Direction-of-Motion Detection and Motion VEP Asymmetries in Normal Children and Children with Infantile Esotropia

Rain G. Bosworth[1] *and Eileen E. Birch*[2,3]

Purpose. To investigate nasal-temporal asymmetries in the detection of horizontal motion and in cortical motion visual evoked potential (mVEP) responses in normal infants and children and in patients with infantile esotropia.

Methods. Monocular motion-detection thresholds were obtained separately for nasalward- and temporalward-moving random-dot patterns in a forced-choice, preferential-looking paradigm. Monocular mVEP responses were obtained while subjects viewed a 6-Hz oscillating, 1 cyc/deg vertical sine-wave grating. Nasal-temporal mVEP asymmetry was investigated with two measures from each subject: asymmetric indices (AIs) and interocular phase differences. Performance was compared in 33 visits of 28 normal subjects and 73 visits of 54 patients with infantile esotropia, ranging in age from 2 months to 5 years.

Results. At 3 to 5 months of age, both normal infants and patients with infantile esotropia had robust nasal-temporal asymmetries in motion-detection and mVEP measures. By 2 years of age, measures in all normal subjects were symmetric, as they were in patients successfully treated with glasses or alignment surgery, whereas patients who had not yet undergone alignment surgery, regardless of surgery status, had highly asymmetric mVEP responses and motion-detection thresholds.

Conclusions. Young normal and esotropic infants exhibited nasal-temporal asymmetries in both motion detection and mVEP. These asymmetries similarly disappeared over time in normal infants and in patients with esotropia who had received successful, timely correction of misalignment. Although the initial capacity for motion processing is normal in the youngest patients with untreated esotropia at 5 months, cumulative abnormal binocular experience in these patients may disrupt motion mechanisms. (*Invest Ophthalmol Vis Sci.* 2007;48: 5523–5531) DOI:10.1167/iovs.07-0666

Infantile esotropia (ET) is a nasalward misalignment of the visual axes, with an onset before 6 months of age and may be treated with surgical alignment or, in some cases with an accommodative component, with glasses. Causes of strabismus originating in the extraocular muscle, innervation of the extraocular muscles, and the sensorimotor function of the visual cortex have been suggested. In patients with strabismus, deficits in vergence eye movements, stereopsis, and fusion capacity are present after a prolonged period of misalignment.[1–3]

Motion processing in adults who had ET during early infancy has been found to be abnormal as well. Nasal-temporal asymmetries or performance deficits have been reported for monocular OKN,[4–10] velocity judgments,[4,11] motion detection,[12,13] and smooth pursuit.[14] Generally, these perceptual measures show a weaker temporalward response; for example, the monocular OKN is slower for temporalward than nasalward motion, the slow phase for pursuit of temporalward motion is reduced compared with that for pursuit of nasalward motion, and temporalward motion is perceived to be slower than nasalward motion.[11]

Studies in which motion (m)VEP was used as a measure of cortical activation in response to viewing visual motion stimuli have consistently shown that cortical responses to nasalward versus temporalward motion are asymmetric in strength in patients with a history of infantile ET.[15–19] Normal infants also show a similar nasal-temporal asymmetry in the mVEP response to an oscillating vertical grating between 2 and 6 months of age, but not at later ages.[15,17,20] Although the mVEP asymmetry in normal infants and in patients with infantile ET has been replicated across studies, the relationship of this finding to perceptual performance is still unclear. The mVEP measure is inherently ambiguous regarding which direction, nasalward or temporalward, yields a stronger response. Two studies attempted to uncover the perceptual direction of this mVEP asymmetry, with inconclusive or opposite findings.[4,21] The mVEP response is not generated by eye movements, as it is still observed when the eyes are paralyzed,[22] nor is it caused by simulated or real latent nystagmus.[17] It correlates strongly with bifoveal fusion[16] and includes stimulus-yoked activation of binocular neurons in primary visual cortex based on local field scalp recordings.[23]

Our first motivation in this study was to determine whether the mVEP asymmetry is similarly observed in psychophysical measures of motion processing, within individual infants, during development. To our knowledge, this is the first study undertaken to investigate the development of two measures of motion detection, psychophysical and electrophysiological, in both a group of pediatric patients with infantile ET and in normal infants and children. We also examined the effects of surgical alignment and patching on both motion-detection asymmetries and mVEP asymmetries, to see whether these are similarly affected.

To allow comparison of our results to other published studies, we used random-dot patterns, which are typically used to study motion processing,[24] and reversing vertical gratings, which are widely used in VEP studies.[17] Random-dot patterns allow activation of motion mechanisms while minimizing contribution of position and orientation mechanisms.[25] Our stimuli and tasks were chosen because they are easily and quickly testable in both normal and infantile ET pediatric subjects, across a wide range of ages. In this study, both young infants and patients with infantile ET demonstrated nasal-temporal asymmetries in both mVEP and perceptual motion detection

From the [1]Department of Psychology, University of California, San Diego, La Jolla, California; the [2]Retina Foundation of the Southwest, Dallas, Texas; and the [3]Department of Ophthalmology, University of Texas Southwestern Medical Center, Dallas, Texas.

Supported by a National Eye Institute Grant EY05236 (EEB).

Submitted for publication June 4, 2007; revised July 25, and August 24, 2007; accepted September 27, 2007.

Disclosure: **R.G. Bosworth**, None; **E.E. Birch**, None

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Corresponding author: Rain G. Bosworth, Department of Psychology, UC San Diego, 9500 Gilman Drive, Mail Code 0109, La Jolla, CA 92093; rbosworth@ucsd.edu.

that disappeared over time in normal infants and in patients with strabismus who underwent successful, timely correction of misalignment.

METHODS

Participants

Patients were referred to the Retina Foundation of the Southwest by local pediatric ophthalmologists in Dallas, Texas. Normal participants were recruited from the newborn nursery of a local hospital. All participants were born within 14 days of their due dates, with no ocular or neurologic abnormalities and no manifest nystagmus. All had monocular acuity assessed with infant preferential-looking Teller Acuity Cards or, in the case of older children, crowded HOTV optotype figures. Unless stated otherwise, acuity was normal.

The research procedures in this study observed the tenets of the Declaration of Helsinki and were approved by the Institutional Review Board of the University of Texas Southwestern Medical Center. Informed consent was obtained from one or both parents before the infant's participation.

Normal Infants. A total of 28 normal subjects provided mVEP data on 33 visits. Average age was 8.2 ± 9.8 (SD) months (median, 4.9; range, 2.1–47.4). The following age groups were created: 2 to 4, 4 to 6, 6 to 9, 9 to 18, and 18 to 60 months, which produced respective mean ages of 3, 5, 7, 14, and 35 postnatal months (*n* per group = 11, 9, 7, 3, and 3, respectively). A smaller subset of 17 normal infants provided *both* mVEP data and monocular motion-detection thresholds within the same visit to our laboratory. Average age was 11.6 ± 12 months (median, 6.3; range, 4.2–47.4), with respective mean ages of 5, 7, 14, and 41 months (*n* per group = 6, 6, 3, and 2, respectively).

Patients with Infantile ET. A total of 54 patients with infantile ET (inf ET) provided mVEP data on 73 visits. A smaller subset of 22 patients provided data on both motion tasks over 29 visits. See Table 1 for background clinical characteristics of these patients. Patients had initial deviation of 30 to 75 prism diopters (pd) at a mean onset age of 2.9 ± 1.6 months (median, 2.0). Age at the time of the motion tests ranged from 4.5 to 52.0 months (median, 11.3).

Twenty-three patients tested underwent successful alignment to within 8 pd after surgery, and 13 patients tested had infantile accommodative ET (*inf acc ET*) that was fully corrected to orthophoria with glasses. The remaining 37 patients tested had a deviation greater than 8 pd. In the subset of subjects who completed *both* tasks concurrently, 11 had successful alignment, 3 had inf acc ET that was fully corrected with glasses, and 15 had a deviation greater than 8 pd, despite treatment. Mean onset ages for the *aligned inf ET* and *not-aligned inf ET* groups were indistinguishable (median age, 2.0 for both groups; 75th percentile, 2.5 and 3 months, respectively), whereas the mean onset age for the inf acc ET group was slightly older (median age, 4.0; 75th percentile, 6 months). The number of patients treated with patching for at least 2 hours per day was 53%, 57%, and 36% in the not-aligned inf ET, aligned inf ET, and aligned inf acc ET groups, respectively.

mVEP Stimuli and Procedures

mVEPs were measured monocularly, separately for each eye of every participant, with a sweep-VEP system (NuDiva; Smith-Kettlewell Eye Research Institute, San Francisco, CA), developed by Norcia et al.[17] The EEG was recorded from two bipolar derivations (0_1 and 0_2, i.e., channels 1 and 2), 2.5 cm to the left and right of a common reference electrode (0_z) placed 1 cm above the inion on the midline. A ground electrode was placed 2.5 cm above the reference electrode. The EEG was recorded from the two channels and adaptively digitally filtered at a sampling rate of 397 Hz, to isolate the VEP signal in response to the motion stimuli.

The mVEP stimulus (shown in Fig. 1A) was presented on a high-resolution video monitor with a mean luminance of 162 cd/m^2. A high-contrast (80%), 1 cyc/deg vertical sinusoidal grating was displayed on a 34° × 25° field. The grating jittered (or alternated) between two positions separated by 90° of spatial phase, creating an oscillating grating moving leftward and rightward. The temporal rate of the positional jitter was 6 Hz (12 direction reversals per second).

The infant or child sat on a parent's lap at a viewing distance of 50 cm from the monitor. Monocular viewing was achieved by occluding one of the eyes with an opaque eye patch (Coverlet; Beiersdorf, Inc., Wilton, CT) in infants or with monocular occluding spectacle frames in older children. A small, transparent toy was dangled in front of the monitor to attract the child's gaze to the center of the monitor during stimulus presentation.

During each trial, the stimulus was displayed for 10 seconds. VEPs were recorded only when the child was calm and alert and when the corneal reflection of the video monitor was centered in the pupil. Recording was interrupted when the child was inattentive or when fixation was interrupted. Between 5 and 10 trials were recorded in each eye. Any trials with artifacts caused by head or body movements were eliminated from the analysis. The EEG signal was subjected to Fourier analysis to extract the amplitude and phase of the VEP at 6 Hz, the first harmonic (F_1), and at 12 Hz, the second harmonic (F_2). Vector averages for each harmonic were calculated with at least five trials for each eye. Only vector averages that were significant based on the T_{circ}^2 statistic[26] were included in the analysis. A vector average met the criteria for analysis if either or both of its F_1 or F_2 harmonics had a signal-to-noise ratio >3.0 and a significant T_{circ}^2 statistic ($P \leq 0.05$).

A symmetric VEP in which the neural response is equal in both leftward and rightward directions is composed primarily of F_2, where the peak of activity occurs at twice the temporal frequency of the stimulus. An asymmetric mVEP, in which the response is dominated by one of the two directions of motion, yields a Fourier spectrum composed primarily of the odd harmonics of the stimulus frequency (F_1). Two measures were calculated to determine whether the Fourier mVEP responses for each individual contain a stronger response to stimulus motion in one direction than the other. These measures are the *asymmetry index* (AI) and the presence or absence of an *interocular phase difference* of 180°. For each individual, four AIs were calculated, one for each channel and eye. Each AI was calculated by dividing the amplitude of F_1 by the sum of the amplitudes of F_1 and F_2. Large AIs indicate a larger F_1 (asymmetric) component than the F_2 (symmetric) component of the VEP. Second, the presence or absence of a 180° ± 40° phase difference in F_1 between the eyes was noted in each individual. If opposite directions of motion produce large F_1 amplitudes in the two eyes, then the phase of the F_1 response differs by 180° between the two eyes, referred to as a *bow tie pattern* (see Fig. 2, for example data). The presence of an interocular phase difference between the two eyes indicates that the asymmetry is related to nasalward (N) versus temporalward (T) motion and not to leftward versus rightward motion (e.g., rightward direction to the left eye is N and T to the right eye). Because the actual phase lag between the VEP component and the stimulation frequency differs across subjects, this method is unable to identify which direction, N or T per se, generates the stronger response.

Motion-Detection Task

The stimuli were random-dot patterns (RDPs), similar to those used by Wattam-Bell,[24] programmed in commercial software (MatLab ver.5.2.1; The MathWorks, Natick, MA). Two RDPs were presented side by side on a 20-in. monitor (Trinitron Multiscan 520GS; Sony, Tokyo, Japan), with a refresh rate of 75 Hz. Each RDP was 20° by 11.5°, with the inner edges separated by 18.4°. Within each RDP, white (102 cd/m^2) dots were presented against a black (3 cd/m^2) background. Dots were 0.32° × 0.32° in size, and dot density (area of pattern illuminated by white) was 5%. These two patterns were surrounded by a gray background, at a luminance equal to that of the mean luminance of the pattern.

The two RDPs were divided into three equally sized top, middle, and bottom segments (6.7° × 11.5°) as illustrated in Figure 1B. In one of the two RDPs, the top and bottom segments contained stationary

TABLE I. Background on Patients Who Completed Both the Motion-Detection Task and the mVEP Task

Subject	Diagnosis	Treatment Status	Initial Angle (pd)	Age at Onset (m)	Age at Motion Tests (m)	Age at Surgery (m)	Duration of ET Prior to Test (m)	Acuity Test	OD (logMAR)	OS (logMAR)	IAD (logMAR)
1a	inf ET	Pre-op	60	2	4.5	—	3	Teller	0.60	1.06	0.46
2a	inf ET	Pre-op	40	2	4.8	—	3	VEP	0.65	0.50	0.15
3	inf ET	Pre-op	65	2	5.0	—	3	Teller	0.86	0.90	0.04
4a	inf ET	Pre-op	57.5	2	5.0	—	3	VEP	0.52	0.66	0.14
5a	inf ET	Pre-op	75	2	6.4	—	4	VEP	**0.71**	0.44	**0.27**
6	inf ET	Pre-op	40	2.5	7.3	—	5	VEP	0.18	0.34	0.16
16	inf ET	Pre-op	25	6	26.0	—	20	Teller	0.45	**0.71**	0.26
12a	inf ET	Pre-op	45	1	13.1	—	12	VEP	**0.62**	0.43	**0.19**
1b	inf ET	Postop aligned	60	2	9.0	8	6	Teller	0.55	0.55	0.00
2b	inf ET	Postop aligned	40	2	7.8	6.5	5	VEP	0.54	0.49	0.05
4b	inf ET	Postop aligned	57.5	2	8.0	5	3	Teller	NA	0.80	NA
8a	inf ET	Postop aligned	50	2	8.2	5	3	Teller	0.53	**0.92**	**0.39**
12b	inf ET	Postop aligned	45	2	25.0	24	22	Teller	0.33	NA	NA
17	inf ET	Postop aligned	65	6	29.2	21	15	Teller	0.60	**0.65**	0.05
19	inf ET	Postop aligned	45	2	35.0	11	9	Allen	0.10	0.10	0.00
1c	inf ET	Postop E(T)	60	2	11.8	8	6	Teller	0.58	0.50	0.08
22	inf ET	Postop ET	70	2	52.0	6, 13, 17	50	HOTVc	0.30	0.20	0.10
9	Inf partially acc ET	Pre-op glasses	35	3	9.2	—	6	VEP	**0.67**	0.53	0.14
10	Inf partially acc ET	Pre-op glasses	30	4	9.7	—	6	Teller	0.70	0.60	0.10
11	Inf partially acc ET	Pre-op glasses	65	6	11.3	—	<5	Teller	**1.04**	**0.93**	0.11
5b	Inf partially acc ET	Postop aligned	75	2	13.8	9	7	Teller	0.54	0.60	0.06
8b	Inf partially acc ET	Postop aligned	50	2	10.8	5	3	Teller	0.43	0.55	0.12
13	Inf partially acc ET	Postop aligned	40	2	18.7	18	16	Teller	0.60	0.71	0.11
18	Inf partially acc ET	Postop aligned	42.5	2	32.6	16	14	Allen	0.30	0.30	0.00
20	Inf partially acc ET	Postop aligned	30	4	35.2	13	9	Allen	0.10	0.10	0.00
7++	Inf acc ET	Ortho cc	35	6	7.4	—	<5	VEP	0.35	0.24	0.11
14	Inf acc ET	Ortho cc	30	5	20.9	—	6	Teller	0.48	0.40	0.08
15	Inf acc ET	Ortho cc	30	6	24.3	—	2	Allen	0.18	0.10	0.08
21	Inf acc ET	Ortho cc	42.5	2	41.1	—	2	HOTV	0.10	0.20	0.11

Bold acuities indicate values that were outside normal age-based monocular acuity limits. In these cases, an amblyopic correct factor was applied to the mVEP data; data were not noticeably changed by this. Letters (1a, 1b,. . .) indicate repeated, consecutive visits. ++, adopted; NA, not available.

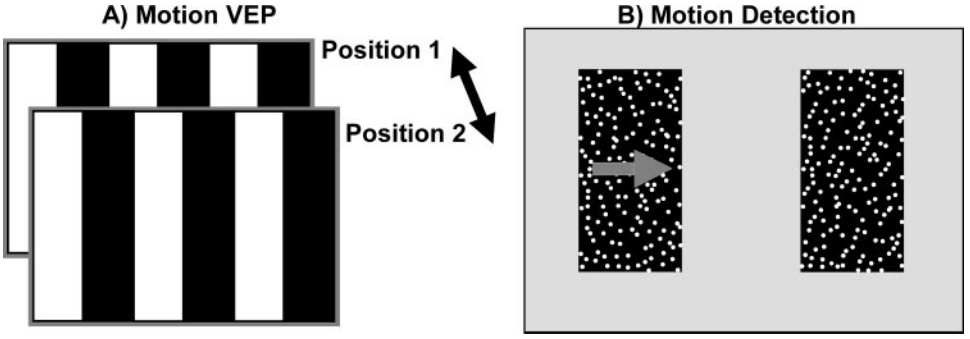

FIGURE 1. (**A**) Illustration of the mVEP stimulus. The grating is shifted 90° left and right every 42 ms. (**B**) Example showing a rightward moving RDP on the left side. Direction of motion (leftward or rightward) and location (right or left side) were randomized across trials. This pattern contains N motion when viewed with the left eye or T motion when viewed with the right eye.

dots, whereas the middle segment contained a variable proportion of moving and stationary dots. All moving dots in the middle segment moved coherently (i.e., at the same temporal and spatial displacement) in one direction, either leftward or rightward, at a velocity of 10° per second, with an unlimited lifetime. Once a dot completed its motion trajectory, it wrapped around to a new random location. The density of the display was sparse enough that no collision or overlap between dots was noted by the authors. The other RDP on the opposite side of the monitor had stationary dots across all three segments.

All subjects were tested at a viewing distance of 40 cm. Infants were seated on a parent's lap in front of the monitor. All normal participants were tested monocularly, with the nonviewing eye occluded with an opaque patch (Coverlet; Beiersdorf, Inc.) or, for older children, monocular occluding spectacle frames. For the normal participants, the eye tested was picked randomly; for patients, the preferred eye was tested, which was determined from medical records. If there was no preferred eye, the eye with better acuity was tested.

At the beginning of each trial, a moving white fixation square (size, 2.3°) oscillated up and down along with a synchronized auditory tone to attract the infant's attention to the center of the monitor. Once the infant's gaze was in the center, the experimenter initiated the trial, the fixation square disappeared, and the stimuli were immediately presented. The experimenter, standing behind the monitor, observed the infant's head and gaze position under the diffuse light from the monitor in an otherwise dark room. The direction of motion and the location of the moving target on any given trial were randomized and unknown to the experimenter. The experimenter made a judgment about the infant's first fixation away from center to the right or left side of the monitor. This precluded using the reflection of the moving stimuli in the infant's pupil or OKN as a cue to the target's actual location.

Thresholds were obtained by using a two-spatial-alternative, two-down-one-up staircase procedure,[27] varying the percentage of coherently moving dots in each trial. Staircases for the N and T motions were interleaved across trials, within one testing session. For each staircase, the first trial started at 100% coherent motion signal, decreasing in 0.2-log-unit steps with each pair of correct responses, until the first incorrect response was made, then the staircase proceeded in 0.1-log-unit steps, until a total of six staircase reversals were completed in each direction. The lowest possible coherent motion signal was 1%. A maximum-likelihood fitting procedure was used to obtain thresholds[28] for the N and T motions. Threshold was defined as the percentage of dots corresponding to 75% correct performance. To assess relative N versus T performance, a log T-to-N threshold ratio was calculated for each subject.

Analysis

To compare clinical groups, two-factor between-subjects ANOVA and independent two-tailed *t* tests assuming unequal variances were used to compare mean AIs, and the Fisher exact test was used to compare the percentage of patients with asymmetries for each group. When

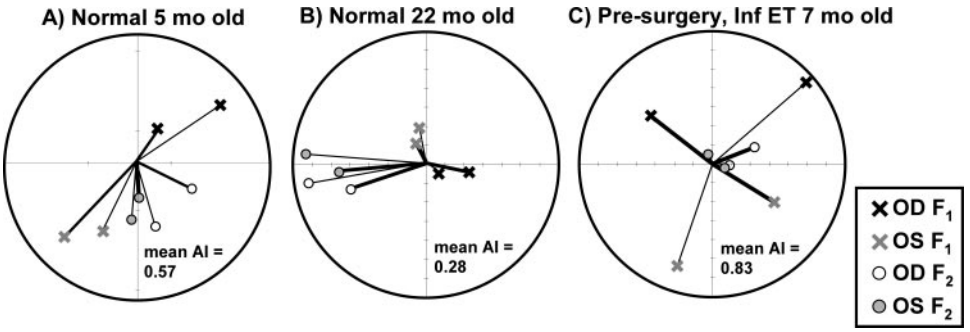

FIGURE 2. Example of mVEP data. Each polar plot showing evoked potential amplitude and phase is from a single individual. The length and angle of each line represent amplitude and phase, respectively, of a vector average of five or more 10-second trials. F_1 and F_2 are shown for both channel 1 (*thin lines*) and channel 2 (*thick lines*). (**A**) For the young normal infant, F_1 responses were approximately 180° out of phase in the two eyes (left eye, *gray symbols*; right eye, *black/white symbols*), whereas the F_2 responses had similar phase in the two eyes. F_1 responses were larger in amplitude than F_2 responses, leading to a high AI (0.57). (**B**) The symmetric older normal subject had F_2 amplitudes and phases that were similar between the two eyes, and larger F_2 than F_1 amplitudes, resulting in a low AI. (**C**) The asymmetric presurgery inf ET patient, aged 5 months, had F_1 responses that were 180° out of phase for each eye, and a greater than normal mean AI, due to large amplitude in F_1 and the same F_2 amplitude.

comparing clinical groups, only *overlapping* age groups were included in each comparison, to create age matching. For example, when the not-aligned inf ET group were compared with the normal group, all four age groups of not-aligned inf ET patients were combined and compared to the three normal age groups that overlapped. ANOVAs were conducted (but not reported) to confirm that age did not significantly differ between clinical groups.

RESULTS

Motion VEP Asymmetry Index

mVEP data for three individuals are shown in Figure 2. Each polar plot represents a single individual, and the six lines in each polar plot represent the mean response amplitude (length of line) and phase (polar coordinates or angle) for each channel, eye, and harmonic. A normal infant, at 5 months of age (Fig. 2A), had large response amplitudes at F_1, with an approximately 180° phase difference between the two eyes. The F_2 responses, on the other hand, had a much smaller phase difference, and were smaller in amplitude than F_1, yielding a moderate AI (mean AI, 0.57). An older normal subject at 22 months (Fig. 2B) had large-amplitude F_2 responses and much smaller amplitude F_1 responses, producing a low AI (mean, 0.28). The F_2 responses for the two eyes had a similar phase, and were consistent in both channels. A presurgery patient with inf ET (Fig. 2C) had large F_1 amplitudes for each channel, with the two eyes 200° and 195° out-of-phase for the two channels and small F_2 amplitudes for each eye and each channel. The relatively larger F_1 than F_2 amplitude produced a mean AI of 0.82 in this patient.

Mean AIs in all individuals tested in each clinical group, as a function of mean age group, are shown in Figure 3A. The youngest normal patients at 3 months of age ($n = 11$) had a high mean AI (mean, 0.64), indicating a large N-T asymmetry. The mean AI steadily declined to 0.38 at 7 months of age and to 0.32 at 35 months. Mean AI was 0.69 for misaligned inf ET patients at 2 to 5 years of age.

As shown in Figure 3A, not-aligned (pre- and postsurgical) inf ET patients had an overall significantly higher mean AI than did normal subjects (all ages included, $F_{(1,68)} = 40.91$; $P = 0.0001$). Only in the youngest age group of 3 months did untreated inf ET patients have mean AIs that were marginally significantly different from normal ($t_{(12)} = 2.10$; $P = 0.06$), whereas patients at all other age groups had significantly higher mean AIs than normal ($P < 0.001$). Inf ET patients with successful alignment had significantly higher mean AIs than did normal subjects ($F_{(1,34)} = 28.55$; $P < 0.0001$). Inf acc ET patients in whom successful alignment had been achieved with glasses did not differ significantly from similar-aged normal subjects, when data were collapsed across the two acc ET age groups and the oldest three normal age groups ($F_{(1,24)} = 1.16$; $P = 0.40$). In the 6 months and older group, mean AIs were lower in patients who had had successful alignment ($n = 23$; mean, 0.62), compared with those had not ($n = 27$; mean, 0.70; $F_{(1,48)} = 4.26$; $P = 0.05$).

For comparison, AIs for the concurrent subset of children who participated in both the VEP and psychophysical motion tasks are shown in Figure 4A. (Note that no patients in the youngest age group in Figs. 3A and 3B were able to perform concurrent mVEP and psychophysical tests.) Results in Figures 3A and 4A are consistent, in that both aligned and not-aligned inf ET patients had elevated mean AIs relative to both normal and inf acc ET subjects who had undergone alignment with glasses.

Prevalence of Asymmetries in mVEP Phase Data

The prevalence of mVEP asymmetries defined by a 180° ± 40° interocular phase difference in the F_1 response is shown in Figure 3B for each age group. (Fig. 4B shows data for the *concurrent* subset of subjects who performed both the VEP and psychophysical motion tasks on the same visit.) Like the AI data, the prevalence of asymmetry defined by the interocular phase criterion decreased sharply in normal subjects, from 64% (7/11) having an asymmetry at 3 months to 14% (1/7) at 7 months of age, and 0% (0/6) of all normal subjects older than 10 months of age. The prevalence of phase asymmetries in the youngest untreated inf ET patients was very similar to normal subjects at 3 months of age (67% vs. 64%); however, unlike normal subjects, it remained abnormally high at approximately 50% prevalence at all older ages. The inf ET patients with successful alignment showed a drastic reduction in asymmetries, from 100% prevalence at the youngest age tested at 8 months to 25% at older ages. That surgical alignment reduced asymmetries is supported by comparison of not-aligned and aligned groups at 2 years of age. Only 25% of aligned patients of older age had asymmetries in the interocular phase, whereas 55% of not-aligned patients did not.

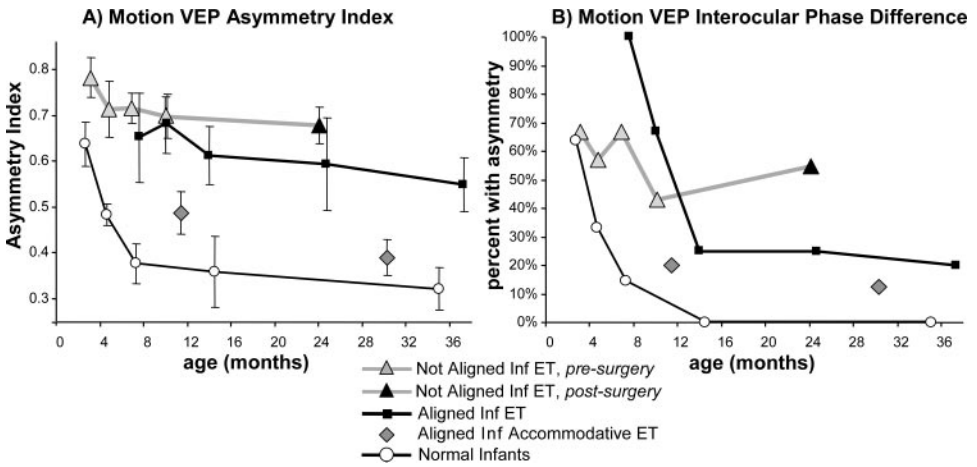

FIGURE 3. Motion VEP results for all participants ($n = 106$). (**A**) Mean AIs for each clinical group are plotted as a function of age group. (**B**) Percentage of subjects with a significant asymmetry, as indicated by a significant interocular phase difference. Groups plotted are normal subjects ($n = 33$); inf ET not aligned ($n = 37$); inf ET aligned ($n = 23$); and inf acc ET aligned by glasses ($n = 13$).

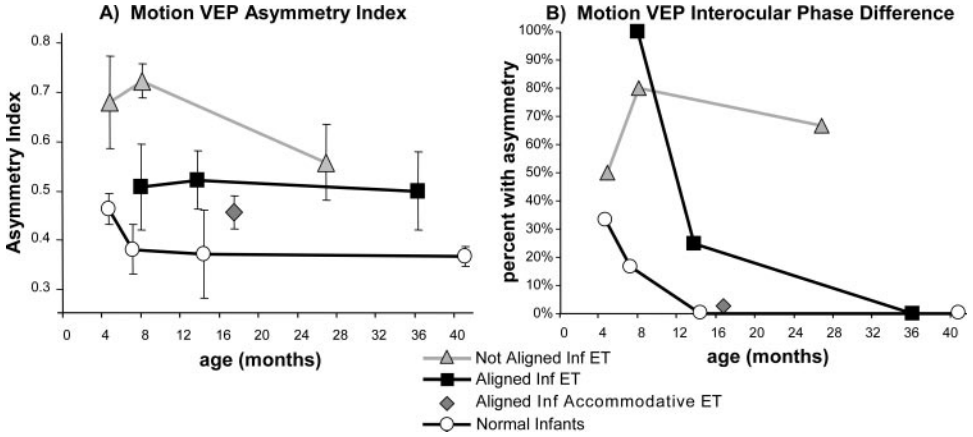

FIGURE 4. Motion VEP results for participants who completed *both* tasks in the same day ($n = 46$ visits). (**A**) Mean mVEP AIs for each clinical group is plotted as a function of age group. Larger values indicate greater N-T asymmetries. (**B**) Percentage of subjects with a significant asymmetry, as indicated by a significant interocular phase difference. Clinical groups plotted are normal subjects ($n = 17$); inf ET not aligned ($n = 15$); inf ET aligned by surgery ($n = 11$); and inf acc ET aligned by glasses ($n = 3$). Error bars denote ± 1 SEM.

Post Hoc Analysis of Onset, Duration of Misalignment, and Occlusion Therapy

We conducted post hoc analyses of several treatment factors in surgically aligned inf ET patients ($n = 23$). First, we compared age at onset in two groups: onset at 0 to 3 months of age (mean age at test, 17.0 months; mean duration of misalignment, 10.5 months) versus onset at 3 to 6 months of age (mean age at test, 23.0 months; mean duration of misalignment, 10.5 months), and found no significant difference in either mean AI ($F_{(1,21)} < 1$) or prevalence of interocular phase asymmetries (Fisher exact test, one-tailed $P = 0.22$). Second, we analyzed the effect of duration of misalignment by comparing infants who had ET of 3 to 6 months' duration (mean age at test, 12 months; mean duration, 5.5 months) versus those with ET of 6 to 12 months' duration (mean age at test, 12 months; mean duration, 8.4 months). (We excluded eight of the oldest children, so that both groups would match in mean age, since there is a strong age effect.) No difference in mean AIs (0.69 vs. 0.66) nor in the prevalence of bow ties (67% vs. 60%) was observed in our short- versus long-duration groups, respectively. However, these results are not surprising, as the example in this study represents, as a whole, early onset (all before 6 months) and short duration (all less than 12 months).

To see whether patching treatment had an effect on our results, patients who had had part-time occlusion therapy (between 1 and 4 hours per day) were compared with patients who had not had any occlusion. Those who were patched had similar AI asymmetry indices (aligned: 0.65 vs. 0.56 and not-aligned: 0.72 vs. 0.70, for the patch versus no-patch groups, respectively) and a slightly greater prevalence of bow ties compared with patients who were not patched (aligned: 54% vs. 33% and not aligned: 67% vs. 56% had bow ties, for the patch versus no-patch groups, respectively).

Concordance between Motion Detection and mVEP

To evaluate whether asymmetries in mVEP correlate with psychophysical performance on a motion detection task, we compared the prevalence of asymmetries in each task in the participants who had provided both measures on the same visit (Fig. 5). Log T-N motion-detection threshold ratios from each participant were averaged for each age group. The ratios in 11 normal subjects (9–60 months of age) provided the normal baseline by calculation of the 95% confidence limit (mean log threshold ratio = −0.02 ± 0.04 [SD]). These infants' and children's thresholds were similar to those of adults (all five adults tested had log threshold ratio = 0.0, i.e., symmetrical performance) and no developmental change in motion-detection performance was seen past 9 months of age. The 95% confidence limits were defined as two standard deviations above/below the mean log ratio of the normal subjects. The percentage of subjects in each age group with a significant N motion-detection bias, defined as having a threshold ratio exceeding the upper confidence limit, is shown by the solid lines in Figures 5A and 5B, and for comparison, the percentage of subjects with an mVEP asymmetry is replotted as dashed lines from Figure 4B (No subjects fell below the 95% lower confidence limit, which would have been a T bias in motion detection.)

As can be seen in Figure 5, asymmetries on the two tasks were similarly affected as a function of age in all clinical groups, with only 9% (1/11) of normal subjects over 6 months of age showing asymmetry on either task. The association in prevalence of asymmetries in inf ET patients between the two tasks was significant (Fisher exact test, one-tailed $P = 0.05$). Most notably, the youngest untreated (not aligned) patients at 5 months of age were identical with normal subjects in prevalence for both tasks (Fig. 5A). At older ages, 8 and 27 months, the prevalence of asymmetries for both tasks in the not-aligned patients was significantly higher than normal (Fisher exact test, $P < 0.04$ for each task). The aligned patients (Fig. 5B), on the other hand, showed a significant decrease in prevalence of asymmetries on both tasks at 14 and 36 months of age (Fisher exact test, $P < 0.03$ for each task). The inf acc ET patients (aligned with glasses; shown only in Fig. 5B) at 17 months showed symmetric performance on both tasks.

Infantile Accommodative ET

In all three measures in the present study discussed thus far, the orthotropic patients with inf acc ET were very similar to normal subjects and were more symmetric than the aligned inf ET corrected by surgery. These two aligned groups had similar mean ages at onset (3 and 4 months of age, respectively) and both groups achieved orthotropia between 4 and 16 months of age. If alignment per se (by either glasses or surgery) led to normal symmetrical performance, then these two groups

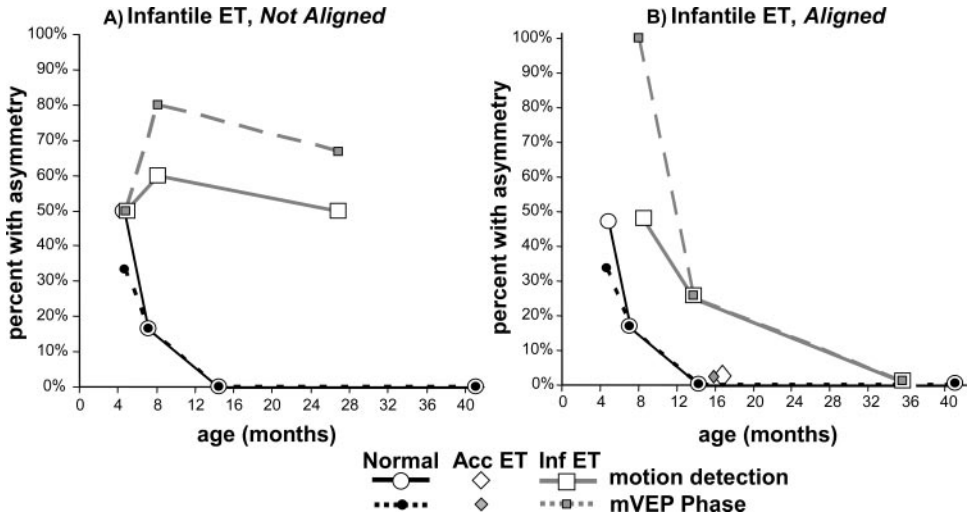

FIGURE 5. Concordance between motion detection and mVEP in subjects who completed *both* tasks in the same day. Percentage of participants within each clinical group who had a significant N asymmetry for the motion-detection task (*solid lines*, *open symbols*) and for the mVEP task (*dotted lines*, *filled symbols*) is plotted as a function of mean age. For the mVEP task, asymmetry is defined by a significant interocular phase difference, and these data are replotted from Figure 4B. Patients were grouped as not adequately aligned (**A**; $n = 15$, *squares*) and aligned to within 8 pd by surgery (**B**; $n = 11$; *squares*) or with glasses (**B**; $n = 3$; *diamonds*). Normal subjects (*black lines, circles*; $n = 17$) are replotted in (**A**) and (**B**) for comparison.

would be expected to be similar. A post hoc contrast of the two groups was conducted, including only the same age range, producing mean ages: 21 months of age for inf acc ET ($n = 11$) and 19.5 months of age for aligned inf ET ($n = 21$). The inf acc ET group had significantly lesser asymmetry ($t_{(30)} = 3.65$; $P = 0.001$) despite both groups' achieving successful alignment. This suggests that the inf acc ET group is qualitatively different from the aligned infantile ET group.

Longitudinal Motion VEP Data

Some subjects returned for follow-up visits, and their subsequent mVEP AI data from each visit are shown in Figure 6.

The three normal subjects plotted in the top left of Figure 6 revealed a good fit to the overall mean data (open circles), with a decline to reach mature symmetrical performance by 6.5 months of age. Of the five patients with misalignment on all visits (Fig. 6, bottom left), three showed increases in AI, whereas two showed decreases, and all remain abnormally asymmetric. In the 10 patients with misalignment on initial visits followed by postalignment visits (Fig. 6, top right), AIs declined after surgery in 7 and remained the same or increased in 3. In four patients with alignment on all visits (Fig. 6, bottom right), dramatic decreases in the AI were observed in three, whereas no change was seen in one who was tested just 2.5 months later. Comparison of patients who underwent surgical alignment "early" (Fig. 6, bottom right) with those who had alignment after 8 months (top right) suggests that surgical alignment before 8 months of age may reduce the VEP asymmetry when the patient is tested between 2 and 4 years of age.

DISCUSSION

Both perceptual and VEP measures of motion processing in this study produced similar patterns of motion asymmetry in normal and inf ET patients, despite different stimuli (random dot patterns versus gratings) used in the two tasks. This study provides further evidence for N-T asymmetries in cortical motion processing in normal infants and in patients with misaligned inf ET.[15–18,20,29] These findings are also compatible with those reported in neonate and strabismic primates.[22,30–32]

N-T asymmetries in mVEP are inherently ambiguous regarding which direction of motion, N or T, produces the stronger signal. In our motion-detection task, we observed a strong advantage in detecting N over T motion. The concurrent N-T asymmetries we observed in both mVEP and motion detection in the same subjects are thus highly likely to be a result of a stronger response to N motion, which is consistent with previous findings.[12]

Motion direction discrimination emerges at 2 to 3 months of age.[24,33,34] Intriguingly, we found a peak in motion asymmetry between 2 and 4 months of age. Our results agree with a previous report of asymmetric motion detection during the first 3 months of life[35] and with reports of a general progression to symmetric motion processing by approximately 6 months of age in normal infants for mVEP.[17,29,36] The present study is the first we know of to report a parallel progression to symmetrical motion processing in both electrophysiological and psychophysical paradigms.

In the present study, the youngest untreated patients with inf ET had mVEP and motion-detection asymmetries similar to those of normal subjects at 5 months of age. The asymmetries in normal subjects diminished, whereas those in the patients with misalignment remained highly asymmetric in all age groups thereafter. These results are consistent with the literature.[16–18,29,37] The fact that patients with inf ET initially resemble normal subjects suggests that they have a normal sensory capacity that is later disrupted with abnormal binocular experience. Similarly, Birch and Stager[2] showed that infants at 3 to 5 months of age with diagnosed inf ET initially have a normal capacity for stereopsis that diminishes with uncorrected misalignment over time. Deficits in stereopsis and motion processing in patients with inf ET develop over time if no correction (with surgery or glasses) occurs. The initial onset of motion and stereopsis capacity may occur without regard to the sensory input, or a certain "threshold" of abnormal binocular input that accumulates over time may be needed before the motion and stereopsis sensory systems go awry. After

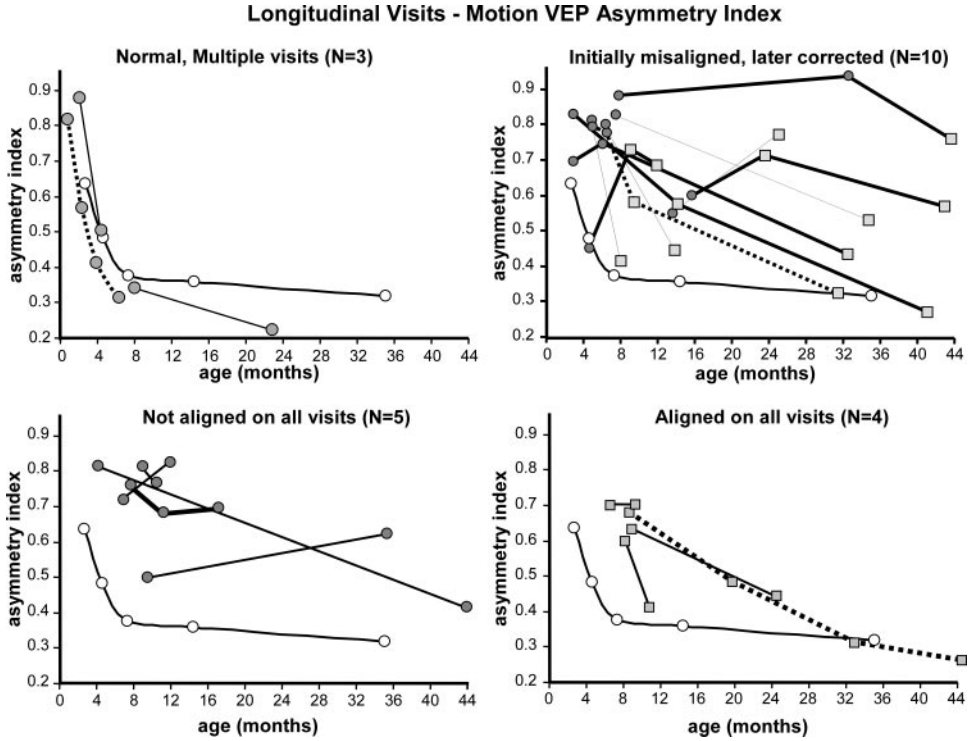

FIGURE 6. Mean mVEP AIs in subjects who returned for multiple visits. Mean values from all normal subjects (*open circles*) are replotted in all panels for comparison. All other lines connect multiple visits from individual participants with two visits (*thin lines*), three visits (*thick lines*), and four visits (*dotted lines*). *Filled circles*: visits in which patients showed misalignment; *squares*: visits in which patients showed alignment.

alignment with glasses or surgery, asymmetries in both mVEP and motion detection were reduced. These early treatment effects demonstrate that binocular motion-processing mechanisms are plastic within a developmental critical period and are dependent on normal binocular input.

We observed reduced asymmetries in both motion VEP and motion detection in patients with infantile ET who had undergone successful alignment with glasses or surgery. These results are consistent with a recent study showing reduction of mVEP asymmetries after early, but not delayed, repair of ocular misalignment in infant monkeys.[31] One may note the seemingly contradictory finding that at 7 months of age, 67% of patients without alignment and 100% of patients with alignment had the mVEP phase asymmetry. However, those patients with alignment at this age were tested just 1 to 4 months after surgery, suggesting that surgical alignment may not *immediately* counteract the preceding abnormal binocular experience but may require a period of normal binocular experience for the VEP response to become symmetric. All older patients (12–44 months) with surgical alignment, had had alignment a minimum of 4 months before testing, and these age groups showed a much lower prevalence of asymmetry: 23% (3/13).

Patients who had occlusion therapy had similar mean AIs and a slightly greater prevalence of significant interocular phase differences compared with patients who did not patch. This finding is not in agreement with Jampolsky et al.[15] who found that occlusion therapy *reduces* mVEP asymmetry. However, in our cohort, patients who received occlusion therapy did so, on average, only 3 hours a day, whereas in the study by Jampolsky et al., the cohort had been treated with full-time alternate occlusion therapy. Given the strong link established between symmetry of the mVEP and fusion,[20] it is possible that full-time alternate occlusion eliminates the opportunity for the abnormal binocular interaction that results in asymmetry, whereas part-time occlusion does not.

Although our motion-detection task does not require involvement of directionally selective motion mechanisms, the differential sensitivity to N versus T motion detection is likely to emerge from directionally selective cells, since flicker detection mechanisms are not expected to show such directional asymmetries. A possible explanation for the motion VEP and motion-detection asymmetry observed in normal newborns and in patients with strabismus may lie in a subpopulation of cortical neurons that project to bilateral midbrain structures. Development of symmetrical motion responses, including OKN eye movements, is dependent on normal development of both the indirect cortical ipsilateral input and the direct retinal contralateral input to the binocular cells in the nucleus of the optic tract (NOT). In infant monkeys, cortical neurons show anomalous binocular suppression and do not drive NOT neurons as strongly.[38] As a result, responses of NOT neurons are dominated by direct retinal contralateral input that favors the T-to-N motion. This early developmental stage could explain the asymmetries in immature infants and in strabismus, whereas increasing symmetry could result with maturation of the binocular cortical input to the NOT. This hypothesis is supported by the findings that strabismic monkeys exhibit reduced cytochrome oxidase activity in ocular dominance columns,[39] weak directional selectivity,[40] lack of binocularity,[41] and anomalous binocular suppression,[40] all of which could which weaken the ipsilateral functional connections from visual cortex to brain stem nuclei. The mVEP asymmetry in esotropic patients, then, may arise from abnormal binocular suppression in a subset of cortical neurons that project to an asymmetric population of cells in NOT.

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