Differential Changes in Color and Motion-Onset Visual Evoked Potentials from Both Eyes in Early- and Late-Onset Strabismic Amblyopia

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Purpose. To examine changes in color- and motion-related visual function in patients with strabismic amblyopia.

Methods. Motion-onset and color visual-evoked potentials (VEPs) were recorded in 16 adult patients with strabismic amblyopia which had an early onset, before 18 months of age, and 14 patients with amblyopia of later onset. The results are compared with those from 21 normal adults.

Results. The peak times of motion-onset VEPs in the amblyopic eye were longer those than in the fellow eye in patients with both early- and late-onset strabismic amblyopia, but peak times in both amblyopic and fellow eyes were shorter than those in normal eyes. In patients with late- but not early-onset amblyopia, the peak times for color VEPs were significantly longer in amblyopic than in fellow and normal eyes.

Conclusions. The patterns of abnormality for motion-onset and color VEPs in patients with strabismic amblyopia are different, probably indicating differential changes in function in magno- and parvocellular pathways. These abnormalities affect both the amblyopic and fellow eyes and are different in patients with an onset of amblyopia before or after 18 months of age. (*Invest Ophthalmol Vis Sci.* 2008;49:4418–4426) DOI:10.1167/iovs.07-1437

Two major parallel pathways predominantly transmit color and motion information to the brain, where it is reintegrated in the visual cortex.[1–4] Cells in the parvocellular pathway respond best to chromatic stimuli of high spatial and low temporal frequencies, whereas cells in the magnocellular pathway respond best to achromatic stimuli of low spatial and high temporal frequency[5–9] and to motion.[8] Anatomic studies of the effects of monocular visual deprivation on the sizes of cells in the lateral geniculate nucleus (LGN) of nonhuman primates have shown differential effects of visual deprivation on magno- and parvocellular cells, marked changes in LGN cells related to the fellow eye, and major differences in the effects of early- and late-onset monocular visual deprivation.[10,11]

Those anatomic findings suggest that color- and motion-related functions are differently affected in amblyopia. A recent psychophysical study of human subjects with strabismic amblyopia showed a reduction in color-contrast sensitivity in both eyes, with the amblyopic eyes being more affected than fellow eyes, and the color contrast sensitivity in the amblyopic eyes of subjects with late onset being more reduced than in those with early-onset amblyopia.[12] Luminance contrast sensitivity was relatively less affected, so that all eyes showed a reduction in color contrast sensitivity relative to luminance contrast sensitivity. This finding suggested that parvocellular function was reduced relative to magnocellular function in both eyes of subjects with strabismic amblyopia, in keeping with the primate studies.[11]

The above findings suggest that color and motion onset VEPs may be differentially affected in amblyopia. It has been suggested on the basis of comparisons between amblyopic and fellow eyes that motion-onset VEPs are relatively spared in amblyopia[13] and one previous study of color VEPs in amblyopia has suggested a relative reduction in parvocellular function.[14] The present study has followed-up the psychophysical study by comparing VEPs to color and motion-onset stimuli in largely the same group of subjects with strabismic amblyopia in whom abnormalities of color and luminance contrast sensitivity were demonstrated.[12]

Methods

Subjects

Sixteen subjects with an early-onset squint and strabismic amblyopia and 14 with late onset were recruited after attendance at a strabismus clinic. The patients were assigned to early- or late-onset groups on the basis of a history of the onset of a squint before or after 18 months of age, a division based on extrapolation from primate studies.[11] In practice, this usually meant distinguishing between onset as an infant within the first year of life and onset at ~2 to 3 years of age. Several subjects also knew when they began patching treatment. Approximately half the patients initially approached were able to give a clear history, sometimes with help from parents or photographs, and only those were recruited. Evidence that those children with an early-onset squint who do become amblyopic do so soon after the onset of the squint has been considered elsewhere, together with evidence that it is unusual for amblyopia to occur before the onset of a large-angle, late-onset squint.[15] Anisometropia was no greater, nor more prevalent in the late than early-onset group (see the Results section). Thus, most of those subjects with an early-onset squint can be expected to have had early onset of amblyopia and vice versa. The assignment to early- or late-onset groups was always made at recruitment, so that it could not be influenced by any of the results. Although it is not possible to be certain that all patients were correctly assigned to early and late groups, any incorrect assignments would tend to reduce any differences between the groups. Because the assignment was always made before any results were obtained, it is difficult to envisage how it could create differences.

All subjects underwent full orthoptic and ophthalmic assessment before testing. The presence or absence of fusion was assessed by cover testing, and suppression was diagnosed on the basis of a manifest squint without diplopia and was confirmed by testing with Bagolini glasses in most subjects, particularly those with small angles. The

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Supported by the Special Trustees, Moorfields Eye Hospital; the Ann Allerton Fund, Royal College of Ophthalmologists; and a Wellcome Trust Basic Science Training Fellowship (AD).

Submitted for publication November 7, 2007; revised February 4 and April 21, 2008; accepted August 11, 2008.

Disclosure: **A.R. Davis**, None; **J.J. Sloper**, None; **M.M. Neveu**, None; **C.R. Hogg**, None; **M.J. Morgan**, None; **G.E. Holder**, None

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Investigative Ophthalmology & Visual Science, October 2008, Vol. 49, No. 10

presence of diplopia was assessed both on history and on examination in the clinic. In most subjects the findings of fusion, suppression, and diplopia were confirmed using the synoptophore. Twenty-six of the subjects had participated in a previous study.[12] The control group consisted of 21 normal young adults with a mean age of 32 years (range, 22–52 years).

Electrophysiological Methods

Monocular VEPs were recorded with the other eye patched. Fixation was maintained with a central red spot and was monitored by observation by an experienced electrophysiologist. Stimuli were presented on a 53-cm monitor (Multisync; NEC, New York, NY) using a mean luminance of 90 cd/m^2 in a dimly lit room. The contrast linearity of the display screen was linear up to 98% (maximal) contrast. For all recordings, the surface electrode impedance was <5 KΩ. The number of responses averaged for each trial was at least 64, with a minimum of two replications being recorded for each condition for each eye. The analysis time was 500 ms. The recording bandwidth was from 1 to 100 Hz (−3 dB) with no line-frequency notch filter. The subjects' refractive correction was checked and was used during testing.

Color VEPS

The color stimulus was a 3.2-cyc/deg, red/green, pattern-onset, sine wave grating (onset, 200 ms; offset, 600 ms). Field size was 16° × 10° at a viewing distance of 1.5 m. For each subject, heterochromatic flicker balance between the luminosities of the R and G and B and G phosphors of the monitor was established, so that all colors subsequently generated for the stimulus appeared isoluminant to the person tested. A small square flickering at 25 Hz was presented to the subject. The flicker was modulated along the L/M axis (protan) by maintaining the red phosphor at a constant luminance and varying the luminance of the green phosphor. The patient balanced the flicker by increasing or decreasing the green luminance with a push-button controller. At the point of isoluminance there was no apparent flicker. These values were then used to generate the red/green grating stimulus for the color VEP.

Responses were recorded from an active electrode at O_z (midline), referenced to F_z (midfrontal), and two electrodes at O_1 and O_2 (10–20-electrode montage), referenced to temporal electrodes 5 cm above the mastoid. A ground electrode was placed on the forehead. The peak time and amplitude of the N130 component were measured offline.

Motion-Onset VEPs

The motion-onset stimulus was a vertically oriented achromatic square wave grating of 0.8 cyc/deg. Field size was 20° × 16° at a viewing distance of 1 m, and the grating moved horizontally from left to right at 4.9 deg/sec. The motion-onset stimulus used was 98% contrast because it was difficult to obtain satisfactory responses at low contrast in amblyopic eyes. In a subset of subjects, responses were also recorded at lower contrast levels. These recordings demonstrated that there was no significant change in the peak time of the response at low contrast, as would be expected for a response coming predominantly from the magnocellular pathway (see the Results section). Responses were recorded to both nasotemporal and temporonasal motion in a sample of 13 eyes and demonstrated no asymmetry in response peak time or waveform with direction of motion. Responses were recorded

Table 1. Clinical Features of Subjects with Early- and Late-Onset Strabismic Amblyopia and Tests Performed

Subject	Age (y)	Diagnosis	Anisometropia	Snellen Acuity		Binocular Status	Color VEPs	Motion VEPs
				Amblyopic Eye	Fellow Eye			
Early onset								
1	22	60Δ Consecutive XT	Y	6/9	6/4	Suppression	+	+
2	35	85Δ Consecutive XT	N	6/9	6/4	Suppression	+	+
3	33	25Δ Residual ET	N	6/9	6/4	Suppression	+	+
4	39	8Δ Consecutive XT	N	6/9	6/6	Suppression	+	+
5	40	45Δ Residual ET	Y	6/12	6/6	Suppression	+	+
6	21	12Δ Consecutive XT	N	6/18	6/4	Suppression	+	+
7	24	4Δ Residual XT	Y	6/18	6/5	Suppression	+	−
8	50	35Δ Consecutive XT	N	6/24	6/5	Suppression	+	+
9	43	25Δ Consecutive XT	N	6/24	6/5	Suppression	+	+
10	24	18Δ Residual ET	N	6/24	6/5	Constant diplopia	+	+
11	33	25Δ Residual ET	N	6/24	6/6	Variable suppression	−	+
12	19	35Δ Consecutive XT	Y	6/24	6/6	Suppression	+	+
13	23	8Δ Residual ET	Y	6/24	6/9	Variable suppression	+	+
14	18	30Δ Residual ET	N	6/36	6/9	Constant diplopia	+	+
15	33	35Δ Residual XT	Y	6/60*	6/5	Suppression	−	+
16	41	40Δ Consecutive XT	Y	HM*	6/4	Suppression	+	+
Mean	31.1							
Late onset								
17	36	35Δ Primary ET	N	6/9	6/5	Suppression	+	+
18	49	25Δ Primary XT	N	6/9	6/4	Suppression	+	+
19	39	Fully Accommodative ET	N	6/12	6/6	Fully accommodative	+	+
20	60	25Δ Residual XT	Y	6/12	6/6	Suppression	+	−
21	38	45Δ Consecutive XT	Y	6/18	6/4	Variable suppression	−	+
22	36	50Δ Consecutive XT	N	6/18	6/5	Constant diplopia	+	+
23	29	40Δ Consecutive XT	Y	6/24	6/5	Constant diplopia	+	+
24	30	45Δ Consecutive XT	N	6/24	6/5	Suppression	+	+
25	27	30Δ Residual ET	N	6/24	6/5	Suppression	+	+
26	34	40Δ Consecutive XT	N	6/36	6/6	Suppression	+	+
27	49	60Δ Consecutive XT	N	6/60	6/5	Suppression	+	+
28	47	45Δ Consecutive XT	N	6/60*	6/6	Suppression	+	+
29	31	45Δ Consecutive XT	Y	2/60*	6/4	Suppression	+	−
30	30	40Δ Consecutive XT	Y	1/60*	6/4	Suppression	+	+
Mean	38.2							

* Eccentric fixation.

TABLE 2. Color VEP Peak Times

Subjects	Amblyopic Eye			Fellow Eye			Amblyopic vs. Fellow Eye	
	Peak Time Mean ± SD (ms)	% Difference from Normal	*P* vs. Normal	Peak Time Mean ± SD (ms)	% Difference from Normal	*P* vs. Normal	% Difference	*P*
Normal (n = 17)	125.2 ± 11.3	—	—	125.2 ± 11.3	—	—	—	—
All amblyopic (n = 27)	140.1 ± 25.5	+11.9	**0.027**	132.0 ± 14.5	+5.4	0.109	+6.1	0.075
Early-onset amblyopic (n = 14)	131.0 ± 22.1	+4.6	0.358	132.3 ± 15.6	+5.7	0.157	−1.0	0.756
Late-onset amblyopic (n = 13)	149.9 ± 25.3*	+19.8	**0.001**	131.7 ± 13.8	+5.2	0.167	+13.8	**0.024**

Values in bold type are statistically significant.
* Significantly different from early-onset amblyopic subjects (P = 0.048; unpaired t-test).

from an electrode at the midline (O_z), referenced to F_z, (midfrontal) and from two electrodes positioned at 5 cm to the right and left of the midline, referenced to linked ears. A ground electrode was placed centrally on the forehead. The peak time and amplitude of the N200 component were measured offline. No significant differences were found between midline and lateral responses and so only results from the right hemisphere channel are presented.

Statistical Analysis

Snellen visual acuities were converted to logMAR equivalents and compared between groups using unpaired t-tests. Correlation with VEP peak times was examined with linear regression. Comparisons of VEP peak times and amplitudes between amblyopic and fellow eye responses were made using paired t-tests and between groups using unpaired t-tests.

The research adhered to the tenets of the Declaration of Helsinki. The subjects gave informed consent after explanation of the nature and possible consequences of the study. The research was approved by the Ethics Committee of Moorfields Eye Hospital.

RESULTS

Most of the subjects with strabismic amblyopia had initially been esotropic as children, although most had now become consecutively exotropic (Table 1). All patients presented as adults with a manifest squint of childhood onset. Most had no or only occasional diplopia, indicating suppression of the deviating eye. Patient 23 had a manifest squint with troublesome diplopia. Subjects 15, 16, 28, 29, and 30 had eccentric fixation and were slow to take up fixation with the amblyopic eye, but were able to maintain fixation. Subjects 10, 13, and 18 had

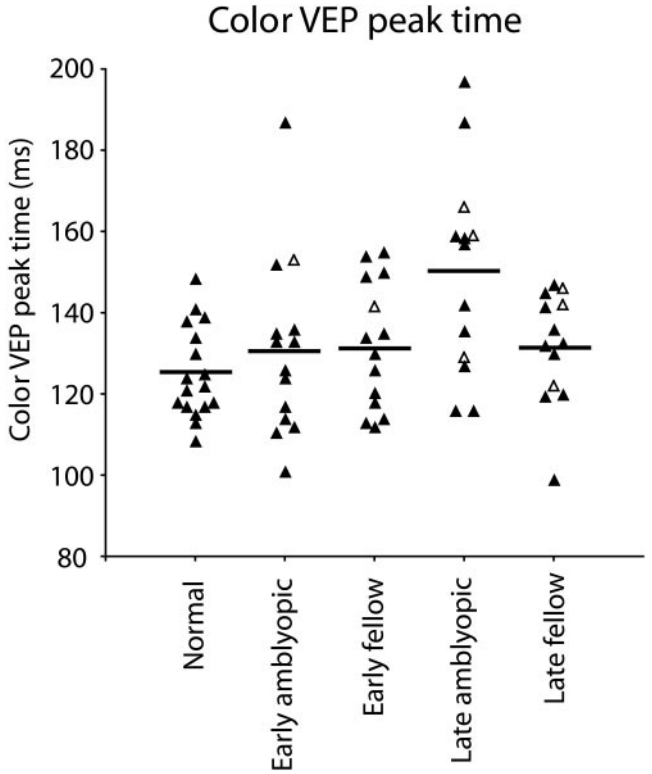

FIGURE 1. *Filled triangles*: color VEP peak times for subjects with early- or late-onset amblyopia and normal control subjects. *Horizontal bars*: means for each series; *open triangles*: patients with eccentric fixation in the amblyopic eye.

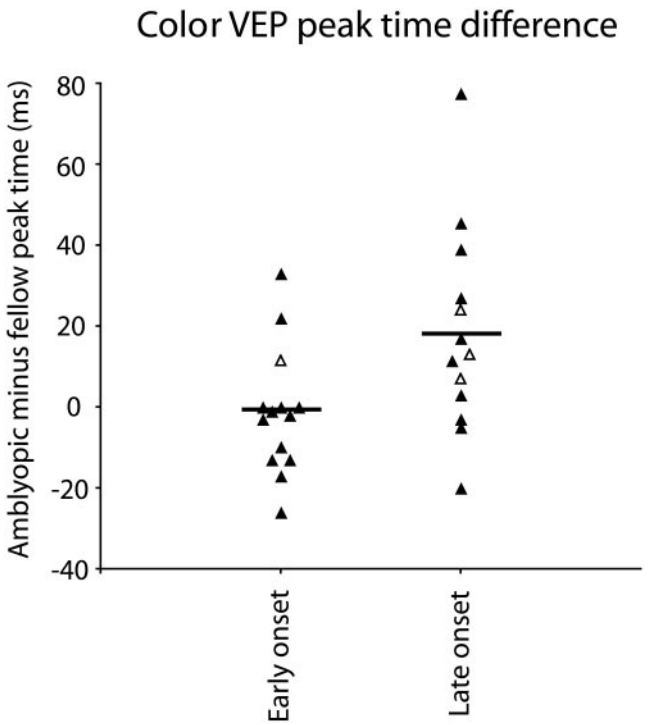

FIGURE 2. *Filled triangles*: the difference in color VEP peak times between amblyopic and fellow eyes in subjects with early- or late-onset amblyopia. *Horizontal bars*: means for each series; *open triangles*: patients with eccentric fixation in the amblyopic eye.

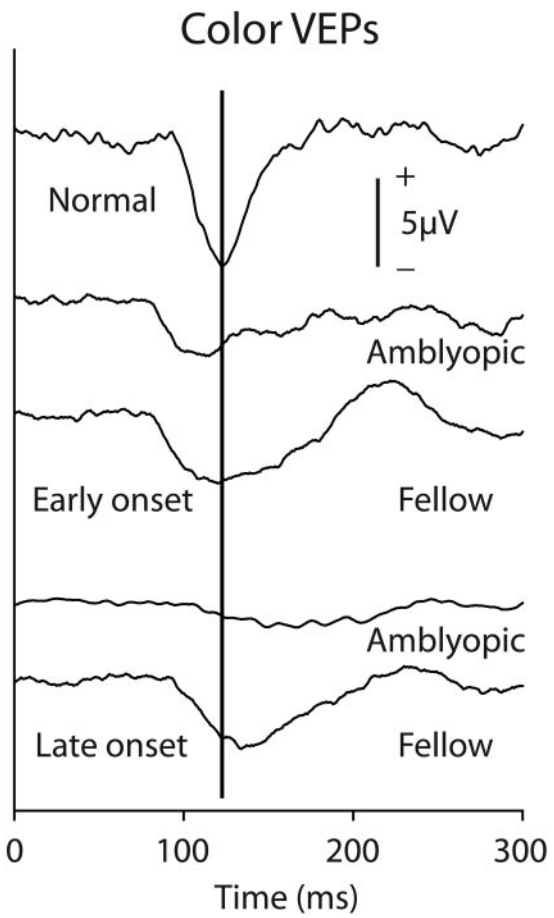

FIGURE 3. Group mean waveforms for color VEPs.

manifest latent nystagmus but were able to maintain fixation, in one case with a face turn.

Most subjects in each group had low hypermetropic refractive errors in both amblyopic and fellow eyes, with no significant differences between early and late groups (mean spherical equivalents: early amblyopia, +1.82 DS; early fellow, −0.14 DS; late amblyopia, +3.09 DS; late fellow, +1.70 DS). Seven early- and five late-onset amblyopic subjects had anisometropia of more than 1.5 D of spherical equivalent (Table 1). Mean anisometropia was 1.96 D of spherical equivalent in the early group and 1.38 D of spherical equivalent in the late group. No control subject had significant anisometropia. Patients in both early- and late-onset groups showed a similar spread of acuities in their amblyopic eyes (logMAR equivalent means: early onset 0.61, Snellen equivalent means ≈ 6/24, 20/80; late onset 0.70, Snellen equivalent ≈ 6/30, 20/100; $P = 0.63$). There was no significant difference in fellow eye acuity between the groups (logMAR equivalent means: early onset, −0.05, Snellen equivalent means ≈6/5, 20/18; late onset, −0.08, Snellen equivalent ≈ 6/5, 20/17; $P = 0.39$) nor any differences from the normal group. All normal subjects had a visual acuity of at least 6/6 in each eye with binocular single vision.

Color VEPs

For the 27 amblyopic subjects taken together, the peak time of the color VEP from the amblyopic eye was significantly longer than normal, although the peak time difference between amblyopic and fellow eyes just failed to reach significance (Table 2). When analyzed separately, the 14 patients with early-onset amblyopia showed no significant difference in peak time between amblyopic and fellow eyes, nor did amblyopic and fellow eyes differ from normal. In contrast, the 13 amblyopic eyes of patients with late onset amblyopia showed a significant increase in peak time when compared to their fellow eyes and to normal eyes (Table 2; Figs. 1, 2, 3). The mean peak time of the VEP from the amblyopic eyes was also significantly longer in subjects with late-onset amblyopia compared with those with an early onset (Table 2).

The amplitude of the color VEP was significantly lower in response to stimulation of the amblyopic eye than that in the fellow eye or normal in all subjects with amblyopia together and in those with early-onset amblyopia alone (Table 3; Fig 4). There was a smaller, nonsignificant reduction in amplitude in the eyes with late-onset amblyopia.

VEPs were also recorded over each hemisphere. There were no significant differences between hemispheres in either peak time or amplitude of responses in normal subjects or in either eye of patients with early- or late-onset amblyopia.

There was no significant correlation between logMAR acuity and color VEP peak time in either early ($r^2 = 0.0002$; $P = 0.96$) or late-onset amblyopic eyes ($r^2 = 0.016$; $P = 0.68$). There were no significant differences in color peak time between all subjects with diplopia and those without or between all those with anisometropia and those without.

Motion-Onset VEPs

When results obtained in all 27 amblyopic subjects were taken together, the peak time of the VEP response to stimulation of the amblyopic eye was slightly, but significantly, longer than that to stimulation of the fellow eye (Table 4; final column). However when compared to normal, the peak times of the VEPs from both the amblyopic and fellow eyes were substantially shortened (Table 4). When analyzed separately, the mean

TABLE 3. Color VEP Amplitudes

Subjects	Amblyopic Eye			Fellow Eye			Amblyopic vs. Fellow Eye	
	Amplitude Mean ± SD (μV)	% Difference from Normal	*P* vs. Normal	Amplitude Mean ± SD (μV)	% Difference from Normal	*P* vs. Normal	% Difference	*P*
Normal ($n = 17$)	7.5 ± 3.4	—	—	7.5 ± 3.4	—	—	—	—
All amblyopic ($n = 27$)	4.9 ± 3.5	−34.3	**0.021**	7.4 ± 4.0	−0.7	0.963	−33.8	**0.002**
Early-onset amblyopic ($n = 14$)	4.5 ± 3.0	−39.1	**0.019**	7.6 ± 4.4	+1.3	0.944	−39.9	**0.012**
Late-onset amblyopic ($n = 13$)	5.3 ± 4.0	−29.1	0.120	7.2 ± 3.7	−3.0	0.867	−27.0	0.100

Values in bold type are statistically significant.

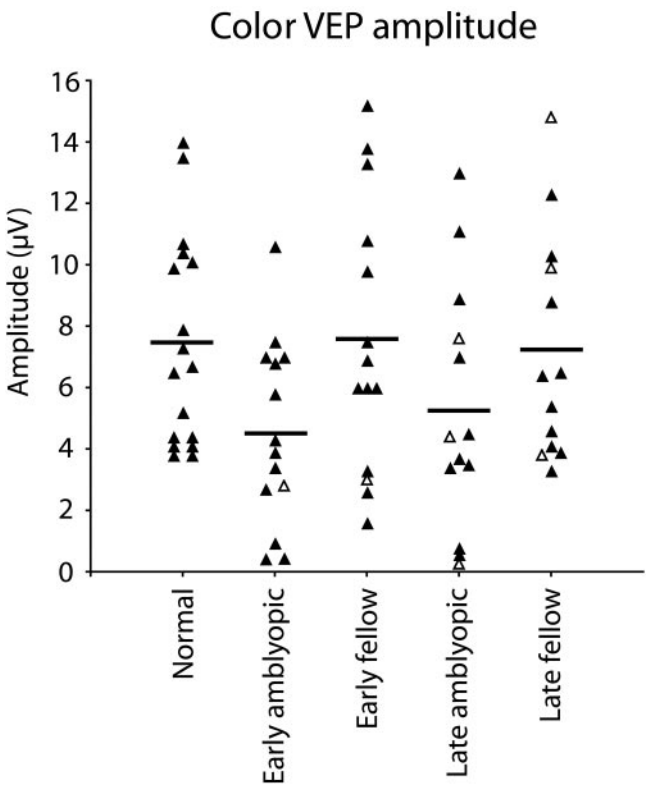

FIGURE 4. *Filled triangles*: color VEP amplitudes for subjects with early- or late-onset amblyopia and normal control subjects. *Horizontal bars*: means for each series; *open triangles*: patients with eccentric fixation in the amblyopic eye.

peak times from the 15 amblyopic eyes of the subjects with early-onset amblyopia and 12 amblyopic eyes of the subjects with late-onset amblyopia were similar, as were the mean peak times from the fellow eyes, with those from the fellow eyes of both groups remaining significantly shorter than normal (Table 4; Figs 5, 6).

There was no significant correlation between logMAR acuity and motion-onset VEP peak time for either early- or late-onset amblyopic eyes ($r^2 = 0.086$; $P = 0.29$ and $r^2 = 0.12$; $P = 0.27$, respectively). There were no significant differences in motion-onset peak time between all subjects with diplopia and those without, or between all those with anisometropia and those without.

The amplitudes of the motion-onset VEPs to stimulation of the amblyopic eye were significantly reduced compared with normal in all amblyopic subjects combined and in both early- and late-onset amblyopic eyes taken separately (Table 5; Fig 7).

Contrast Dependence

Pilot recordings showed that it was not possible to obtain reliable motion-onset VEPs from amblyopic eyes using a low-contrast stimulus and so a stimulus with 98% contrast was used. Motion-onset VEPs at both 98% and 5% contrast were recorded in 11 normal subjects. For these, the mean peak time at 98% contrast was 174.1 ± 22.3 ms and at 5% contrast, 168.9 ± 49.6 ms ($P = 0.26$; paired *t*-test). Full-contrast series were recorded in two normal subjects, of which an example is shown in Fig. 8.

Peak Time Difference between Motion-Onset and Color VEPs

To analyze further the differences between color and motion-onset results, a peak time difference was calculated by subtracting the peak time of the color VEP from the peak time of the motion-onset VEP. Thirteen patients with early-onset amblyopia, 11 with late-onset amblyopia, and 17 normal subjects had both motion-onset and color VEPs recorded. The difference was calculated for each subject, and the mean and SD of the difference was then calculated for each group (Table 6). When compared to normal subjects, the peak time difference between motion-onset and color VEPs was markedly reduced for both amblyopic and fellow eyes of both early- and late-onset amblyopic subjects.

DISCUSSION

This study of adult patients with strabismic amblyopia has demonstrated abnormalities in the VEPs recorded in response to both color and motion-onset stimuli. These abnormalities affect both the amblyopic and fellow eyes, are different for color and motion-onset stimuli, and are different in subjects with an onset of amblyopia before or after 18 months of age.

A previous study of motion-onset VEPs in persons with amblyopia described a small difference in peak time between amblyopic and fellow eyes and concluded that motion-onset responses were relatively spared in amblyopia.[13] The present study has confirmed the presence of a small difference in peak time between amblyopic and fellow eyes, but has also shown that the VEPs from both amblyopic and fellow eyes are abnormal compared with those from normal subjects, being of substantially shorter peak time and reduced amplitude. These abnormalities of motion-onset VEPs are similar in subjects with early- and late-onset amblyopia. Deficits of motion processing have been well described in various forms of amblyopia using

TABLE 4. Motion VEP Peak Times

Subjects	Amblyopic Eye			Fellow Eye			Amblyopic vs. Fellow Eye	
	Peak Time Mean ± SD (ms)	% Difference from Normal	*P* vs. Normal	Peak Time Mean ± SD (ms)	% Difference from Normal	*P* vs. Normal	% Difference	*P*
Normal ($n = 19$)	178.1 ± 9.5	—	—	178.1 ± 9.5	—	—	—	—
All amblyopic ($n = 27$)	171.0 ± 12.4	−4.0	**0.041**	167.6 ± 10.7	−5.9	**0.001**	+2.0	**0.024**
Early-onset amblyopic ($n = 15$)	170.1 ± 13.8	−4.5	0.055	166.3 ± 11.3	−6.6	**0.002**	+2.3	0.096
Late-onset amblyopic ($n = 12$)	172.0 ± 10.8	−3.4	0.111	169.1 ± 10.1	−5.0	**0.018**	+1.7	0.144

Values in bold type are statistically significant.

both psychophysical methods (e.g., Refs. 16–19) and functional MRI[20] and have been shown to affect the fellow eye as well as the amblyopic eye.[16,18,21] Abnormalities of motion-onset VEPs affecting both eyes are thus not unexpected. However, it is surprising that the most striking abnormality is the shortening of the peak time response to stimulation of either the amblyopic or fellow eye. Possibly loss of some components of cortical processing, abnormal binocular interaction or some change in interaction between magno- and parvocellular pathways results in faster motion processing.

One previous study has examined changes in color responses in amblyopia, but differed from the present study in several important respects.[14] It used reversal, rather than color-onset VEPs and its subjects were children 5 to 10 years of age with no indication of age of onset. Many appear to have had binocular function. Despite these differences, both studies indicate a delay in the color VEP from the amblyopic eye. A study in which steady state VEP responses to achromatic checks of different sizes and temporal frequencies was examined also indicated a selective reduction in the response to the parvocellular-biased stimulus from the amblyopic eye of subjects with anisometropic amblyopia.[22]

In the present study, the difference in peak time to a color stimulus between amblyopic and fellow eyes was only significant for the patients with late-onset amblyopia. This peak time was also delayed compared with normal, whereas peak times from the fellow eye and for both eyes of early-onset amblyopic patients did not differ significantly from normal. The pattern of change seen with a color stimulus was thus different from that seen for the motion-onset VEPs. In particular, there was a much greater change of the color VEP in the patients with late-onset amblyopia. Early studies of cell size change in non-human primates showed a reduction in parvocellular size relative to magnocellular cell size for both deprived and undeprived LGN cells after monocular visual deprivation.[10,11] A previous psychophysical study in essentially the same group of subjects with strabismic amblyopia as studied in the present study[12] demonstrated reduced color contrast sensitivity in both eyes, with the amblyopic eye being more affected than the fellow eye, and a relative reduction of color contrast sensitivity compared with luminance contrast sensitivity in both amblyopic and fellow eyes. These parameters probably reflect mainly parvo- and magnocellular functions, respectively, and indicate a reduction of parvocellular relative to magnocellular function, which was more marked in subjects with late-onset amblyopia. It is likely that the motion-onset stimulus used in the present study activates predominantly the magnocellular pathways and the color stimulus activates mainly parvocellular pathways. The above findings would thus reflect a different pattern of change in the magno- and parvocellular pathways in strabismic amblyopia.

The general picture that emerges is of a reduction of parvocellular function relative to magnocellular function in strabismic amblyopia, with the reduction being more marked in amblyopia of later onset. However, other results indicate that the difference between early- or late-onset amblyopia may be more complex. In a previous study of similar groups of patients with early- or late-onset amblyopia,[15] the peak time of the achromatic pattern onset VEP response to a 30-minute check was shortened in both eyes in patients with early-onset amblyopia. This resembles the changes found with motion-onset VEPs in patients with both early- or late-onset amblyopia in the present study. However, in the previous study, patients with late-onset amblyopia showed very different responses to the same 30-minute pattern-onset check, with a prolonged peak time from the amblyopic eye and a normal peak time from the fellow eye. This resembles the changes found here with the

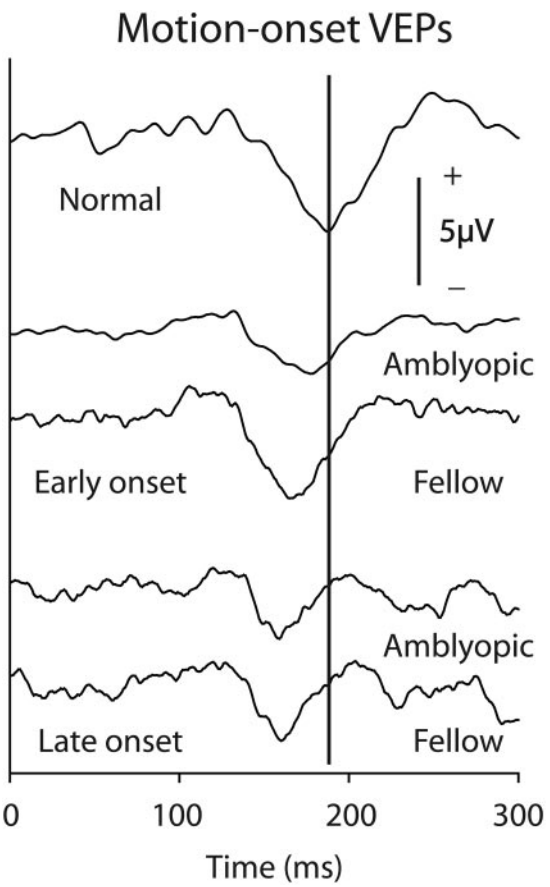

Figure 6. Group mean waveforms for motion-onset VEPs.

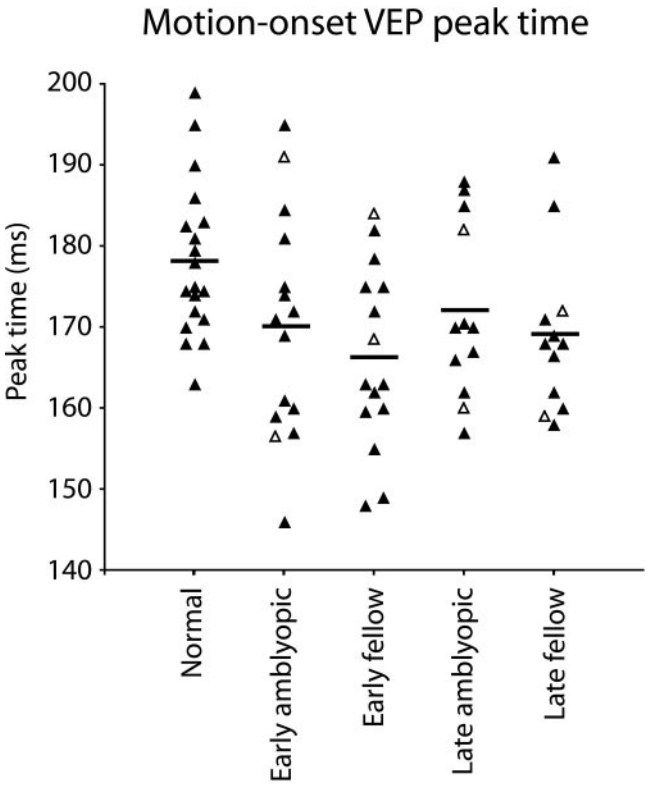

Figure 5. *Filled triangles*: motion-onset VEP peak times for subjects with early- or late-onset amblyopia and normal control subjects. *Horizontal bars*: means for each series; *open triangles*: patients with eccentric fixation in their amblyopic eye.

TABLE 5. Motion VEP Amplitudes

Subjects	Amblyopic Eye			Fellow Eye			Amblyopic vs. Fellow Eye	
	Amplitude mean ± SD (μV)	% Difference from Normal	*P* vs. Normal	Amplitude Mean ± SD (μV)	% Difference from Normal	*P* vs. Normal	% Difference	*P*
Normal (n = 19)	6.8 ± 3.3	—	—	6.8 ± 3.3	—	—	—	—
All amblyopic (n = 27)	4.2 ± 2.1	−37.8	**0.003**	5.4 ± 2.1	−19.4	0.108	−22.8	**0.011**
Early-onset amblyopic (n = 15)	4.3 ± 2.4	−36.3	**0.023**	5.7 ± 2.5	−15.8	0.311	−24.4	0.078
Late-onset amblyopic (n = 12)	4.1 ± 1.7	−39.7	**0.016**	5.1 ± 1.5	−24.0	0.125	−20.6	**0.05**

Values in bold type are statistically significant.

color VEPs in the subjects with late-onset amblyopia. The same achromatic pattern-onset stimulus thus gave very different results in the subjects with early- or late-onset amblyopia. This stimulus contained elements that would be expected to stimulate both the magno- and parvocellular pathways. In the early-onset amblyopia, the results appear to be dominated by the magnocellular pattern of change, whereas in late-onset amblyopia, they appear to be dominated by the parvocellular pattern. Abnormal visual experience starting at different ages would seem to affect the interaction between the magno- and parvocellular pathways differently.

The problems of recombining and binding information relating to the color and motion of an object are of considerable theoretical interest,[4,23–28] and under certain conditions, it is possible to produce misbinding illusions by making them combine incorrectly.[29] In general, these psychophysical studies in normal human subjects have provided evidence that the perception of the movement of an object is delayed in relation to perception of its color and contour. It is intriguing that the delays reported in some of those studies are similar to the difference in peak time between the motion-onset and color VEPs observed in our normal subjects. In our patients with strabismic amblyopia, this difference in peak time was reduced by up to half in amblyopic and fellow eyes, because the peak time of the motion-onset VEP was reduced and that of the color VEP increased. If the published psychophysical results and the present VEP data relate to the same underlying processes, it would be predicted that the difference in perception times for color and motion would be substantially reduced in both eyes of patients with strabismic amblyopia. It would be of considerable interest to study the questions of binding and misbinding of color and motion in these amblyopic patients, both for the understanding of the basic mechanisms involved and because it may demonstrate previously unsuspected abnormalities of visual perception, particularly in the fellow eyes, and may explain some the instabilities of the visual image described in amblyopia.[30,31]

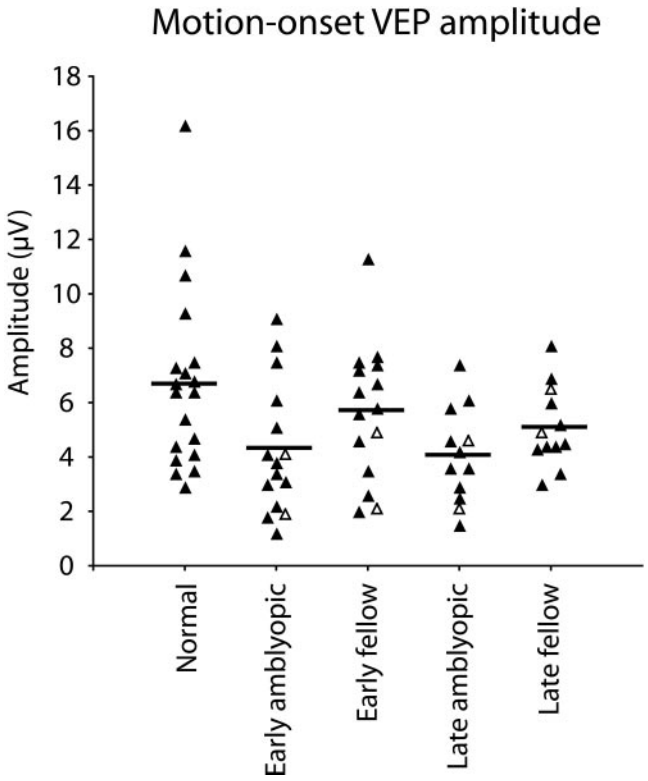

FIGURE 7. *Filled triangles*: motion-onset VEP amplitudes for subjects with early- or late-onset amblyopia and normal control subjects. *Horizontal bars*: means for each series; *open triangles*: those patients with eccentric fixation in the amblyopic eye.

Changes in the fellow eyes of patients with strabismic amblyopia are of particular importance, because in most instances that is the eye that subjects rely on for vision in everyday life. Early studies in nonhuman primates described expansion of fellow eye ocular dominance columns in area 17 after early visual deprivation,[32,33] and studies of cell sizes in the LGN showed changes in cells in the undeprived laminae which were different with early- or late-onset deprivation and different in the magno- and parvocellular laminae.[10,11] Previous studies of fellow eye function have reported both increases[15,34] and decreases in certain visual functions.[16,21,35–43] The present study and a previous psychophysical study[12] have shown that the change in the fellow eye is not a simple increase or decrease in function, but a relative decrease in parvocellular relative to magnocellular function. Although this is evident mainly as a decrease in parvocellular sensitivity, the difference found between eyes in luminance contrast sensitivity is as much due to an increase in fellow eye sensitivity as a decrease in the amblyopic eye,[12] and the reduction in the difference between color and motion VEP peak time is as much due to shortening of the motion-onset peak time as the increase in color VEP peak time. The alterations in fellow eye function in amblyopia are complex, and the changes found are likely to depend on the spatial and particularly temporal characteristics of the stimulus used and whether it activates mainly magno- or parvocellular pathways. It is of interest that the two studies showing supranormal function of the fellow eye used rapidly presented, computer-generated stimuli that are more likely to activate magnocellular pathways.[12,34] It is not yet known whether this change in magno- to parvocellular balance in the fellow eye

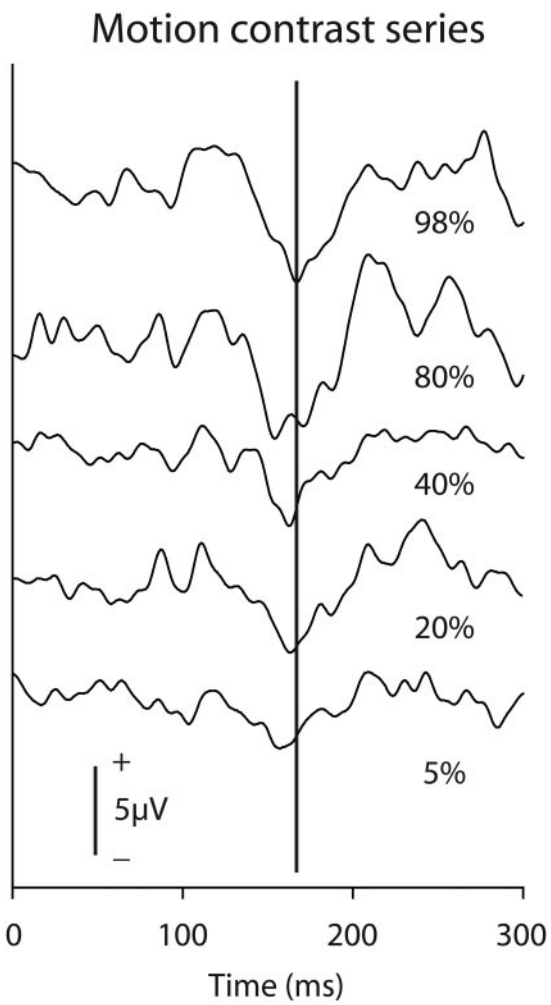

FIGURE 8. Motion-onset VEPs recorded in response to a series of contrast levels from 5% to 98% in a normal subject.

affects everyday visual perception in patients with amblyopia. They may have previously unsuspected visual difficulties, or indeed, abilities.

One of the surprising aspects of the present results is the greater relative sensitivity of the parvocellular pathways to abnormal visual experience with later onset of amblyopia. This may not represent a true increase in sensitivity as, although the visual acuity of the early- or late-onset groups were similar in this and the previous study,[12] it may be that more abnormal visual experience was needed to produce this change of acuity in the late-onset groups. However, it is well recognized in animal studies that sensitivity of some visual functions to abnormal visual experience increases with age.[44] In anatomic studies of the primate LGN, the change in size of undeprived parvocellular cells produced by 2 months of monocular lid closure increased between 3 and 6 months of age (Fig. 13 in Headon et al.[10]). There is evidence that parvocellular pathways continue to show developmental change at a later age than for the magnocellular system.[45–47] Against this background, it would not be surprising if there were a true increase in the sensitivity of the parvocellular system to abnormal visual deprivation as it matures.

The differential effects of abnormal visual experience on the magno- and parvocellular pathways may have implications for the treatment of amblyopia. Not only do the magno- and parvocellular pathways respond differently to the initial abnormal experience, but LeVay et al.[32] illustrate an instance in which closure of one eye from birth in a nonhuman primate was followed by reopening of the eye and closure of the other eye at 3 weeks of age—an experimental model of patching (Figs 38 and 39 in LeVay et al.[32]). That animal showed re-expansion of the ocular dominance columns in layer IVCβ, but no re-expansion of the columns in the immediately overlying IVCα. What effect this dissociation of magno- and parvocellular change may have on visual function has never been examined, but such residual disorganization of the visual pathways after amblyopia and patching may be a factor in those children whose acuity does not improve despite good compliance.

This study has shown that the changes that occur in the central visual pathways in strabismic amblyopia are complex. Not only are different changes found in parallel components of the pathway, but the interactions between the components are different, and both the changes and the interactions differ according to the age of onset of the amblyopia. Although patching is frequently effective in improving visual acuity, it does not selectively treat these different components of the visual pathway. In view of the complexity of the changes, it is perhaps not surprising that the response to patching varies greatly between children of a similar age, that some continuing deficit in acuity is common and that some children fail to respond to occlusion, even with good compliance. Understanding these complexities should lead to novel and selective forms of treatment that may need to be tailored according to the characteristics of the individual child.

TABLE 6. Difference between Motion-Onset and Color VEP Peak Times*

	Amblyopic Eye			Fellow Eye			Amblyopic vs. Fellow Eye	
Subjects	Difference in Peak Time Mean ± SD (ms)	% Difference from Normal	*P* vs. Normal	Difference in Peak Time Mean ± SD (ms)	% Difference from Normal	*P* vs. Normal	% Difference	*P*
Normal (n = 17)	52.6 ± 12.9			52.6 ± 12.9				
All amblyopic (n = 24)	30.6 ± 25.5	−41.9	**0.0022**	34.4 ± 14.0	−34.7	**0.0001**	−11.1	0.52
Early-onset amblyopic (n = 13)	36.1 ± 21.4	−31.5	**0.0137**	31.0 ± 14.9	−41.1	**0.0002**	+16.4	0.35
Late-onset amblyopic (n = 11)	24.0 ± 29.3	−54.3	**0.0015**	38.4 ± 12.2	−27.1	**0.0072**	−37.3	0.13

Values in bold type are statistically significant.

* Motion-onset peak time minus color peak time in milliseconds.

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