

# Congenitally Impaired Disparity Vergence in Children With Infantile Esotropia

Krista R. Kelly,<sup>1</sup> Joost Felius,<sup>1,2</sup> Santoshi Ramachandran,<sup>1</sup> Blesson A. John,<sup>1</sup> Reed M. Jost,<sup>1</sup> and Eileen E. Birch<sup>1,2</sup>

<sup>1</sup>Retina Foundation of the Southwest, Dallas, Texas, United States

<sup>2</sup>Department of Ophthalmology, University of Texas Southwestern Medical Center, Dallas, Texas, United States

Correspondence: Krista R. Kelly, Crystal Charity Ball Pediatric Vision Evaluation Center, Retina Foundation of the Southwest, 9600 N. Central Expressway, Suite 200, Dallas, TX 75231, USA; [kkelly@rfsww.org](mailto:kkelly@rfsww.org).

Submitted: November 8, 2015

Accepted: March 25, 2016

Citation: Kelly KR, Felius J, Ramachandran S, John BA, Jost RM, Birch EE. Congenitally impaired disparity vergence in children with infantile esotropia. *Invest Ophthalmol Vis Sci*. 2016;57:2545-2551. DOI:10.1167/iov.15-18606

**PURPOSE.** We examined whether congenital impairment of disparity vergence in infantile esotropia (ET) exists in children with short duration ET ( $\leq 3$  months) compared with long-duration ET and healthy controls. A short duration of misalignment would allow for a substantial amount of balanced binocular input during the critical period of binocular disparity development.

**METHODS.** A total of 19 children aged 5 to 12 years and treated for infantile ET with a short ( $\leq 3$  months;  $n = 10$ ) or long ( $\geq 5$  months;  $n = 9$ ) duration of constant misalignment before alignment were enrolled. A total of 22 healthy control children were enrolled as a comparison group. Eye movements during disparity vergence and accommodative vergence were recorded using an EyeLink 1000 binocular eye tracker. Mean response gain was compared between and within groups to determine the effect of duration of misalignment and viewing condition.

**RESULTS.** Compared with controls, children with short ( $P = 0.002$ ) and long ( $P < 0.001$ ) duration infantile ET had reduced response gains for disparity vergence, but not for accommodative vergence ( $P = 0.19$ ).

**CONCLUSIONS.** Regardless of duration of misalignment, children with infantile ET had reduced disparity vergence, consistent with a congenital impairment of disparity vergence in infantile ET. Although early correction of misalignment increases the likelihood that some level of binocular disparity sensitivity will be present, normal levels may never be achieved.

**Keywords:** disparity vergence, infantile esotropia, binocular disparity, visual development

Infantile esotropia (ET) is a large-angle deviation that emerges before 6 months of age. After optimal surgical alignment, monofixation—a 3 to 5° foveal suppression scotoma—is typically present during binocular viewing.<sup>1,2</sup> The absence of bifoveal fusion is accompanied by impairments of binocular disparity mechanisms, including vergence.<sup>3-6</sup> Nonhuman primate models of infantile ET show normal disparity vergence responses following a short duration (3 weeks) of induced binocular decorrelation.<sup>5</sup> Based on these findings, the current consensus is that impaired disparity vergence is acquired as a result of decorrelated binocular input during the critical period of visual development and that it can be prevented or rehabilitated with early surgical intervention.<sup>2,5</sup> However, the nonhuman primate model may be fundamentally different from the human with infantile ET; the ET is induced in an otherwise normal visual system that lacks any genetic or prenatal factors that may be associated with infantile ET in humans. Thus, esotropic nonhuman primates may have a potential to develop normal disparity vergence responses that the human congenitally lacks.

We explored the hypothesis that the impairment in disparity vergence associated with monofixation in infantile ET is, at least in part, congenital. This hypothesis is supported by the lack of normal stereoacuity in 96% of esotropic children with early surgical alignment before 6 months of age.<sup>7,8</sup> Although stereopsis and disparity vergence are separate processes,<sup>9</sup> they

are both reliant on disparity processing within the central 3 to 5° of vision.<sup>1,10</sup> A simulated monofixation scotoma of 4 to 8° in normally sighted adult controls results in abnormal disparity vergence responses with a high prevalence of saccades,<sup>11</sup> suggesting a link between monofixation and abnormal disparity vergence in infantile ET. Indeed, esotropic humans and nonhuman primates have abnormal disparity vergence responses, including reduced response gain, pure saccades, or a combination of both.<sup>3-6,12,13</sup> However, none of these studies have assessed whether the duration of constant misalignment has an effect on disparity vergence responses in esotropic children.

To challenge the hypothesis that the impairment in disparity vergence is acquired, we followed the same protocol used by Tychsen<sup>5,6</sup> who determined that a short duration (3 weeks) of binocular decorrelation did not disrupt disparity vergence in the nonhuman primate model of infantile ET. We compared disparity vergence in children aged 5 to 12 years with a short ( $\leq 3$  months) or long duration ( $\geq 5$  months) of constant infantile ET before alignment with healthy control children. Duration groups were based on research showing better binocular disparity sensitivity outcomes with early surgery and a duration of misalignment of 3 months or less,<sup>5,14</sup> and a correspondence between a duration of 3 months in humans to 3 weeks duration in the nonhuman primate model.<sup>5,6</sup> If disparity vergence responses in children with a short duration of constant infantile



ET are comparable with control children, the currently accepted hypothesis of an acquired disparity vergence deficit would be supported. However, if disparity vergence responses in short duration children are abnormal when compared with control children, the proposed hypothesis of a congenital disparity vergence deficit would be supported.

## METHODS

### Participants

A total of 19 children (mean age 8.7 years [SD 1.8]; range, 5.3–12.3 years of age) diagnosed with classic infantile ET<sup>7,8</sup> were referred for this study at the Retina Foundation of the Southwest by nine pediatric ophthalmologists. Age at diagnosis and duration of constant infantile ET were based on medical record review. From these records, we identified 10 children with a short duration of constant ET ( $\leq 3$  months) and 9 children with a long duration of constant ET ( $\geq 5$  months) before alignment. Duration of constant ET was defined as the number of months between the initial diagnosis of constant ET and the age of alignment. Age at alignment was defined as the age in months at which alignment within 0 to 6 prism diopters (PD) was first achieved and maintained for at least 12 months. Coupled with a short duration of ET, the 6 PD criterion is associated with the recovery of binocular function.<sup>14–16</sup> Both disparity sensitivity and disparity vergence develop rapidly during the first year of life, so later misalignments would be expected to have little effect on disparity vergence.<sup>17,18</sup> At the time of testing, all children had 0.2 logMAR (20/32) or better visual acuity in each eye and were aligned within 6 PD of orthotropia by simultaneous prism and cover test at near; misalignment that exceeds 6 PD precludes high grade stereoacuity.<sup>1,19</sup> In addition, 22 age-similar control children (mean age 8.5 years [SD 2.2]; range, 5.2–11.8 years of age) with healthy visual acuity, normal Randot stereoacuity, and no history of vision disorders were enrolled. All children wore their habitual optical correction during testing if applicable. Exclusion criteria were prematurity  $\geq 8$  weeks, coexisting ocular or systemic disease, congenital infections or malformations, and developmental delay.

### Ethics

The research protocol observed the tenets of the Declaration of Helsinki, was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center, and conformed to the requirements of the United States Health Insurance Portability and Privacy Act. Informed consent was obtained from a parent or legal guardian prior to testing and after explanation of the nature and possible consequences of the study.

### Procedure

Prior to vergence testing, crowded monocular best-corrected visual acuity was obtained for each eye using the e-ETDRS protocol<sup>20,21</sup> for children  $\geq 7$  years of age, or the Amblyopia Treatment Study HOTV protocol for children  $< 7$  years of age.<sup>22,23</sup> Stereoacuity was also measured using the Randot Preschool Stereoacuity and Stereo Butterfly Tests (Stereo Optical Co., Inc., Chicago, IL, USA).

**Apparatus and Eye Movement Recording.** Testing took place in a dimly lit room. Eye movements were recorded using a 500 Hz remote high-speed video binocular eye tracker (EyeLink 1000; SR Research, Ontario, Canada). Stabilization of the child's head was accomplished using a chin/forehead rest. The visual display consisted of four red light-emitting diodes

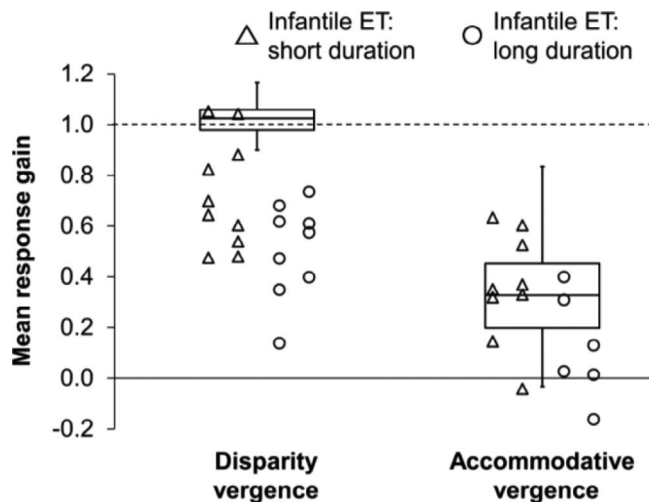
(LEDs; dominant wavelength 625 nm; spectral line half width 45 nm) 0.5 cm in diameter; three were 74 cm from the child in a horizontal line at 0° (far) and at  $\pm 10.7^\circ$ . The remaining red LED (near) was 26 cm from the child at 0° but displaced above the far LEDs by 10.7°. Physically displaced LEDs provide binocular disparity cues and elicit robust vergence responses in nonhuman primates.<sup>5,24</sup> Because the LEDs are at different distances from the eye, they also provide some accommodative (blur) cues to the accommodative vergence system. Stationary, monochromatic lights have been shown to be sufficient accommodation stimuli in humans.<sup>25</sup> When illuminated, the LEDs blinked at 7 Hz to enhance their visibility. A chirping sound was presented simultaneously to maintain the child's attention. The child was instructed to follow the light as it jumped from LED to LED. Individual three-point horizontal calibration was achieved under binocular viewing using the three LEDs at 74 cm.

**Vergence Eye Movements.** Methods were similar to those used by Tychsen<sup>6</sup> to investigate long latency disparity vergence in an animal model of infantile ET. Long latency (150–250 msec) vergence responds to disparities up to approximately 10° during fixation.<sup>26</sup> The task consisted of blocked disparity vergence (binocular viewing) and accommodative vergence (preferred eye viewing) trials with at least 10 vergence responses. For each trial, the child initially fixated on the blinking far LED, which was extinguished and the near LED was illuminated, requiring a convergence response. The duration of the far LED was varied manually to eliminate anticipatory eye movements to the near LED. The near LED remained illuminated for a duration of 2 seconds to ensure a maximum vergence response, then it was turned off. Mean interpupillary distance was 50 mm, requiring a convergence angle of 3.8° to bifixate the far LED and 10.9° to bifixate the near LED. This resulted in approximately  $\Delta 7.1^\circ$  in vergence demand (approximately  $\Delta 3.6^\circ$  per eye). The magnitude of the vergence demand varied somewhat with individual differences in interpupillary distance but all were within the resolution of the EyeLink 1000 system. Accommodative vergence was assessed during preferred eye viewing (left eye for control children) with a Hoya R72 infrared (IR; blocks  $< 720$  nm; LED dominant wavelength was 625 nm) filter over the nonpreferred eye that passes only IR wavelengths, eliminating any disparity cues but still allowing for both eyes to be tracked. The step change in accommodative demand was 2.4 diopters.

### Data Analysis

All data were processed using a custom Matlab (The MathWorks, Inc., Natick, MA, USA) algorithm that shifted individual traces vertically to coincide at baseline. For each viewing condition, at least three artifact-free responses were required for analyses that met established criteria for valid data<sup>5</sup>: a stable fixation on the far LED prior to onset of the near LED, a response within 1 second of the near LED onset, movement of at least one eye by  $2.5 \pm 1.5^\circ$  in the correct direction, and the new position stabilized for  $\geq 0.5$  seconds. Because the near and far LEDs were vertically displaced, a vertical saccade was used as an indicator for vergence initiation; if no vertical saccade occurred, the trial was discarded. Once a vertical saccade was observed (i.e., vergence was initiated), we identified an analysis window that consisted of the segment of the 0.5 to 2 seconds of the eye movement record, during which the new eye position was maintained for 0.5 to 2 seconds.

The calculation of vergence response gain was based on the step change in vergence (in degrees) from the far LED to the near LED and was calculated separately per child for binocular



**FIGURE 1.** Box-and-whisker plots of the distribution of response gain for healthy controls for disparity vergence and accommodative vergence. The horizontal line within each box represents the median normal control score, and the boxes correspond to the 25th to 75th percentiles, the whiskers correspond to the fifth and 95th percentiles. Individual data points for children with short-duration (open triangles) and long-duration (open circles) infantile ET are also plotted. A value of 1 (dotted line) indicates that the gain matches the demand of converging to the near LED.

and preferred eye-viewing conditions. The mean vergence response gain was calculated by dividing the mean vergence angle of all valid trials by the vergence demand (approximately  $\Delta 7.1^\circ$ ) required to shift vergence from the far LED to the near LED (response gain = vergence angle/vergence demand). Positive values indicate convergence, whereas negative values indicate divergence. A mean response gain of 1.0 represents a convergence response that matches the demand of converging from the far LED to the near LED.

One-way analyses of variance were conducted to determine the effect of duration of infantile ET (short, long) on the mean response gain for disparity vergence and on the mean response gain for accommodative vergence when compared with controls. A significant analysis of variance was followed with post hoc planned comparisons or separate-variance *t*-tests when homogeneity of variance was violated. Paired *t*-tests comparing the mean response gain for disparity vergence versus accommodative vergence were also conducted per group (short-duration infantile ET, long-duration infantile ET, healthy control) to determine the effect of viewing condition. Disparity is a more powerful stimulus to vergence than accommodative blur in controls.<sup>4</sup> If disparity is not driving vergence in infantile ET, there should be minimal to no difference between disparity and accommodative vergence responses.

## RESULTS

Individual patient characteristics at time of testing, alignment history, and mean response gain for disparity vergence are found in Table 1. No difference in age was found between groups ( $F_{2,44} = 0.72$ ,  $P = 0.54$ ). Four children with infantile ET (two short duration, two long duration) had mild amblyopia at the time of testing (20/20 in preferred eye, 20/32 in nonpreferred eye). Eight children with infantile ET (three short duration, five long duration) had been treated previously for mild amblyopia and recovered. Reduced (subnormal but measurable) stereoacuity was found in 3 children with

infantile ET, and nil stereoacuity in the remaining 16 children with infantile ET. Of the 10 children with short-duration infantile ET, six were orthotropic at the time of testing; five of the six orthotropic children were aligned at the 6-week visit following the initial surgery and maintained alignment long term. Of the nine children with long-duration infantile ET, four were orthotropic at the time of testing; three of these were aligned following a second surgery during infancy and maintained that alignment long term. The remaining children had intermittent or constant strabismus  $\leq 6$  PD at the time of testing.

### Effect of Duration of Constant Infantile ET

**Disparity Vergence.** Mean response gain was significantly different among groups ( $F_{2,38} = 42.05$ ,  $P < 0.001$ ). Children with short-duration infantile ET had a significantly reduced gain by 28% (0.73 [0.22]) when compared with healthy controls (1.02 [0.07];  $P = 0.002$ ). Children with long-duration infantile ET had a significantly reduced gain by 49% (0.52 [0.19]) when compared with healthy controls ( $P < 0.001$ ), and by 29% when compared with short-duration infantile ET ( $P = 0.003$ ) (see Fig. 1). Both infantile ET groups still exhibited significantly reduced gain when children who were mildly amblyopic at the time of testing were excluded from the analysis ( $P < 0.001$ ). Response gain was not different between children who were previously or currently mildly amblyopic and those who were never amblyopic ( $P_s \geq 0.25$ ).

Figure 2 shows typical disparity vergence responses from one healthy control and three children with infantile ET. Because it is difficult for children to maintain a stable head position, even with a chin/forehead rest, there is some ambiguity in whether small amplitude saccades might have been an artifact associated with inaccurate head position. Overall, the majority of children with infantile ET had a reduced response gain for disparity vergence, and one child with long-duration infantile ET produced a pure saccade rather than a disparity vergence response. Although all 22 healthy control children exhibited disparity vergence responses that approximately matched demand; that is, disparity vergence response gain was approximately 1.0, only two children with short-duration infantile ET exhibited a response gain within the range of healthy controls.

**Accommodative Vergence.** Accommodative vergence data from 2 of the 22 controls and 1 of the 10 children with short-duration infantile ET provided insufficient data because of fatigue and/or motion artifacts. Accommodative vergence for three of the nine children with long-duration infantile ET was not possible because of a large phoria that manifested under cover. A similar result has been found during monocular viewing for one monkey induced with infantile ET.<sup>6</sup> The mean response gain for accommodative vergence did not differ significantly among groups (short-duration infantile ET = 0.37 [0.21]; long-duration infantile ET = 0.13 [0.21]; controls = 0.34 [0.30];  $F_{2,32} = 1.73$ ,  $P = 0.19$ ; see Fig. 1).

### Effect of Viewing Condition in Children With Infantile ET and Controls

Only children who provided data for both disparity vergence and accommodative vergence were included in this analysis. All groups showed a significantly higher mean response gain for disparity vergence than accommodative vergence (short-duration infantile ET: 0.70 [0.20] vs. 0.37 [0.21];  $t_8 = 2.97$ ,  $P = 0.018$ ; long-duration infantile ET: 0.52 [0.19] vs. 0.13 [0.21],  $t_5 = 7.51$ ,  $P < 0.001$ ; controls: 1.02 [0.07] vs. 0.34 [0.30];  $t_{19} = 10.06$ ,  $P < 0.001$ ; see Fig. 3).

TABLE 1. Individual Patient Characteristics at Time of Testing, Alignment History, and Mean Response Gain

PT	Age, y	VA OD, logMAR	VA OS, logMAR	Amblyopia	RDS, Arc Secs	Glasses	Current Near Tropia	Duration Constant ET, m	Pre-op Tropia,* N/D	6-Week Post-op Tropia,* N/D	3-Month Post-op Tropia,* N/D	6-Month Post-op Tropia,* N/D	1-Year Post-op Tropia,* N/D	Disparity Vergence Gain
S1	6.4	0.00	0.10	Never	nil	No	0	<3	ET30/ET25	EC(T)14/ EC(T)14	0/0	0/0	0/0	0.71
S2	5.3	0.20	0.00	Mild OD	nil	Yes	0	3.5	ET50/ET50	0/0	0/0	0/0	0/0	1.05
S3	12.3	-0.10	-0.10	Never	nil	Yes	ET2	2	ET75/ET75	EC(T)4/0	0/0	0/0	ET2/0	0.55
S4	7.6	0.10	0.00	Never	nil	Yes	0	2	ET35/ET30	0/0	0/0	0/0	0/0	0.61
S5	6.8	0.10	0.20	Never	nil	No	EC(T)4	3.0	ET85/ET85	EC(T)25/0	EC(T)6/0	EC(T)6/0	0/0	0.83
S6	8.5	0.10	0.20	Never	800	Yes	0	2	ET30/ET30	0/0	0/0	0/0	0/0	1.06
S7	11.0	-0.10	0.10	Recovered mild OS	nil	Yes	0	2	ET25/ET30	0/0	0/0	0/0	0/0	0.89
S8	9.5	0.00	0.00	Never	nil	Yes	EC(T)6	1	ET35/ET35	0/0	0/0	0/0	0/0	0.49
S9	9.3	0.20	0.10	Never	nil	Yes	0	1.5	ET50/ET50	0/0	0/0	0/0	0/0	0.49
S10	6.0	0.00	0.20	Mild OS	nil	Yes	RHT2	2.5	ET30/ET35	ET6/ET2	ET4/ET2	Missed appt	ET4/ET2	0.65
L1	9.2	0.00	0.20	Mild OS	nil	Yes	X(T)4	5	ET40/ET40	ET8/ET8	ET20/ET10	ET25/ET20	0/0	0.15
L2	10.5	0.20	0.10	Recovered mild OD	nil	Yes	0	7	ET50/ET50	EC(T)8/EC(T)8	ET15/ET15	0/0	0/0	0.74
L3	7.8	0.20	0.00	Mild OD	nil	No	0	>11	ET45/ET45	0/0	E8/E8	ET12H4/ ET12HT4	0/0	0.58
L4	7.9	0.00	0.00	Never	nil	No	ET4	12	ET35/ET30	ET25/ET12	ET10/0	ET25/ET25	ET25/ET25	0.69
L5	10.1	0.10	0.00	Recovered mild OD	nil	Yes	LHT3 X(T)4	7	ET35/ET35	ET10/ET8	XI6/XI6	XI20HT16/ XI8HT16	X(T)12/H(T)10/ X(T)4/H(T)10	0.41
L6	9.4	0.00	0.00	Never	nil	Yes	0	7	ET35/ET35	0/EC(T)20	0/0	0/0	0/0	0.36
L7	7.0	0.10	0.10	Recovered mild OS	nil	Yes	ET6	>12	ET25/ET45	0/0	ET2/E2	0/ET10	ET8/ET8	0.63
L8	10.0	-0.10	-0.10	Never	nil	Yes	ET6	10	ET55/ET55	ET8/ET20	ET8/ET20	0/0	0/EC(T)10	0.48
L9	9.9	0.10	0.00	Never	nil	Yes	0	>12	ET85/ET85	ET25/ET25	ET25/ET25	ET30/ET30	ET10/ET10	0.62

PT, patient identification; S, short duration ET; L, long duration ET; RDS, Randot stereoacuity; N/D, Near/Distance; VA, visual acuity; OD, right eye; OS, left eye; XT, exotropia; HT, hypertropia.  
\* Measured with habitual optical correction, if any.

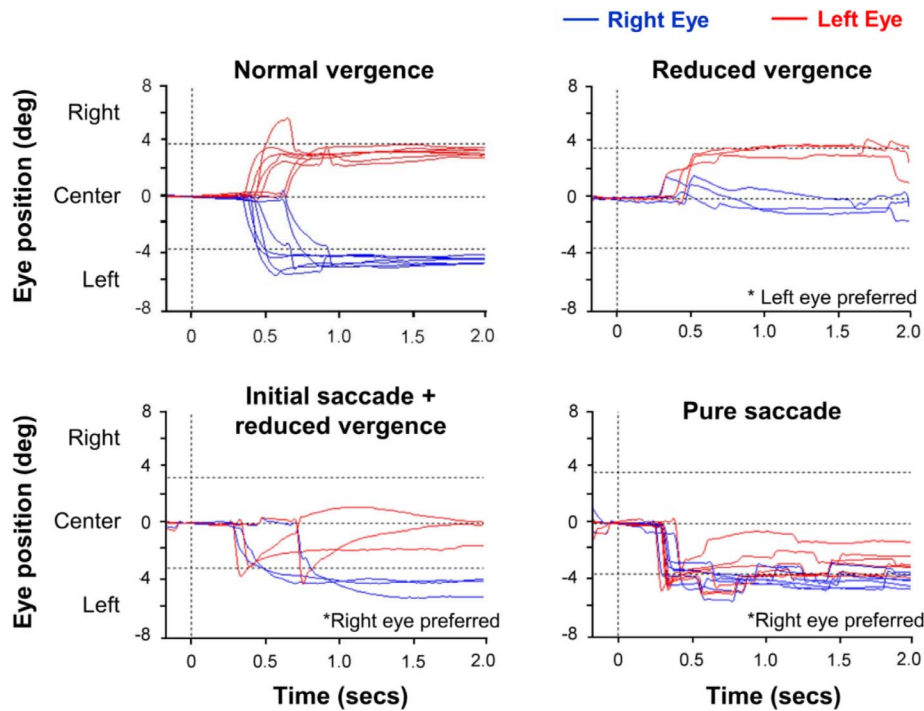


FIGURE 2. Examples of normal disparity vergence in a typical control child, and reduced disparity vergence with and without an initial saccade, and pure saccade responses in children with infantile ET. The horizontal dotted lines near  $\pm 3.6$  represent the demand for each eye to converge from the far LED to the near LED. The vertical dotted line represents stimulus onset. Eye positions to the right have a positive value, and eye positions to the left have a negative value. Fixation instability (square-wave oscillations) is apparent in the records of the child who had a pure saccade response to the disparity vergence stimulus.

DISCUSSION

Our finding of reduced gain for disparity vergence in children with a short duration of constant misalignment points to a congenital defect in disparity vergence in infantile ET that, even with early surgery and treatment, may never be restored.

A congenital explanation challenges the currently accepted acquired explanation for a disparity vergence impairment that is supported by studies showing that early intervention can result in normal disparity vergence in nonhuman primate models of infantile ET. In our study, we closely followed the same protocol used to evaluate disparity vergence in the nonhuman primate studies,<sup>5,6</sup> but we found impaired disparity vergence was present even with only a short duration of constant infantile ET. However, the deficit was more pronounced following long-duration infantile ET, suggesting a congenital deficit that is further compounded by prolonged abnormal binocular experience.

The short-duration infantile ET group had less than 3 months of constant misalignment; this is a critical distinction from intermittent misalignment because it has been shown that intermittent misalignment is not sufficient to disrupt the development of disparity sensitivity.<sup>27</sup> It is possible that a constant ET of less than 3 months duration is still sufficient to disrupt disparity vergence in infants who, at the time of surgery, were less than a year in age. Yet Tychsen<sup>5</sup> showed that disparity vergence was normal following 3 weeks of binocular decorrelation in nonhuman primates, which is the equivalent of 3 months duration in humans.<sup>28,29</sup> In our study, even those who had just 1 month of constant ET showed reduced disparity vergence. The stark difference in results between our study and Tychsen's provides support for the hypothesis that disparity vergence impairments in children with infantile ET are congenital.

Our alignment criterion of  $\leq 6$  PD was based on the limit that precludes high-grade stereoacuity.<sup>1,19</sup> This criterion resulted in many infantile ET children as ineligible for the study because they would not have been able to experience balanced binocular input. Deviations of  $\leq 6$  PD may still have the potential to disrupt disparity vergence. However, even

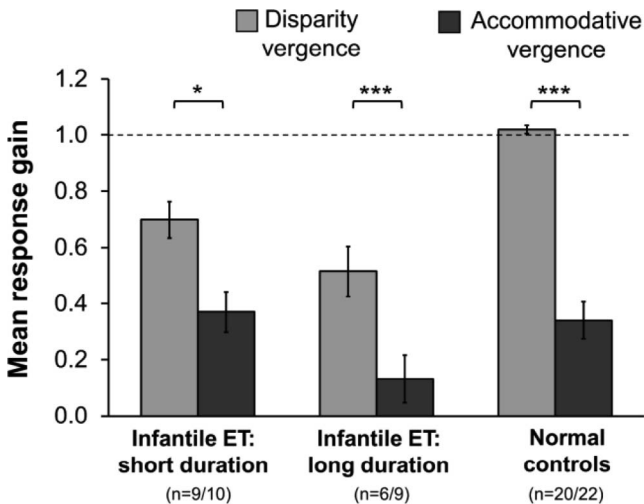


FIGURE 3. Bar graphs showing within-group differences for mean response gain for disparity vergence (light gray bars) and accommodative vergence (dark gray bars). A value of 1 (dotted line) indicates that the gain matches the demand of the near LED. The number of children for which both disparity vergence and accommodative vergence data were available of the total number of children per group are included. Error bars represent  $\pm$  standard error of the mean (SEM). \* $P < 0.05$ ; \*\*\* $P < 0.001$ .

those children who achieved orthoposition following early alignment surgery and maintained alignment long term had reduced disparity vergence.

Qualitatively, we observed abnormal eye movements in response to disparity vergence in infantile ET that have also been reported by others,<sup>3-6,12</sup> including reduced response gain (with or without an initial saccade) and a pure saccade only. In our study, the majority of children exhibited reduced response gain, but only one child who had long-duration infantile ET exhibited a pure saccade. Similar to Morad et al.,<sup>3</sup> who reported saccadic vergence in only two of nine children with infantile ET, our patients had a long history of constant ET and multiple eye alignment surgeries. Two children with short-duration infantile ET exhibited normal response gain for disparity vergence, which appears to be inconsistent with our theory of a congenital disparity vergence impairment. Yet binocular function was still abnormal in these children: one child had markedly reduced stereoacuity (800 arcsec), whereas the other had nil stereoacuity and exhibited large amplitude fusion maldevelopment nystagmus syndrome (manifest latent nystagmus). At least in these two children, normal disparity vergence was not associated with normal stereoacuity, consistent with prior research showing that stereopsis and vergence are separate binocular disparity mechanisms.<sup>9,30</sup>

Reduced gain for disparity vergence in infantile ET may be because of inaccurate nonpreferred eye position as a result of relying on nonfoveal, peripheral disparity sensitivity in the absence of central disparity sensitivity.<sup>12</sup> Because disparity information improves vergence responses in children with infantile ET (i.e., larger gain for disparity than accommodative vergence), impaired disparity vergence is likely not related to immaturities in ocular muscles or subcortical nuclei responsible for eye movements.<sup>5</sup> Instead, the congenital deficit may lie in early visual cortex responsible for processing binocular disparity information (e.g., V1).<sup>5,31</sup> Other potential congenital factors include perinatal insult, maldevelopment of the geniculostriate pathway, and genetic error.

In contrast to reduced gain for disparity vergence, children with short- and long-duration infantile ET exhibited response gain for accommodative vergence (preferred eye viewing) comparable to healthy controls. Reduced gain for accommodative vergence versus disparity vergence indicates that the IR filter was sufficient to block disparity cues even in healthy controls; that is, vergence gain with the IR filter in place was reduced by 67%. However, the LED in our study did not contain high-resolution information and was not a typical accommodative target such as a small letter.<sup>32</sup> Thus, our LED was probably a weak accommodative stimulus. In addition, it is possible that proximal cues (i.e., an awareness of a near object) rather than accommodative (blur) cues were driving accommodative vergence, which may eliminate group differences. Yet, stationary monochromatic lighted targets are sufficient stimuli for accommodation,<sup>25</sup> and gain for accommodative vergence in our control children fell within the limits for that previously reported (34% [30] vs. ~38% [22]).<sup>4</sup> Even if accommodation was so weak that these children were relying on proximal vergence, this does not affect the main finding that disparity vergence is reduced in infantile ET.

As a result of noisy data, underlying phoria, and/or fatigue, our sample size for accommodative vergence was reduced when compared with disparity vergence. Therefore, the analysis could have been underpowered. Yet all but one child with infantile ET had the same pattern as healthy controls—significantly reduced gain for accommodative vergence when compared with disparity vergence—a finding that has been previously reported in controls.<sup>4,6</sup> Thus, the same pattern of results would likely be found for accommodative vergence if our sample size was larger. Our data show that disparity

information was available to children with infantile ET to improve disparity vergence responses when compared with accommodative vergence, consistent with previous data from esotropic children.<sup>4</sup> However, disparity cues to vergence are not being used as accurately or efficiently as seen in controls, further supporting the hypothesis that monofixation is an outcome of a congenital bifoveal (or central) fusion deficit. This deficit may force children with infantile ET to rely on peripheral disparity sensitivity (peripheral fusion) to drive vergence responses during binocular viewing.

Inconsistency in binocular disparity sensitivity outcomes between previous studies and ours can be explained by differences in methodology and patient characteristics. We used physically displaced lighted LEDs to assess disparity vergence; other studies assessed disparity vergence using prisms to induce fusional convergence.<sup>3,30</sup> Furthermore, we tested children diagnosed with large-angle infantile ET unlikely to resolve without surgery and who had been successfully aligned within 6 PD. In monkey models of infantile ET, the ET was induced in an otherwise normal visual system using prisms, alternate occlusion, or surgical misalignment, resulting in small-angle ET or recovery prior to testing.<sup>5,6,30</sup> Last, previous studies included heterogeneous groups of patients with varying degrees of current manifest deviation (both esotropic and exotropic), late age at surgery, and a large range of duration of misalignment.<sup>3,4,12,13</sup> It is difficult to determine potential causes of abnormal vergence responses with heterogeneous groups or to assess binocular eye movements when the eyes are not straight.

In conclusion, we found evidence supporting a theory of congenitally impaired binocular disparity vergence among children with infantile ET, even with early intervention. These findings are contrary to the current theory that the deficit is acquired and requires an entirely new paradigm for how researchers think about and treat binocular disparity sensitivity impairment in infantile ET. Although our data support a congenital deficit in disparity vergence in infantile ET, it is also clear that disparity vergence may be further degraded when constant misalignment is prolonged early in life.

### Acknowledgments

The authors thank Angie De La Cruz, Sarah Morale, and Kirby Mateja for their help with data collection. This study was conducted at the Retina Foundation of the Southwest and presented at the ARVO 2015 Annual Meeting. Supported by the National Eye Institute (EY02313). The authors alone are responsible for the content and writing of the paper.

Disclosure: **K.R. Kelly**, None; **J. Felius**, None; **S. Ramachandran**, None; **B.A. John**, None; **R.M. Jost**, None; **E.E. Birch**, None

### References

1. Parks MM. The monofixation syndrome. *Trans Am Ophthalmol Soc.* 1969;67:609-657.
2. Tychsén L. Can ophthalmologists repair the brain in infantile esotropia? Early surgery, stereopsis, monofixation syndrome, and the legacy of Marshall Parks. *J AAPOS.* 2005;9:510-521.
3. Morad Y, Lee H, Westall C, et al. Dynamic fusional vergence eye movements in congenital esotropia. *Open Ophthalmol J.* 2008;2:9-14.
4. Horwood AM, Riddell PM. Accommodation and vergence response gains to different near cues characterize specific esotropias. *Strabismus.* 2013;21:155-164.
5. Tychsén L. Causing and curing infantile esotropia in primates: the role of decorrelated binocular input (an American Ophthalmological Society thesis). *Trans Am Ophthalmol Soc.* 2007;105:564-593.

6. Tychsen L, Scott C. Maldevelopment of convergence eye movements in macaque monkeys with small- and large-angle infantile esotropia. *Invest Ophthalmol Vis Sci.* 2003;44:3358-3368.
7. Birch EE, Stager DR. Long-term motor and sensory outcomes after early surgery for infantile esotropia. *J AAPOS.* 2006;10:409-413.
8. Pediatric Eye Disease Investigator Group. Spontaneous resolution of early-onset esotropia: experience of the Congenital Esotropia Observational Study. *Am J Ophthalmol.* 2002;133:109-118.
9. Lutgheid AJ, Wilcox LM, Allison RS, Howard IP. Vergence eye movements are not essential for stereoscopic depth. *Proc Biol Sci.* 2014;281:20132118.
10. Irvine S. A simple test for binocular fixation: clinical application useful in the appraisal of ocular dominance, amblyopia ex anopsia, minimal strabismus, and malingering. *Am J Ophthalmol.* 1944;27:740-746.
11. Eizenman M, Sapir-Pichhadze R, Westall CA, et al. Eye-movement responses to disparity vergence stimuli with artificial monocular scotomas. *Curr Eye Res.* 2006;31:471-480.
12. Kenyon RV, Ciuffreda KJ, Stark L. Dynamic vergence eye movements in strabismus and amblyopia: asymmetric vergence. *Br J Ophthalmol.* 1981;65:167-176.
13. Kenyon RV, Ciuffreda KJ, Stark L. Dynamic vergence eye movements in strabismus and amblyopia: symmetric vergence. *Invest Ophthalmol Vis Sci.* 1980;10:60-74.
14. Birch EE, Fawcett S, Stager DR. Why does early surgical alignment improve stereoacuity outcomes in infantile esotropia? *J AAPOS.* 2000;4:10-14.
15. Birch EE. Marshall Parks lecture. Binocular sensory outcomes in accommodative ET. *J AAPOS.* 2003;7:369-373.
16. Fawcett S, Leffler J, Birch E. Factors influencing stereoacuity in refractive accommodative esotropia. *J AAPOS.* 2000;4:15-20.
17. Birch EE, Salomão S. Infant random dot stereoacuity cards. *J Pediatr Ophthalmol Strabismus.* 1998;35:86-90.
18. Hainline L, Riddell PM. Binocular alignment and vergence in early infancy. *Vision Res.* 1995;35:3229-3236.
19. Leske DA, Holmes JM. Maximum angle of horizontal strabismus consistent with true stereopsis. *J AAPOS.* 2004;8:28-34.
20. Beck R, Moke P, Turpin A, et al. A computerized method of visual acuity testing: adaptation of the early treatment of diabetic retinopathy study testing protocol. *Am J Ophthalmol.* 2003;135:194-205.
21. Cotter SA, Chu RH, Chandler DL, et al. Reliability of the electronic early treatment diabetic retinopathy study testing protocol in children 7 to <13 years old. *Am J Ophthalmol.* 2003;136:655-661.
22. Moke PS, Turpin AH, Beck RW, et al. Computerized method of visual acuity testing: adaptation of the amblyopia treatment study visual acuity testing protocol. *Am J Ophthalmol.* 2001;132:903-909.
23. Holmes JM, Beck RW, Repka MX, et al. The amblyopia treatment study visual acuity testing protocol. *Arch Ophthalmol.* 2001;119:1345-1353.
24. Maxwell JS, King WM. Dynamics and efficacy of saccade-facilitated vergence eye movements in monkeys. *J Neurophysiol.* 1992;68:1248-1260.
25. Aggarwala KR, Nowbotsing S, Kruger PB. Accommodation to monochromatic and white-light targets. *Invest Ophthalmol Vis Sci.* 1995;36:2695-2705.
26. Tychsen L, Richards M, Wong AMF, et al. Decorrelation of cerebral visual inputs as the sufficient cause of infantile esotropia. *Am Orthopt J.* 2008;58:60-69.
27. Fu VLN, Stager DR, Birch EE. Progression of intermittent, small-angle, and variable esotropia in infancy. *Invest Ophthalmol Vis Sci.* 2007;48:661-664.
28. Boothe RG, Dobson V, Teller DY. Postnatal development of vision in human and nonhuman primates. *Annu Rev Neurosci.* 1985;8:495-545.
29. O'Dell C, Boothe RG. The development of stereoacuity in infant rhesus monkeys. *Vision Res.* 1997;37:2675-2684.
30. Harwerth R, Smith E, Crawford MIJ, von Noorden GK. Stereopsis and disparity vergence in monkeys with subnormal binocular vision. *Vision Res.* 1997;37:483-493.
31. Hubel DH, Wiesel TN. Functional architecture of macaque monkey visual cortex. *Proc R Soc London Ser B.* 1977;198:1-59.
32. Kergoat H, Lovasik JV. Influence of target color and vergence of light on ocular accommodation during binocular fixation. *Curr Eye Res.* 1990;9:935-953.