Stereoacuity Outcomes Following Treatment of Infantile and Accommodative Esotropia

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Abstract

Purpose—To review what is known about the normal maturation of stereoacuity, the stereoacuity deficits associated with infantile and accommodative esotropia, the rationale for making improved stereoacuity a goal of treatment, and strategies for improving stereoacuity outcomes.

Methods—Studies of stereoacuity maturation during normal development, studies of stereoacuity outcomes following treatment for infantile and accommodative esotropia, and studies of primate models of esotropia are reviewed.

Results—Stereoacuity maturation normally proceeds rapidly during the first year of life. Infantile and accommodative esotropia are associated with profound and permanent disruption of stereopsis. While rehabilitation of stereoacuity following treatment of esotropia remains a challenge, even the achievement of subnormal stereoacuity may have real benefits to the child.

Conclusions—Some abnormalities in stereoacuity may exist before the onset of esotropia, but others may result directly from abnormal binocular experience. Several strategies for improving stereoacuity outcomes in esotropia are currently under active investigation. Improved stereoacuity outcomes are associated with better long term stability of alignment, reduced risk for and/or severity of amblyopia, improved achievement of sensorimotor developmental milestones, better reading ability, and improved long-term quality of life.

Keywords
stereoacuity; infantile esotropia; accommodative esotropia

Normal Maturation of Stereoacuity

Prior to 1980, there was scarcely any information about the normal maturation of stereopsis during infancy. As a result of the development of the forced-choice preferential looking (FPL) method for testing infant visual perception1, we were able for the first time to quantitatively assess stereoacuity maturation. The first studies of infant stereoacuity began at MIT and Vanderbilt University in 1979, with the first publications in 1980.2-4 Since that time, a variety of psychophysical, electrophysiological, and eye movement laboratory protocols for the assessment of local and global stereopsis during infancy and early childhood have been developed.3-16
Regardless of the methodology, most studies agree that stereopsis has an abrupt onset at 3 to 4 months of age and that, during months 4-12, the rate of stereoacuity maturation is rapid \(8^\text{th} - 11\). For example, Figure 1 provides results from several of our own studies that show good agreement among FPL and VEP protocols to study the maturation of local and global stereoacuity during the first year of life. Slower improvement in stereoacuity continues beyond 18 months of age \(7, 10, 11\). The onset of stereopsis is not determined simply by the maturation of eye alignment nor the maturation of visual acuity\(17, 18\), although there is some evidence that contrast sensitivity may be a limiting factor in rate of stereoacuity improvement with age\(12\).

Infants older than 4 months of age are not only able to discriminate binocular disparity but appear to experience the perception of depth. They preferentially look at and track horizontally disparate stimuli that give rise to the perception of depth in adults but not vertically disparate stimuli\(3, 9\). In addition, they have appropriate reaching behavior in response to horizontally disparate targets.\(19\)

### Abnormal Stereopsis in Infantile and Accommodative Esotropia

The ability to assess stereopsis during infancy and early childhood has allowed us to examine the causes and rehabilitation of abnormal stereopsis in pediatric patients. Most research in this area has focused on esotropia, a convergent strabismus that typically has an onset during infancy (infantile esotropia) or early childhood (accommodative esotropia). Both infantile esotropia and accommodative esotropia are associated with abnormal binocular sensory function. Recently, clinical research on stereoacuity has been accelerated by the commercial availability of stereoacuity tests for infants and young children, such as the Infant Randot Stereoacuity Cards\(10, 11\) (which utilize the Teller Acuity Card format devised for rapid infant visual acuity assessment by Teller, Dobson, McDonald and colleagues\(20, 21\)), the Randot Preschool Stereoacuity Test\(22, 23\), the Randot Stereo Smile Test\(13\), and the Distance Randot Stereoacuity Test\(24-27\). These new tests provide standardized, quick, and valid methods for assessing stereoacuity at near and at distance in infant and pediatric patients with binocular sensory dysfunction.

Infantile esotropia has a prevalence of 0.3 – 1% \(28-33\); onset of a constant, large angle nasalward misalignment of the visual axes occurs by 6 months of age. Infantile esotropia is associated with an increased risk of amblyopia and abnormal binocular sensory function. Outcomes with regard to amblyopia are generally good. For example, in a recent prospective study of 129 children diagnosed with infantile esotropia by 6 months of age and followed for a minimum of 5 years, over 90% of the children were treated for amblyopia one or more times during follow-up, yet fewer than 10% had persistent amblyopia at the final outcome visit and the majority of persistent cases of amblyopia were mild\(34\). On the other hand, treatment for binocular sensory dysfunction is rarely successful. Even with optical correction and early surgery, less than 0.5% of this prospective cohort developed normal stereoacuity by 5 years of age and over 60% had nil stereoacuity (Figure 2).\(34\)

Accommodative esotropia has a prevalence of 1 – 2% \(28-30, 33, 35\) onset of an initially intermittent nasalward misalignment of the visual axes usually begins at 18-48 months of age, associated with hypermetropia and/or an abnormal AC/A ratio. Despite the later age of onset, accommodative esotropia frequently is associated with abnormal binocular sensory function. In fact, even when children with accommodative esotropia were examined at the earliest stage of their disease, while the deviation was still intermittent, over 40% had abnormal stereoacuity \(36\). Even more children develop deficits in stereoacuity later in the course of the disease, so that only 18% had normal stereoacuity at the final visit 4-11 years later (Figure 2).\(36\)
Should Rehabilitation of Stereopsis Be a Goal for Treatment of Esotropia?

In patients with infantile esotropia, even the achievement of subnormal stereoacuity postoperatively may have real benefits to the child. Early surgical correction of infantile esotropia is associated with both improved stereoacuity outcomes and improved achievement of sensorimotor developmental milestones during infancy. This is not surprising since it is appreciated that accurate prehension, particularly grasp-point selection, is known to rely on binocular disparity cues. Stereovision continues to influence acquisition of sensorimotor skills into early childhood, including skills as simple as learning to catch a ball. Among kindergarteners and first graders with average intelligence, stereoacuity is correlated with standardized reading scores and teachers’ ratings of reading ability.

Children with stereopsis also have better long term stability of alignment, meaning that they are less likely to need additional surgery to restore horizontal alignment. Because there are fewer recurrent and consecutive deviations, stereopsis is also associated with improved long-term quality of life, including self-image, self-confidence, employment opportunities, satisfaction in interpersonal relationships, and success in school and sports. Stereopsis is also associated with reduced risk for and/or severity of amblyopia. If stereopsis prevents amblyopia, it may further impact quality of life, because visual acuity of the amblyopic eye has been shown to be an important determinant of quality of life.

Why Are Stereoacuity Outcomes So Poor in Infantile and Accommodative Esotropia?

There is substantial evidence that the profound stereoacuity deficits associated with infantile esotropia do not result from a congenital absence of binocular sensory function, and do not reflect persistence of a neonatal pre-binocular state. Instead, the stereodeficit appears after an initial period of normal maturation, suggesting that the abnormality results from prolonged abnormal experience. Data from a primate model of infantile esotropia similarly show an initial period of low vulnerability to abnormal experience, followed by a period of high susceptibility to abnormal experience that peaks just after the onset of stereopsis. Moreover, the benefit of early repair of esodeviation is more strongly associated with decreased duration of abnormal experience than with earlier age at repair in both human disease and primate models of infantile esotropia. Taken together, the data suggest that very early surgical repair of esodeviation, near the time of onset of stereopsis, might yield excellent stereoacuity outcomes. It was unexpected, then, to find that early surgical repair of infantile esotropia increased the prevalence of stereopsis but normal stereoacuity remained a very rare outcome (Table 1). Possible reasons for this will be addressed later, together with the question of whether or not normal stereoacuity can be achieved in infantile esotropia.

For several reasons, stereoacuity outcomes following the treatment of accommodative esotropia might be anticipated to be excellent. First, this disease typically has an onset after 18 months of age, after the bulk of stereoacuity maturation is normally complete. Second, accommodative esotropia most often presents as an intermittent deviation so that the child enjoys some normal binocular experience even after the onset of disease. In many cases, the esodeviation can be eliminated by providing optical correction alone. Indeed, there are numerous publications in the literature that utilize a cohort of children with accommodative esotropia as a comparison group for an infantile esotropia cohort, with the implicit assumption that they have normal binocular vision. Somewhat surprisingly, then, even at the earliest intermittent stage, 40% of children with accommodative esotropia have subnormal stereoacuity. These stereodeficits may be primary. In some cases, the stereodeficit may be genetic; in other cases, it may be due to other factors that caused a stereodeficit prior to the onset of esotropia such as a perinatal event or anisometropia. There is evidence for a genetic
basis for both accommodative esotropia and for stereodeficits (primary monofixation syndrome) as well as evidence for an association between accommodative esotropia and hyperopic anisometropia. Additional evidence for the primary nature of these stereodeficits is that hyperopic refractive error alone is not sufficient to cause accommodative esotropia; 63% of children with $\geq+4.00$ D and 79% of children with $\geq+3.50$ D never develop an esodeviation. Thus, hyperopic refractive error may need to occur in conjunction with abnormal stereoacuity in order to precipitate the onset of accommodative esotropia, particularly in cases of moderate hyperopia. With additional follow-up, more children with accommodative esotropia develop stereodeficits so that, by age 6 years, less than 20% have normal stereoacuity. 

Can Normal Stereoacuity Be Achieved in Infantile Esotropia?

On the basis of our 25 years of data on the maturation of stereopsis in infantile esotropia, its susceptibility to disruption by abnormal experience, and its potential for rehabilitation via early surgery, it is clear that despite predictions, early surgery is not sufficient to support the development of normal stereoacuity. Here we consider other factors that may contribute to poor stereoacuity outcomes in infantile esotropia.

First, current surgical techniques for infantile esotropia may not be sufficiently accurate to restore alignment within Panum’s area and support stereopsis. Panum’s area includes corresponding points on the two retinas as well as small areas of surrounding noncorresponding retinal points that can still be fused with resultant stereopsis. Panum’s area is ±5-20 min of arc (0.1 – 0.6 prism diopter (pd)) in the fovea and alignment within this window may be necessary to support high grade stereoacuity. Other authors have suggested that alignment within 2 or 3 deg (4 to 6 pd) is necessary to achieve stereopsis. For example, Tychsen states that surgery must realign the eyes within 2.5 to 5 deg (5 to 10 pd) so that the ocular dominance columns (ODCs) mediating fusion in the visual cortex will be separated by no more than 1 to 2 horizontal neuron lengths. Leske & Holmes evaluated patients with various angles of strabismus and concluded that stereopsis may only be achievable when the horizontal alignment is within 4 pd. However, as is apparent in the Leske & Holmes data set, alignment within 4 pd, while it supports stereopsis, is not sufficient to guarantee high grade stereoacuity.

The hypothesis that subnormal stereoacuity outcomes result from inaccurate surgical alignment is supported by data from children with infantile esotropia who were treated with botulinum toxin rather than surgery. Very early (≤6 months of age) treatment with botulinum toxin results in better stereoacuity outcomes than very early surgical alignment. Better stereoacuity outcomes may arise from the temporary incomitance that results from the injection providing an opportunity for the infant to refine alignment to orthotropia by developing a face turn. Note that botulinum appears to be less beneficial for stereoacuity outcomes if the treatment is delayed.

Second, early surgery for infantile esotropia (at ≤6 months of age) may still not be early enough. Highly developed stereoacuity is dependent on a normal complement of binocular neurons in the visual cortex. Researchers agree that the presence of highly sensitive disparity encoding mechanisms in the early stages of cortical processing in V1 is a prerequisite for stereopsis in normal subjects. However, relative disparity appears to be calculated in V2 and stereopsis has been attributed to V2. Using a macaque model of infantile esotropia, Kumagami et al have shown that V1 susceptibility to abnormal experience peaks just after the onset of
stereopsis. Maruko et al. show a similar critical period for V2 with considerable maturation of disparity sensitivity between 2 and 8 weeks of age, that parallels monkey psychophysical stereoacuity development and (converting weeks to months) human stereoacuity development. If as these studies suggest, the repair of esotropia must occur before the onset of stereopsis to avoid abnormal binocular suppression in the visual cortex and to achieve the optimal disparity sensitivity, then surgical alignment in humans would need to be completed by 2–3 months of age (corresponding to 2–3 weeks in the macaque). Recently, the Pediatric Eye Disease Investigator Group has defined a clinical profile for which persistence of esotropia was sufficiently likely (>98%) that early surgery could be considered, namely <+3.00D and ≥40 pd esotropia on at least 2 visits at ≥2.5 months of age. This profile could be used to identify patients that may be excellent candidates for very early surgery.

Third, even a brief delay (≤3 months) in surgery from the time of onset of esotropia may be too long. Evidence from a macaque monkey model of infantile esotropia shows that V1 can be severely affected by very brief periods of abnormal visual experience. Mori et al. found that a brief 2-week misalignment after the emergence of stereopsis is sufficient to drastically reduce the functional binocular connections in V1, and longer periods of strabismus result in little additional loss in disparity sensitivity. Zhang et al. found that 3 days of optically imposed strabismus (decorrelation) at the peak of the critical period strikingly altered the V1 cortical circuits that support binocular vision. Thus, V1 is extremely sensitive to very brief periods of interocular decorrelation of input signals just after the onset of stereopsis. In human infants, surgery for infantile esotropia is associated with better stereopsis outcomes when the surgery is completed early enough to limit the duration of misalignment to less than 3 months. Similarly, Tychsen, working with a macaque monkey model of infantile esotropia, found that the visual cortex could repair horizontal connections as long as the image decorrelation caused by esotropia was repaired by 3 weeks of age (equivalent to 3 months in humans); a full complement of V1 connections with normal metabolic activity (no suppression) was recovered. Both data from animal models and human clinical data suggest that delay between the onset of infantile esotropia and the age at surgical alignment is a critical factor in determining binocular sensory outcomes. Based on these data, Tychsen proposed that alignment within 60 days of onset of esotropia is necessary to achieve high grade stereoacuity.

Fourth, while there is substantial evidence that a congenital absence of binocular sensory function is not found in infantile esotropia, the possibility remains that binocular function is abnormal. There may be genetic, gestational, or perinatal factors that subtly affect brain development. Evidence from identical twins shows precision of stereoscopic depth perception may be heritable. The fact that the prevalence of primary monofixation syndrome in parents of children with congenital esotropia is higher than in the general population also supports the hypothesis that a hereditary abnormality in disparity sensitivity may be associated with infantile esotropia.

In summary, stereoacuity maturation normally proceeds rapidly during the first year of life. Infantile and accommodative esotropia are associated with profound and permanent disruption of stereopsis. Some abnormalities in stereoacuity may exist before the onset of esotropia, but others may result directly from abnormal binocular experience. Maintaining or rehabilitating normal stereoacuity remains a challenge, especially with our limited understanding of genetic factors that are associated with esotropia. However, several strategies for improving stereoacuity outcomes in esotropia are currently under active investigation. New surgical approaches and devices that may improve alignment accuracy are currently under development. In addition, new approaches to early accurate diagnosis are being developed so that very early surgery will be an option. Improved stereoacuity outcomes are associated with better long term stability of alignment, reduced risk for and/or severity of amblyopia, improved
achievement of sensorimotor developmental milestones, better reading ability, and improved long-term quality of life.

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Figure 1.
Maturation of local\textsuperscript{9} and global\textsuperscript{8,10} stereoacuity during the first year of life evaluated by forced choice preferential looking (FPL)\textsuperscript{9,10} and visual evoked potential (VEP)\textsuperscript{8} protocols.
Figure 2.
Stereoacuity outcomes at age \( \geq 5 \) years following treatment for infantile or accommodative esotropia\(^{34, 36}\).
Figure 3.
Stereacuity outcomes at ≥5 years following treatment for infantile esotropia with botulinum toxin at <12 months of age, surgery at ≤6 months of age, or botulinum toxin at 7-23 months of age.

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Table 1
Stereoacuity outcomes at ≥ 5 years of age from children who had surgery for infantile ET.34,44,64-66

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<thead>
<tr>
<th>Age at Alignment</th>
<th>Nil</th>
<th>3000-100 secs arc</th>
<th>≤ 60 secs arc</th>
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<tr>
<td>≤6 months</td>
<td>24%</td>
<td>75%</td>
<td>1%</td>
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<tr>
<td>7-12 months</td>
<td>64%</td>
<td>35%</td>
<td>1%</td>
</tr>
<tr>
<td>13-18 months</td>
<td>61%</td>
<td>38%</td>
<td>1%</td>
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