trol of cell proliferation and the stimuli that evoke it in the cornea.

**Key words:** cell cycle, cornea, epithelium, flow cytometry, wound healing

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**References**


**Anomalous Motion VEPs in Infants and in Infantile Esotropia**

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Visual evoked potentials (VEPs) were recorded monocularly in response to vertical gratings that underwent oscillatory apparent motion at a temporal frequency of 10 Hz. In normal infants 6 months or younger and in patients with a history of constant strabismus onset before 6 months of age, the oscillatory motion VEP contains a prominent first harmonic component that is temporally 180° out of phase in the two eyes. This pattern is not seen in normal adults and is consistent with the presence of a nasally/temporalward asymmetry of cortical responsiveness in infants and in patients with early onset strabismus. Invest Ophthalmol Vis Sci 32:436–439, 1991

The oculomotor behavior of patients with a history of infantile esotropia bears a striking resemblance to that of normal neonates. Monocular optokinetic nystagmus is asymmetric in both esotropic patients and neonates; slow-phase gain is higher for nasally directed motion. Esotropic patients are known to show asymmetric smooth pursuit of small targets and to have sluggish open-loop pursuit acceleration for temporally directed motion in the step-ramp task. These patients also perceive nasally directed motion to be faster than temporally directed motion of the same velocity. Since visual cortex provides the dominantafferent input to the pursuit system and since there is a perceptual correlate of the nasalward vs temporalward motion asymmetry, the visual cortex may be involved in the genesis of the oculomotor asymmetries found in infantile esotropia. In this report, VEP evidence for cortical involvement in the production of asymmetric eye movements is presented.

**Materials and Methods.** Observers: Thirteen members of the laboratory staff participated in the study. None had a history of abnormal binocular vision, and each had acuity correctable to 6/6 or better in each eye. Eleven normal infants between 6–26 weeks of age, who had no strabismus or significant refractive errors, were recruited from parent education classes. Fifteen patients who had constant esotropia onset before 6 months of age were also tested. Onset of esotropia was documented either by history or from medical records. Each patient had 20/30 or better acuity in their worst eye, and no patient had more than an octave acuity difference between eyes. Twelve of the fifteen esotropic patients had strabismus surgery after 2 yr of age. The three patients...
who had a first surgery before 2 yr of age required a second surgery before 2.5 yr. The patient group ranged in age from 9–41 yr (mean: 17.5). Informed consent was obtained from the adult participants and the parents of the infants and children before they were tested.

**Visual Evoked Potential (VEP) Recording:** Motion VEPs were measured monocularly in response to vertical sinusoidal gratings displayed on a video monitor. The gratings were presented on a 10 × 20° field with a space average luminance of 80 cd/m² and a Michelson contrast of 80%. The gratings were square-wave alternated between two positions separated by 90° of spatial phase. The temporal rate of stimulation was 10 Hz (20 changes of direction/sec). The gratings appeared to vibrate back and forth. The spatial frequency of the grating was scaled to be at least five times lower than the observer’s expected acuity based on age: infants were tested with 0.5 to 1 cycles/degree gratings; children were tested at 3 c/deg and adults were tested at 3 or 6 c/deg. The gratings were presented for 10 sec, and several trials were recorded from each eye. Two bipolar derivations were used: O₁ vs O₂ and O₂ vs O₁. The VEP was subjected to Fourier analysis to extract the amplitude and phase of the evoked response at 10 and 20 Hz. The general methods we have described elsewhere were used.⁶

**Fourier Method to Detect Motion Asymmetry:** Symmetric and asymmetric motion VEPs produce characteristic Fourier spectra. A VEP in which the response to the two directions of motion is equal yields a response spectrum that is completely composed of even harmonic multiples of the 10-Hz stimulation frequency. An asymmetric VEP will contain significant additional response components at the odd harmonic multiples of the stimulation frequency. If opposite directions of motion produce larger responses in each eye, as presumed to be the case when a nasalward vs temporalward asymmetry is seen, the temporal phase of the odd harmonic responses from each eye will be 180° out of phase in the two eyes.

**Results.** Figure 1A shows the motion VEP responses of a normal adult observer. The response amplitude and phase are plotted in polar coordinates, and each vector represents the response from a single trial (3-μV full scale). The motion response in normal adults is dominated by the second harmonic, with very little response at the first harmonic. Figure 1B shows the motion VEP responses of a normal 16-week-old infant (3-μV full scale). The infant response pattern differs from the adult response pattern in two main ways. First, there is a sizable first harmonic component in the infant’s response that is much larger than that of a normal adult and second, the first harmonic responses from each eye are approximately 180° out of phase with respect to one another. Figure 1C shows the motion VEP responses of an adult with a history of infantile esotropia (2-μV full scale). The response of this 30-year-old patient, who had a history of onset of constant esotropia before 6 months of age, also contains a large first harmonic component that is nearly 180° out of phase in the two eyes.

We tested whether infants, infantile esotropes, and adults differ in the relative magnitude of their first and second harmonic responses by performing a four-way repeated measures Analysis of Variance (ANOVA) with the factors diagnosis, eye, channel, and harmonic. The ANOVA was calculated on the signal to noise ratios (SNR) of the first and second harmonic—each referenced to the electroencephalogram (EEG) amplitude at two frequencies near each of the response frequencies. There were no main effects or interaction terms involving eye or channel; thus, we have no evidence for hemispheric asymmetries in the motion VEP. There was a significant effect of harmonic (F = 19.4; P < 0.0001) and a significant harmonic/diagnosis interaction (F = 10.3; P < 0.0003). These effects were due to the fact that normal adults have a much smaller first harmonic (F₁ SNR: 2.9) and larger second harmonic (F₂ SNR: 12.75) than the infants (F₁ SNR: 6.79; F₂ SNR: 6.96) or the patients (F₁ SNR: 6.44; F₂ SNR: 8.59).

The distribution of the difference in first harmonic phase between left and right eyes for the normal adults, infants, and esotropic patients can be seen in Figure 2. Phase angles were calculated from the vector average of all trials taken from a given eye. Four normal adult observers had measurable first harmonic responses in each eye. These responses tended to be in the same phase in each eye, which is seen as an increased frequency in the first and last bins of the interocular phase-difference histogram (Figure 2A). In these four observers, the relative phase difference between first harmonics recorded from the two eyes averaged 61°. Aside from this, there was no consistent phase relationship between the first harmonics recorded from each eye of normal adults. Figure 2B plots the relative phase difference between left eye (LE) and right eye (RE) first harmonics for the normal infants. In contrast to the normal adults, infants showed a clear peak, which is centered around 180°, in the relative phase difference between the two eyes. The average relative phase difference was 179.7 ± 20.5° (95% confidence) for the O₁ – O₂ derivation and 186.1 ± 33.6° for the O₂ – O₁ derivation. The esotropic patient group showed a pattern of interocular phase differences that was similar to that of normal infants (Fig. 2C). The distribution is strongly un-
Fig. 1. Polar plots of evoked potential amplitude and phase for a normal adult observer (A), a normal 16-week-old infant (B) and an adult with a history of infantile esotropia (C). Each vector is the result of a 10-sec trial. Solid lines plot the response from the RE; dashed lines represent the LE. Filled and open symbols plot the vector average of the RE and LE responses, respectively. The upper plot in each panel shows the first harmonic responses (F1), and the lower plot shows the second harmonic responses (F2). Data from the recording channel over the left hemisphere are shown. The response of the normal adult is dominated by the second harmonic of the stimulus frequency (F2). There is a small F1 component that has the same phase in the two eyes. Both the normal infant and the esotropic patient show substantial first harmonic responses that are approximately 180° out of phase in the two eyes.

Discussion. Normal infants and patients with a history of infantile esotropia show anomalous monocular motion VEPs. The form of the anomaly is consistent with an asymmetry of motion responsiveness for nasalward vs temporalward motion in each eye that arises from visual cortex. Our technique cannot determine whether it is the nasalward or the temporalward direction that elicits the larger response; it can only determine that a response asymmetry exists such that either the nasalward or the temporalward response is dominant.

There are other possible mechanisms for the production of asymmetric motion VEPs. Patients with a history of infantile esotropia are known to have latent nystagmus. Latent nystagmus could produce asymmetric image motion on the retina that could lead to an apparent asymmetry of the cortical evoked potential. To determine whether asymmetric retinal slip could produce VEP asymmetries comparable to those we have seen in infants and adult patients, we performed simulated nystagmus experiments on four normal adults. The observers tracked a small target that underwent sawtooth motion (1°/sec ramps over 1° of motion) superimposed on the VEP display. This image motion was typical in waveform and slow-
Fig. 2. Distribution of the relative difference in phase of between the LE and RE first harmonic responses for normal adults (A), normal infants (B) and patients with infantile esotropia (C). Each observer contributed two values to the histograms, one for each recording channel. The first and last bins in each histogram plot the same range of phase difference (−30° to +30°) and are thus identical. Infants and esotropic patients show a strongly unimodal distribution of phase differences centered around 180°.

Phase velocity to latent nystagmus in patients. We were unable to induce an asymmetry in two of the observers. In the other two observers, we were able to induce a just measurable asymmetry that was an order of magnitude smaller than that seen in the esotropic patients. It was also unlikely that direct or indirect effects of latent nystagmus were the sole cause of the VEP asymmetries we have seen, since normal infants showed a motion asymmetry of comparable magnitude to that of esotropic patients in the absence of latent nystagmus.

Eye alignment appears to be critical for the normal development of the motion system, since pursuit eye movements did not develop in either infantile esotropic patients or normal infant monkeys with surgically induced strabismus. These results, coupled with our cortical recordings, indicate that at least some, if not all, motion-sensitive mechanisms require normal binocular interaction to develop completely. Given this, monocular measurements of the symmetry of motion processing may prove to be sensitive indicators of cortical binocularity.

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