Reduced Binocular Beat Visual Evoked Responses and Stereoacuity in Patients with Duane Syndrome

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Purpose. To study the effects that the abnormal eye movements of patients with Duane retraction syndrome have on the development of binocular function.

Methods. Pattern reversal visual evoked responses (VEPs) to 15-minutes-of-arc and 60-minutes-of-arc checks and binocular beat VEPs to diffuse sinusoidally modulated 18- and 20-Hz stimuli were recorded in 10 patients with Duane retraction syndrome who maintain binocular function by using an abnormal head posture. Visual acuity, stereoacuity, and eye movements were measured. The results have been compared to those from 10 normal subjects.

Results. The patients with Duane retraction syndrome had reduced stereoacuity compared to the normal control group (TNO mean, 82.5 seconds of arc compared to 37.5 seconds of arc; Titmus mean, 143 seconds of arc compared to 44 seconds of arc). The binocular beat VEPs showed a significantly reduced difference beat response at 2 Hz in the patients with Duane syndrome compared to normal subjects (mean signal-to-noise ratio 2.40 ± 1.05 compared to 4.30 ± 2.66; $t = 2.21$, $df = 18$, $P < 0.05$). Binocular enhancement of the P100 pattern reversal amplitude to 15-minute checks was increased in these patients, because of a reduction of the monocular P100 amplitudes compared to the normal group.

Conclusions. Patients with Duane syndrome who maintain binocular function using an abnormal head posture have reduced stereoacuity and show electrophysiological evidence of reduced cortical binocular interaction. (*Invest Ophthalmol Vis Sci.* 2001;42:2826–2830)

Most patients with Duane retraction syndrome maintain binocular single vision by using an abnormal head posture to compensate for their restricted ocular motility.[1–4] However, their stereoacuity is reduced compared to normal subjects of a similar age[5] and it has been suggested that this is due to the intermittent misalignment of their eyes during visual development.[6] In a study reported in a companion article in this issue of *IOVS*,[7] it has been shown that such patients demonstrate an increase in binocular enhancement of contrast sensitivity, and it has been suggested that the combination of this with reduced stereoacuity may be explained by a partial loss of binocularly driven cortical neurons. In the present study, we investigated binocular function electrophysiologically in a further group of patients with Duane syndrome, by using pattern reversal and binocular beat VEPs.

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Some of the data in this study have been presented earlier.[8]

Subjects and Methods

Ten patients with Duane syndrome, aged between 11 and 19 years, were studied and compared to 10 normal subjects of similar ages. Patients were recruited either during a clinic visit or were contacted from clinic records and were the first 10 patients with Duane syndrome and binocular single vision who were willing to participate in the study. Ocular motility was examined clinically. All patients with Duane syndrome showed failure of abduction of one or both eyes, together with retraction on attempted adduction of the eye.[9–11] Three had had previous squint surgery. With their head postures, nine had bifoveal binocular single vision with no movement on the cover–uncover test and a normal result in the Worth 4-dot test indicating no central suppression. The remaining patient had binocular single vision with microtropia. Visual acuity was measured using a standard Snellen chart and the appropriate spectacle correction (Table 1). All had Snellen acuity of at least 6/9 in each eye with the exception of one bifoveal patient who was 6/18 in the affected eye after patching for anisometropic amblyopia. All normal subjects had normal cover tests and ocular movements (Table 2). Stereoacuity was measured with the Titmus and TNO stereotests at a standard distance in patients wearing their normal spectacle corrections, if any. Patients were allowed time to find the optimum head posture for these tests.

Pattern reversal VEPs were recorded by standard methods in patients wearing their distance spectacle corrections, if any. No patient had difficulty in maintaining fixation monocularly with either eye during recording; this was confirmed by observation of the subjects. Pattern reversal VEPs were recorded to black-and-white checks subtending 15 minutes of arc or 60 minutes of arc of the visual angle, with a midline occipital electrode at Oz and an earlobe reference. Patients who were binocular with an abnormal head posture used it during binocular recording. Amplitude and latency of the peak of the P100 response were measured. Binocular enhancement was calculated as the binocular P100 amplitude divided by the mean of the monocular P100 amplitudes or by the greater monocular amplitude. Delay was calculated as the P100 latency from the affected or more affected eye minus the P100 latency from the fellow eye.

Binocular beat VEPs were recorded using the same recording arrangements as used for pattern reversal VEPs. The stimulus was produced by custom-built goggles with red LEDs producing a large diffuse field, with luminance modulated sinusoidally at 18 Hz for one eye and 20 Hz for the other eye. For each subject, two runs of approximately 4 minutes each were recorded at a mean luminance of 40 candelas (cd)/m^2 and two at 20 cd/m^2, both with a modulation depth of 100%. Responses were analyzed by fast Fourier transform. Signal-to-noise ratio was measured at the difference frequency of 2 Hz, using the average of the 0.5-, 1-, 1.5-, 2.5-, 3-, and 3.5-Hz bins to calculate the noise level for that frequency and at the input frequencies of 18 and 20 Hz, using the average of the 15-, 17-, 19-, 21-, and 23-Hz bins to calculate the noise level for those frequencies.

Statistical comparisons of electrophysiological data between Duane syndrome and control groups were made using Student's *t*-test for independent groups; comparisons between eyes within groups were made using paired *t*-tests. Stereoacuity results were analyzed using the Mann-Whitney test corrected for tied values.

This research conformed with the tenets of the Helsinki Declaration. Informed consent was obtained from all subjects and their par-

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TABLE 1. Clinical Data for 10 Patients with Duane Syndrome

					Snellen Acuity		Stereoacuity	
Subject	**Age (y)**	**Sex**	**Affected Eye**	**Surgery**	**Right Eye**	**Left Eye**	**TNO**	**Titmus**
1	11	M	Left	No	6/4	6/5	120	80
2	11	M	Left	Yes	6/6	6/4	60	40
3	11	M	Right	No	6/4	6/6	60	100
4*	12	M	Left	Yes	6/4	6/18	—	400
5	13	F	Left	No	6/5	6/5	60	50
6	13	F	Left	Yes	6/5	6/9	120	80
7	14	F	Left	No	6/5	6/5	60	100
8†	14	M	Right	No	6/9	6/9	—	400
9	15	F	Left > Right	No	6/5	6/9	120	80
10	19	F	Left	No	6/6	6/6	60	100

* Anisometropic.
† Microstrabismic.

ents, if appropriate, after the nature and possible consequences of the study were explained. The research was approved by the hospital ethics committee.

RESULTS

Clinical data for the Duane patients and normal control subjects are shown in Tables 1 and 2. All subjects in both groups had corrected acuity of 6/9 or better, with the exception of one eye in a patient with Duane syndrome who had undergone patching for anisometropic amblyopia.

The patients with Duane syndrome had reduced stereoacuity compared to the normal group (TNO mean excluding two negative subjects, 82.5 seconds of arc compared to 37.5 seconds of arc, $P < 0.001$; Titmus mean, 143 seconds of arc compared to 44 seconds of arc, $P < 0.001$; both Mann-Whitney test; $n = 10$).

Binocular Beat VEPs

Averaged binocular beat waveforms in a patient with Duane syndrome are shown in Figure 1A and in a normal subject in Figure 1B. Although present, the 2-Hz component of the waveform was less consistent in the subject with Duane syndrome than in the control subject. Fourier analyses of these waveforms is shown in Figures 1C and 1D. These confirm the reduced 2-Hz component in the patient with Duane syndrome. Overall the difference beat response at 2 Hz was significantly reduced in the patients with Duane syndrome compared to the normal age-matched group (Fig. 2A), with the mean 2-Hz signal-to-noise ratio for the Duane patients being 2.40 ± 1.05 compared to 4.30 ± 2.66 for the control subjects ($t = 2.21$, $df = 18$, $P < 0.05$). To show that this reduction was specific for the 2-Hz difference frequency the results were also calculated as the ratio of the 2-Hz signal-to-noise ratio divided by the mean of the 18- and 20-Hz signal-to-noise ratios for each subject (Fig. 2B). This ratio was also significantly reduced in the patients with Duane syndrome compared to the normal control subjects (ratio in the Duane group 0.58 ± 0.28 compared to 1.14 ± 0.72 in the control group; $t = 2.44$, $df = 18$, $P < 0.05$). This shows that the reduction of the response in the patients with Duane syndrome was specific for the difference frequency in relation to the input frequencies.

TABLE 2. Clinical Data for 10 Normal Control Subjects

			Snellen Acuity		Stereoacuity	
Subject	**Age (y)**	**Sex**	**Right Eye**	**Left Eye**	**TNO**	**Titmus**
11	9	F	6/6	6/5	30	40
12	9	F	6/6	6/5	30	40
13	10	F	6/6	6/6	60	40
14	10	M	6/5	6/5	60	40
15	11	F	6/6	6/5	30	40
16	12	M	6/5	6/5	30	40
17	13	F	6/4	6/4	15	40
18	15	F	6/5	6/5	30	40
19	16	M	6/9	6/5	60	80
20	19	M	6/4	6/4	30	40

Pattern Reversal VEPs

The amplitude of the P100 response to 15-minute checks was greater under binocular than monocular conditions in patients with Duane syndrome and in normal subjects (Fig. 3). The binocular enhancement to the mean monocular amplitude for 15-minute checks was significantly greater in the patients with Duane syndrome than in normal subjects (Table 3). This was because the mean P100 amplitudes of the monocular responses were significantly smaller in the Duane group than in the normal group, whereas the amplitude of the binocular responses was similar in both groups. A comparable difference was not seen with the 60-minute check size. The binocular enhancement to the larger monocular amplitude was also greater with 15-minute checks in patients with Duane syndrome than in normal subjects (mean, 1.78 ± 0.4 compared to 1.09 ± 0.2; $P < 0.001$), but not with 60-minute checks (mean, 1.29 ± 0.3 compared to 1.24 ± 0.3; $P = 0.74$).

There was no significant difference in the P100 latency between fellow and affected eyes of the patients with Duane syndrome for either check size (Table 4). The binocular P100 latency was significantly shorter than the mean monocular latency for normal subjects for both 15-minute checks (118.9 compared to 121.6 msec; $t = 2.70$, $df = 9$, $P < 0.05$) and 60-minute checks (114.0 compared to 120.3 msec; $t = 3.36$, $df = 10$, $P < 0.01$). For the Duane patients the difference was significant for 60-minute checks (114.0 compared to 118.0 msec; $t = 2.51$, $df = 10$, $P < 0.05$) but not for the 15-minute checks (118.0 compared to 119.7 msec; $t = 1.25$ $df = 9$, $P = 0.24$).

DISCUSSION

In the companion article[7] it was shown that patients with Duane syndrome have reduced stereoacuity but increased binocular enhancement of their contrast sensitivity. It was suggested that these abnormalities arise because of intermittent

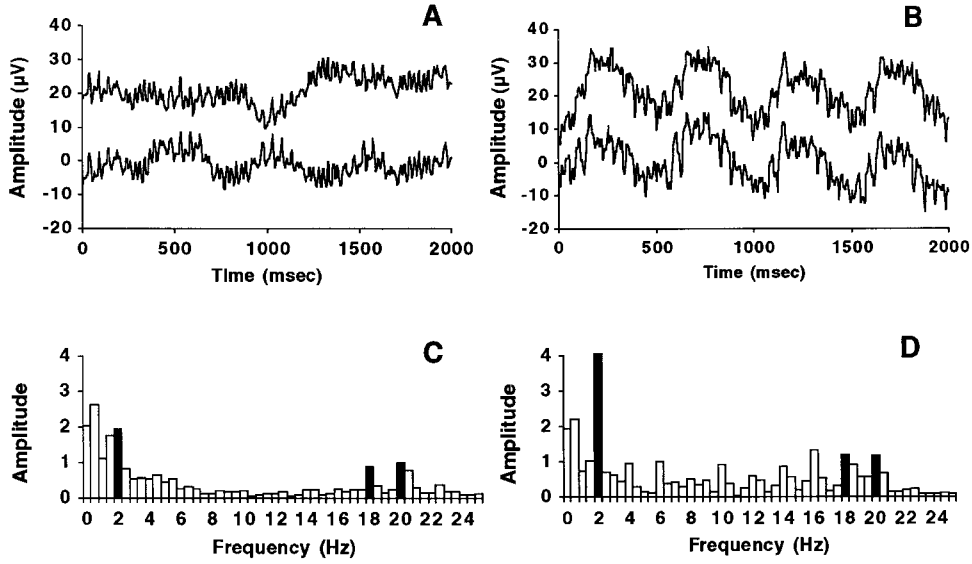

FIGURE 1. (**A**) Binocular beat VEP recorded from a patient with Duane syndrome. Although present, the 2-Hz component was not as strong as in the normal subject. (**B**) Binocular beat VEP recorded from a normal subject. A strong 2-Hz component was present. (**C**) Fast Fourier analysis of the waveform of (**A**) of a patient with Duane syndrome. The input frequencies were at 18 and 20 Hz, with a weak difference beat response at 2 Hz. (**D**) Fast Fourier analysis of the waveform of (**B**) of a normal subject. The components at the input frequencies of 18 and 20 Hz were similar to those in (**C**), but the difference beat response at 2 Hz was much more prominent.

ocular misalignment during the early years of life, leading to the loss of a proportion of binocularly driven cortical cells, and a model of how this could lead to the apparently paradoxical combination of reduced stereoacuity and increased binocular enhancement was proposed. The present study, using electrophysiological techniques, has demonstrated a reduction of the binocular beat VEP but increased binocular enhancement of the P100 response of the pattern reversal VEP to small checks. These electrophysiological abnormalities show striking parallels to the psychophysical findings.

A binocular beat VEP is produced by stimulating each eye with a diffuse sinusoidally modulated stimulus at a slightly different frequency for each eye. In addition to the stimulating frequencies, the beat VEP normally contains new beat frequencies generated by the nonlinear addition of the input frequencies by binocularly driven cortical cells.[12] It has been shown that these beat frequencies are reduced or absent in both animals and patients with abnormal or absent binocularity.[13,14] The reduced difference beat responses seen in patients with Duane syndrome thus indicate that they have a reduced population of binocular cells in the cortex, as proposed in the companion article.[7]

Binocular enhancement of the pattern reversal VEP has been suggested as a measure of binocularity in patients with squints.[15–20] However, no correlation between stereoacuity and binocular enhancement has been shown in a previous study of normal development in humans which showed that binocular enhancement to small checks decreases with age,

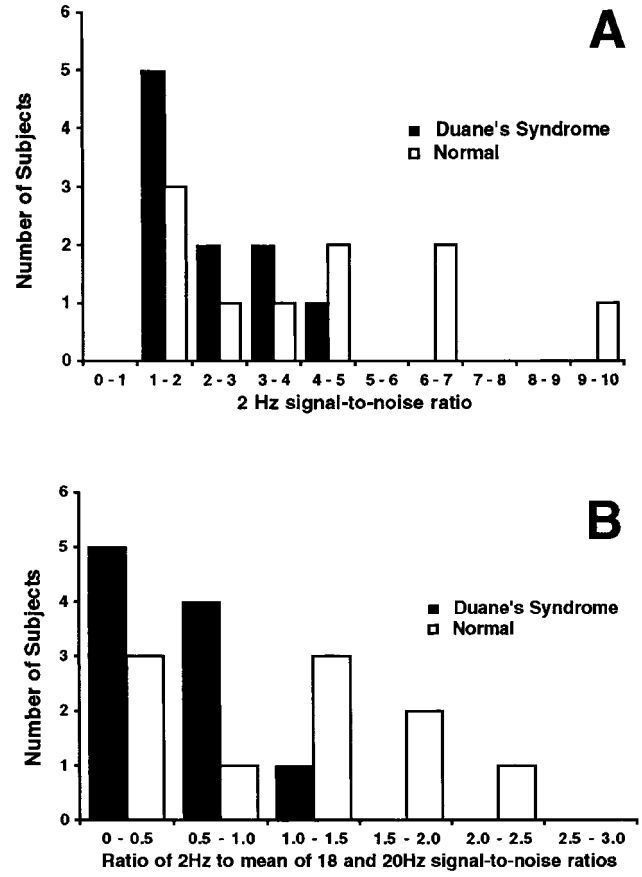

FIGURE 2. Comparison of (**A**) signal-to-noise ratios at the difference beat frequency of 2 Hz and (**B**) the ratio of signal-to-noise ratios at 2 Hz to those at the input frequencies of 18 and 20 Hz in 10 patients with Duane syndrome and 10 normal subjects.

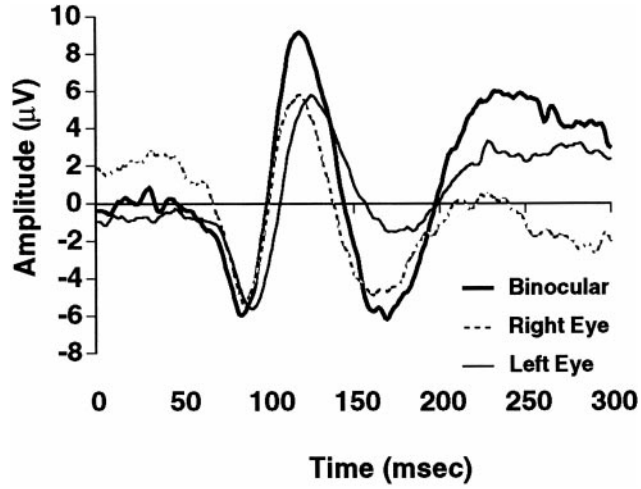

FIGURE 3. Pattern reversal VEP to 15-minute checks from a patient with Duane syndrome. The P100 amplitude was larger with binocular than with monocular stimulation.

TABLE 3. Binocular Enhancement of the P100 VEP Amplitude for 10 Patients with Duane Syndrome

	P100 Amplitude to 15-Minute Checks (μV)				P100 Amplitude to 60-Minute Checks (μV)			
Subject	Binocular	Fellow Eye	Affected Eye	Binocular Enhancement	Binocular	Fellow Eye	Affected Eye	Binocular Enhancement
1	21.7	9.5	11.7	2.05	24.3	18.4	16.9	1.38
2	8.7	6.9	6.2	1.33	22.3	13.4	13.6	1.65
3	38.2	18.1	16.5	2.21	23.5	21.9	23.5	1.04
4	10.2	6.8	4.2	1.85	22.4	16.4	8.8	1.78
5	12.5	7.0	6.2	1.89	13.6	9.6	8.6	1.49
6	21.9	14.7	15.2	1.46	20.4	16.5	14.7	1.31
7	16.6	7.0	7.6	2.27	19.4	11.9	11.7	1.64
8	6.7	2.6	2.2	2.79	15.0	9.1	9.9	1.58
9	14.9	11.0	11.3	1.34	12.4	9.7	13.9	1.05
10	—	—	—	—	21.2	19.2	24.3	0.97
Mean ± SD	16.8 ± 9.6	9.3 ± 4.7*	9.0 ± 4.9*	1.91 ± 0.5†	19.5 ± 4.3	14.6 ± 4.5	14.6 ± 5.6	1.39 ± 0.3
Normal Mean ± SD	17.3 ± 7.8	15.2 ± 4.7‡	14.4 ± 5.1§	1.15 ± 0.3	21.6 ± 4.9	18.0 ± 6.3‡	17.6 ± 6.1§	1.30 ± 0.4

* Significantly less than corresponding normal eye $P < 0.05$.
† Significantly greater than normal $P < 0.001$.
‡ Right eye.
§ Left eye.

whereas stereoacuity increases.[21] A subsequent study of binocular patients with Duane syndrome showed that they also demonstrated binocular enhancement, but that this did not reduce significantly with age.[6] Patients in the present study are older that those in this previous study and show that the failure of reduction of binocular enhancement during development produces a greater than normal enhancement to small checks in this older group. This is an interesting parallel to the greater than normal binocular enhancement of contrast sensitivity described in patients with Duane syndrome.[7] In both instances the increased enhancement occurs because monocular responses are reduced, whereas the binocular response is normal. The P100 amplitude probably reflects the response of both monocular and binocular cells. It is proposed that the number of cells available to each eye is reduced, because cells that were previously binocular are lost to the other eye, but this increased population of cells driven only by the other eye is then recruited under binocular conditions and gives an enhanced response, as with the contrast sensitivity.[7] However, even a total loss of binocular cells can account for a binocular enhancement ratio of only two, and it is likely that other mechanisms are also involved. In particular, many patients with Duane syndrome show interocular suppression under nonbinocular conditions, and this may also contribute to reduced monocular responses.

Because the underlying motor pathophysiology is reasonably well understood, patients with Duane syndrome provide an interesting model in which to study the effects of intermittent motor misalignment on sensory visual development. The disruption of binocular function seen in Duane syndrome is usually relatively minor and generally stays stable into adult life, probably because of the way the patients are able to maintain ocular alignment by using anomalous head postures. The minority of patients who lose binocular function completely and develop a constant squint usually have a second abnormality, such as anisometropia[6] and patients with Duane syndrome are particularly sensitive to disruption of binocularity by refractive abnormalities. It appears that binocular function in Duane syndrome is surprisingly resistant to intermittent ocular misalignment, but that different anomalies can have an additive affect in the disruption of binocularity. This may be important in understanding the deterioration in control seen in some children with intermittent squints. These findings are likely to be of relevance to other forms of intermittent squint, such as intermittent exotropias, congenital fourth nerve palsies, and convergence excess esotropias. If a similar loss of binocularly

TABLE 4. P100 VEP Latencies for 10 Patients with Duane Syndrome

	P100 Latency to 15-Minute Checks (msec)			P100 Latency to 60-Minute Checks (msec)		
Subject	Binocular	Fellow Eye	Affected Eye	Binocular	Fellow Eye	Affected Eye
1	116	118	116	110	116	122
2	114	116	116	110	118	108
3	122	122	124	116	116	118
4	114	118	116	114	132	114
5	112	122	120	112	116	118
6	124	118	122	120	112	120
7	116	112	112	116	130	124
8	126	122	138	126	116	130
9	118	116	126	110	110	116
10	—	—	—	106	110	114
Mean ± SD	118.0 ± 4.9	118.2 ± 3.4	121.1 ± 7.8	114.0 ± 5.8	117.6 ± 7.6	118.4 ± 6.1
Normal Mean ± SD	118.9 ± 2.0	122.2 ± 3.7*	120.9 ± 3.8†	114.0 ± 6.3	119.6 ± 6.9*	121.0 ± 4.3†

* Right eye.
† Left eye.

driven cells is present in these other intermittent squints, studying them may lead to an understanding of why binocular function breaks down in some patients and not in others.

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