 18 months of age in this review). This paper reviews the basic and clinical science literature on the critical periods of sensory and ocular motor development, then discusses the neural mechanisms that underlie the deficits typically seen in infantile esotropia. Following this, it examines current evidence in support of early surgery and discusses the clinical profile of infants who will most likely benefit from early surgery.

## Critical periods of sensory and motor development

### *Stereopsis*

The critical period for binocular visual development occurs around the first 4 to 6 months of life.[33–35] Binocular disparity sensitivity and fusion are absent in infants

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younger than several months of age.[33,34,36–38] Stereopsis emerges abruptly during the first 3 to 5 months of life, and is nearly mature by 6 months of age.[33,34,39,40] Humans with a history of infantile esotropia have abnormal binocularity.[9,41–47] Experimental findings in cats and monkeys showed that a short period of deprivation during the critical period of binocular development results in severe, irreversible deficits in stereopsis[48–52] and permanent loss of binocular cortical neurons.[32,53,54]

### *Optokinetic nystagmus*

The development of the ocular motor systems, including OKN, smooth pursuit, and vergence, is also exquisitely sensitive to the effects of early abnormal binocular visual experience. OKN is a reflexive pattern of eye movements that tracks the motion of large regions of the visual field. It is believed to be mediated by a subcortical system that includes the pretectal nucleus of the optic tract (NOT) and the dorsal terminal nucleus (DTN) of the accessory optic system.[55,56] During monocular viewing, normal neonates exhibit asymmetric monocular OKN that favours nasalward over temporalward motion.[57,58] This nasotemporal asymmetry disappears by 6 months of age.[57–59] In children[16,59,60] and adults[14,59–63] with a history of infantile esotropia, asymmetric monocular OKN persists. OKN asymmetry is also evident in cats[64,65] and monkeys[66] that experience various forms of monocular or binocular deprivation early in life. It is generally believed that at birth only the subcortical system is functional. The monocular OKN is asymmetrical in the neonatal period because neurons in the NOT-DTN are innately selective for ipsiversive target motion.[67] As binocularity emerges and as an indirect ipsilateral cortical projection from the middle temporal area (MT) to the NOT matures,[68] monocular OKN becomes symmetrical because of the dominating effects of this binocular cortical pathway over the subcortical pathway.[67,69]

### *Smooth pursuit*

Smooth pursuits are slow-tracking eye movements that hold the image of a moving target on the fovea. Humans and monkeys with early-onset strabismus have a striking nasotemporal asymmetry of pursuit favouring nasalward motion during monocular viewing.[12,14,17,70–72] The asymmetry is exhibited transiently in normal human and monkey infants before the onset of binocularity,[58,59] but it persists permanently if strabismus develops in the neonatal period.[12,70] It is not seen in strabismus that develops after infancy.[17,73] When patients were asked to judge the speed of moving targets, they systematically underestimated the speed of a temporalward-moving target and overestimated that of a nasalward-moving target, even though the targets moved at identical speed.[12,74] Taken together, these observations suggest a link between aberrant binocularity and abnormal visual motion processing that affects pursuit pathways during the critical period for ocular motor development.[70,75–81] However, motion perception biases both similar[82] and opposite[62,82] to those reported earlier,[12,74] as well as no or small motion biases,[83,84] have also been reported.

### *Vergence*

Vergence eye movements are disjunctive movements that move the eyes in opposite directions (i.e., convergence and divergence), so that the images of a single object fall on the fovea of both eyes simultaneously. Two major visual cues that stimulate vergence are image displacement on the retinae (i.e., binocular disparity) and image defocusing (i.e., accommodative blur).[85,86] Vergence,[87–89] accommodation,[88,89] and disparity sensitivity are all immature at birth[33,36,37] but develop rapidly in the first few months of life. Humans[18–20] and monkeys[90] with a history of infantile esotropia have major deficits in disparity-induced vergence, but they have normal accommodative vergence. During binocular viewing with far and near targets placed in the subjects' midline (i.e., symmetric vergence stimuli), normal humans respond predominantly with symmetric vergence. In contrast, strabismic patients respond predominantly with asymmetric vergence, accompanied by a disjunctive saccade.[19,20] During monocular viewing, the vergence behaviour in strabismic patients does not change, whereas vergence in normal humans becomes remarkably strabismic-like, with a 4- to 5-fold increase in asymmetric saccadic vergence.[19,20] These findings suggest that vergence in strabismic humans during binocular viewing is achieved by monocular, accommodative vergence driven chiefly by visual inputs to the dominant eye.[19,20]

### *Motion visual evoked potentials*

Abnormal motion processing, measured by recording the visual evoked potential (VEP) responses to monocularly viewed oscillating horizontal gratings, has also been demonstrated in patients with infantile esotropia.[7,21,22,26,91–94] Motion VEP (mVEP) arises predominantly from binocular, direction-selective neurons within the primary visual cortex (V1).[7,93] Normal neonates (≤1 month) exhibit symmetric mVEPs, indicating that their cortical responses are equally strong to nasalward and temporalward directions of motion.[21] Nasotemporal mVEP asymmetry emerges in normal infants at 2 to 3 months of age, but it rapidly diminishes and becomes adult-like by 6 to 8 months.[7,21,22,26] mVEP asymmetry is typically observed in patients[7,21,22,26,91–94] and monkeys with a history of infantile esotropia.[95] In addition, there is a strong association between abnormal binocularity and mVEP asymmetry during normal maturation and in infantile esotropia.[21] Because mVEP signals are inherently ambiguous regarding direction, attempts to reveal the perceptual directional bias of mVEP asymmetry have yielded inconclusive or opposite findings, with some studies finding a nasalward bias[26,62] and others a temporalward bias.[96]

### *Global motion perception*

Global motion refers to an overriding perception of a

single direction in complex textured displays that consist of a large number of small elements moving in different directions. During normal development, very young (5–6 weeks) infants have symmetric global motion perception during monocular viewing.[25,26,97] Asymmetric global motion perception favouring nasalward movements first appears at 2 months and disappears by about 6 months of age.[25,26,97] Asymmetry of global motion perception is observed in patients with a history of infantile esotropia.[24–27] Physiologic,[98,99] psychophysical,[100–102] and neuropsychologic[103–106] studies indicate that global motion perception is mediated via specific visual pathways (magnocellular, dorsal extrastriate) and extrastriate areas (MT).

## Neural mechanisms of the sensory-motor deficits in infantile esotropia

What are the neural mechanisms that underlie the sensory-motor deficits typically seen in infantile esotropia? At present, it is generally accepted that horizontal binocular connections in V1 play a critical role.

Visual signals from each eye are completely segregated in the lateral geniculate nucleus and at the input layer 4C of V1.[107,108] Binocular visual processing first occurs via horizontal binocular connections in layers 4B and 2–6, above and below input layer 4C, which link ocular dominance columns (ODCs) of opposite ocularity (i.e., the right and left eyes).[79,107,109] Maturation of horizontal binocular connections in V1 requires correlated activity between the inputs from the right and left eye.[110] Infantile strabismus results in decorrelated inputs from the eyes and hence, a loss of horizontal binocular connections.[79,109] The reduction of horizontal binocular connections in V1 results in deficits in disparity sensitivity and binocular responsiveness in V1 neurons,[31,50,111] which manifest behaviourally as poor fusional vergence and stereopsis.[77,112]

Binocular signals from layer 4B of V1, in turn, are projected onto the extrastriate cortex, MT, and medial superior temporal (MST) areas.[113] Neurons in MT and MST are sensitive to motion direction and to binocular disparity.[114,115] MT and MST mediate smooth pursuit/OKN,[116,117] vergence,[115,118] as well as complex motion perception.[98,99] MST in each cerebral hemisphere encodes ipsiversive pursuit/OKN and gaze holding. In newborns, the outputs from V1 to each MST are monocular, with an innate connectivity bias favouring the contralateral MST.[70] For example, inputs from the viewing left eye make a stronger connection, through V1 of both hemispheres, to MST of the right hemisphere. MST on the side ipsilateral to the viewing eye can only be accessed through binocular horizontal connections in V1 and in MT;[70] however, these binocular horizontal connections are weak at birth and require correlated visual activity in order to mature during the first few months of life.

This innate, monocular, contralateral-MST connectivity bias provides a plausible mechanism for the nasalward pursuit/OKN bias, evident before onset of binocularity, in infant monkeys and humans. Left eye viewing activates left eye ODCs in each primary visual cortex. Left eye ODCs make stronger connections to the right MST. The right MST mediates ipsiversive (rightward) pursuit/OKN, which are nasalward movements with respect to the viewing left eye. During normal development, horizontal binocular connections mature so that the left eye ODCs also gain access to the left MST, and the nasalward bias disappears. However, decorrelated visual activity in infantile strabismus leads to a loss of horizontal binocular connections; hence, the nasalward bias persists and is amplified. This bias is manifested clinically as nasotemporal asymmetries of smooth pursuit and OKN, as well as nasalward drift of gaze holding (i.e., latent fixation nystagmus).

## Early versus standard surgery

In light of the myriad scientific and clinical evidence that showed the devastating effects of infantile strabismus on early visual and ocular motor development, as well as the poor functional outcomes of these patients despite successful realignment of the eyes, a logical question is whether early surgery performed during the critical periods of development would be beneficial. Specifically, can early surgery restore correlated visual inputs between the 2 eyes and promote maturation of horizontal binocular connections in V1, thereby enhancing the development of fusion, stereopsis, and various eye movements? To answer these questions, we fitted prism goggles in infant macaques at day 1 of life to induce an optical strabismus.[77,79–81,119–123] The early correction group wore the prism goggles for 3 weeks (the equivalent of 3 months before surgical repair in humans[124]). The standard/delayed correction group wore the prism goggles for 3 or 6 months (the equivalent of 12 or 24 months before surgical repair in humans). We found that standard/delayed correction resulted in deficits typically associated with infantile esotropia, including abnormal stereopsis,[120] long-term eye misalignment,[121] latent fixation nystagmus,[123] as well as nasotemporal asymmetries of monocular smooth pursuit, OKN, and mVEPs.[77,80] In contrast, none of the animals with early correction developed these abnormalities.

Our neuroanatomic data, furthermore, indicated that both the behavioural and mVEP recoveries in early correction monkeys were associated with normal development of area V1, whereas standard/delayed correction and unrepaired naturally strabismic monkeys had striking structural and metabolic abnormalities in V1.[120,122] The major structural deficit was a paucity of binocular connections between ODCs of opposite eyes.[120,122] This defect of binocular connectivity was apparent in layer 4B and in interpatch compartments of layers 2/3 in V1. Most interestingly, these behavioural and anatomical deficits were tightly linked; the animals with the most severe sensory, ocular motor, and mVEP abnormalities also had the

largest reduction in horizontal binocular connections in V1.[120,122] Our data also suggested that the critical periods for normal maturation are different from those for functional recovery; extrapolating from our animal data, it appears that normal development of stereopsis and eye movements occurs most rapidly in the first 6 months of life in humans, whereas the critical periods of functional recovery occur sometime between the first 3 and 12 months postnatally.

New knowledge about sensory and ocular motor development in humans in the 1980s provided further support for early surgery. Costenbader,[125] Parks,[4] and others[126] are all notable advocates for early surgery. Their early work has inspired a number of classic clinical studies[9,127–130] that showed that surgical realignment of the eyes during the first 2 years of life is associated with a higher prevalence of stereopsis than surgical alignment later in life. Recent studies suggest that surgical alignment during the first year of life may enhance stereopsis further,[8,9,127–129,131–135] and that surgical alignment during the first 6 months of life may be optimal (Fig. 1).[28,29,127,131–133] Interestingly, although both age at alignment and duration of misalignment are linked to better stereoacuity outcomes, Birch et al.[132,133] found that the duration of misalignment appears to be the more important factor. Better stereoacuity, in turn, is associated with more stable long-term eye alignment.[133]

The effects of early surgery on other outcomes are less well studied in humans. Birch et al.[21] found that only rare patients with surgery during the first 10 months of life achieved symmetric mVEPs. Recent mVEP data from our group[136,137] are more promising. Eight patients with early surgery at ≤11 months of age, 8 with standard surgery at 11 to 18 months of age, and 7 age-matched controls were studied prospectively. We found that the normal controls and patients with early surgery exhibited symmetric mVEPs, whereas patients with standard surgery exhibited asymmetric mVEPs (Fig. 2).

In another study[26] that investigated the codevelopment of motion detection and mVEPs, early surgery during the first year of life was found to improve the nasotemporal asymmetries of both motion detection and mVEPs. Interestingly, although this same research group suggested that duration of misalignment is better than age at surgery in predicting stereopsis outcome,[133] they found no difference in these 2 other outcomes, mVEPs and motion detection, between patients with a short duration (3–6 months) versus a long duration (6–12 months) of misalignment.[26] We also found that patients with early surgery developed more symmetric OKN (Fig. 3) and motion detection than those with standard surgery.

## Who will benefit from early surgery?

A frequently cited rationale against early surgery is the possibility of spontaneous resolution. This concern has led to 2 studies: the Congenital Esotropia Observational Study (CEOS)[138] and the Early Surgery for Congenital Esotropia (ESCET) collaborative clinical trial,[134] which was a proposed multicenter randomized clinical trial. The CEOS[138] found that infantile esotropia persists in 98% of infants who have large-magnitude (≥20° or 40 PD) constant esotropia with onset after 10 weeks of age and refractive error ≤3.00 diopters. Thus, the CEOS[138] and other studies[134,139,140] successfully defined a clinical profile of infants most likely to benefit from early surgery (Fig. 4). The ESCET, unfortunately, was not funded because experience from the CEOS indicated that recruitment of eligible patients would be too low to make a randomized clinical trial feasible.[134]

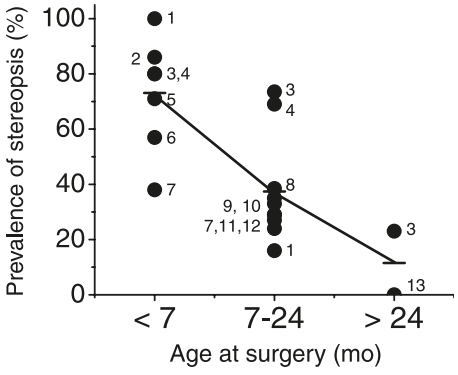


Fig. 1—Summary of stereopsis outcome by age at surgery. Each circle indicates the prevalence of stereopsis from each study cited. Short horizontal dashes represent mean prevalence of stereopsis for different age groups. (1, Birch et al.[21]; 2, Ing[29]; 3, Ing[127]; 4, Ing and Okino[131]; 5, Wright et al.[28]; 6, Birch et al.[134]; 7, Birch and Stager[132]; 8, Birch et al.[9]; 9, Birch et al.[8]; 10, Kushner and Fisher[129]; 11, Hiles et al.[135]; 12, Zak and Morin[128]; 13, Taylor.[130])

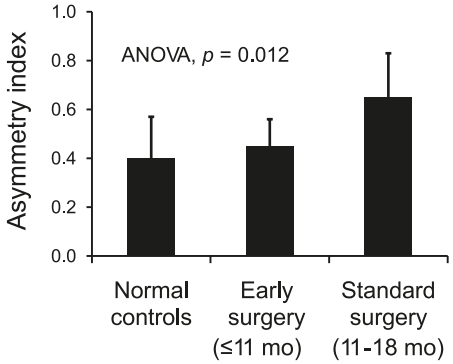


Fig. 2—Motion visual evoked potential (mVEP) outcome by age at surgery. The symmetry of mVEP is measured by an asymmetry index. The higher the asymmetry index, the more abnormal and asymmetric the mVEP responses. The mean asymmetry index in the early surgery group was similar to that in age-matched control subjects, and was significantly lower than that in the standard surgery group.

Another concern regarding early surgery is the lack of stability of deviation in young infants.[3,134,138,141,142] This issue was addressed by a recent prospective study,[132] which found that neither the instability of misalignment nor the accuracy of orthoptic measurement had any negative impact on long-term eye alignment in patients who had early surgery.[132]

## Conclusion

Infantile esotropia is a common health problem in childhood. It is important to clinicians because it is difficult to treat and it is almost always associated with abnormal sensory and ocular motor outcomes despite standard surgery. It is important to vision scientists because it is accompanied by profound maldevelopment of stereopsis, motion processing, and eye tracking. The proper timing of surgery has been debated for decades. There is mounting evidence from clinical and animal studies that surgery during the early critical periods of development enhances sensory and ocular motor outcomes. The CEOS[138] has defined a clinical profile of infants who will benefit most from early surgery, and several studies[132,139] have shown that early surgery poses no adverse long-term effects. Clinicians now should consider offering early surgery to infants with infantile esotropia who fit the clinical profile described by the CEOS.[138]

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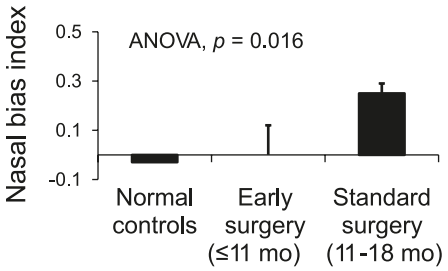


Fig. 3—Optokinetic nystagmus (OKN) outcome by age at surgery. The symmetry of OKN is measured by a nasal bias index. The higher the nasal bias index, the more abnormal and asymmetric the OKN responses. The mean asymmetry index in the early surgery group was similar to that in age-matched control subjects, and was significantly lower than that in the standard surgery group.

1. Presence or persistence of esotropia between 10 weeks and 6 months of age
2. Constant esotropia ≥20° or 40 prism diopters at near (1/3 m) on two examinations, separated by 2–4 weeks
3. Refractive error ≤3.00 diopters
4. Absence of any of the following conditions:
   a. Gestational age <34 weeks
   b. Birth weight ≤1500 g
   c. Ventilator treatment in the newborn period
   d. History of meningitis or other major medical event
   e. Developmental delay
   f. Incomitant or paralytic strabismus
   g. Manifest nystagmus or head bobbing
   h. Prior eye muscle surgery
   i. Presence of structural ocular anomalies

Fig. 4—Clinical profile of infants who will benefit most from early surgery.[138]

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