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Pattern visual evoked potential in response to monocular and binocular stimulation in normal and amblyope subjects

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Abstract

Background: Amblyopia is a relatively common condition with an incidence of 2-2.5% in which visual acuity through an eye is subnormal despite no overt pathology. The use of pattern visual evoked potential (P-VEP) has been the primary technique for electrophysiologically detecting amblyopia in patients unable to undergo conventional testing. This study was performed to evaluate the effectiveness of P-VEP parameters in amblyopic patients under monocular and binocular conditions.

Methods: Visual function was measured using P-VEP and Snellen acuity test in 30 children with amblyopia (12 strabismic and 18 anisometropic amblyopes) and 30 visually normal control subjects.

Results: Totally, visual evoked potentials elicited by high contrast small checkerboard patterned stimuli were significantly reduced in amplitude and prolonged in latency in amblyopic eyes. The mean intraocular amplitude difference was significantly larger in amblyopics than in normal groups. There was also no difference between the healthy eye in the amblyopic group and the control one. On binocular viewing, the amount of VEP amplitude was significantly greater in normal subjects than that in both amblyopic groups. Regarding the type of amblyopia, the mean binocular VEP amplitude as compared to that in the non-amblyopic eye was greater for the anisometropic than the strabismic groups.

Conclusion: In both amblyopic groups, the VEP responses were significantly reduced in amplitude and prolonged in latency. In binocular viewing, the amount of VEP amplitude was greater in normal subjects than both amblyopic groups. The mean binocular amplitude was significantly greater for the anisometropic than for the strabismic group.

Keywords: Ambyopia; VEP; Anisometropia; Strabismus

Introduction

Amblyopia, with an incidence of 2-2.5%, is a relatively common condition in man, in which visual acuity through an eye is subnormal despite no overt pathology. The major causes are occlusion, strabismus and anisometropia.[1] The pattern visual evoked potential (P-VEP) has been successfully used to assess visual function in infants or preverbal children. The use of P-VEP has been the primary technique for electrophysiologically, detecting amblyopia in patients unable to undergo conventional testing.[2] P-VEP recorded from human amblyopic eyes might show attenuated amplitudes and prolonged latencies. Oner et al,[3] used P-VEP parameters in visual acuity in amblyopic patients under occlusion therapy. They measured P100 amplitude of VEP in 34 children with anisometropic amblyopia and found that the P-VEP test parallels the improvement in subjective visual acuity in amblyopic eyes under occlusion therapy. They demonstrated that the VEP test was useful in monitoring the visual acuity in the preverbal or nonverbal patched patients. Zhang and Zhao,[4] recorded VEPs in eleven patients with early and

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eleven with late-onset strabismus amblyopia with a similar range of visual acuity and eleven normal control subjects. They found no significant difference in latency or amplitude between amblyopic and fellow eyes for the early-onset amblyopic group, whereas in the late-onset amblyopic group, latencies were significantly prolonged and amplitudes attenuated in the amblyopic eyes.

An important but unanswered question concerns the quality of vision that amblyopics have on binocular viewing. When visual performance is measured with a pattern visual evoked potential, the amplitude of VEP responses is enhanced on binocular compared with that on monocular viewing by 30 to 40%.[5] Holmes et al,[6] compared monocular and binocular flash VEP amplitude with abnormal retinal correspondence (ARC) in strabismic and normal subjects. Where there was no suppression, they showed that strabismic patients with ARC exhibited binocular summation approximately the same as normal subjects. They also noted no summation, when suppression was present with striated lenses (Bagolini lenses). The aims of this study were to evaluate the efficiency of interocular VEP difference in the detection of amblyopia and to compare the binocular VEPs between normals and anisometropic and strabismic amblyopics.

Materials and Methods

The subjects of this study comprised 30 amblyopics (12 strabismic and 18 anisometropic amblyopics) and 30 age-matched visually normal children with an age range of 5 to 15 years (median 9.9 years). Amblyopia was operationally defined as acuity poorer than 20/25 with best correction, in the absence of observable pathology. The subjects were recruited from the clinic of Optometry at Mashhad University of Medical Sciences. Written informed consent from each patient or his/her guardian was obtained before examination. All the patients underwent a vision analysis and an orthoptic evaluation. Those subjects with amblyopia had no other pathology. Biomicroscopic and ophthalmoscopic investigation showed clear media and no fundus abnormalities. The orthoptic evaluation included subjective and objective strabismometry and determination of fixation characteristics. The subjects were refracted to ensure an exact optical correction, and then, if necessary the old correction was changed.

Subjective visual acuity was measured for monocular (right eye, left eye, amblyopic and nonamblyopic eyes) and binocular states for both groups of normal and amblyopes. All tests were performed with the subjects wearing their best refractive correction. The VEP responses were recorded by using Toennies Neuroscreen equipped with the pattern reversal VEP. The check size was 15 min arc at a viewing distance of 1.00 meters, and full field display. The amplifier bandwidth filters were set at 1.0-100 Hz. The average analysis time was set at 3 reversals per second. The mean screen luminance was 89 cdm-2 with the mean contrast being 82%. The active electrode was positioned 2.5 cm above the inion on the midline (QZ), referenced to the centre of the forehead with a ground electrode on the right wrist by the use of a clip. The inter-electrode impedance had to be below 5 kohm before recording could commence. A fixation spot was used on the center of the screen. The fixation was monitored by an observer and the data were collected only when the child was looking at the pattern.

The VEP waves consisting of 300 sweeps were randomly recorded for the monocular (right eye, left eye, amblyopic and non-amblyopic eyes) and binocular states for both groups of normal and amblyopics. Figure 1 shows a typical set of results from an individual subject in the normal group for the right eye, left eye and binocular VEP waves. A similar set of results for an individual subject in the amblyopic group for the amblyopic, non-amblyopic and binocular VEP waves are shown in Figure 2. Figure 2 shows that the VEP wave from the right eye is approximately equal in amplitude and wave form to that of the left eye and the binocular wave is larger than the monocular wave. However, the VEP wave from the amblyopic eye is very much smaller than the fellow non-amblyopic eye and the binocular VEP amplitude is larger than either the amblyopic or non-amblyopic eye.

Paired Samples test was performed on the means to compare the P1N2 amplitude of the right and left eyes and binocular conditions, to compare the amplitude of amblyopic and non-amblyopic eyes for 30 subjects and to compare the binocular amplitude with that of the non-amblyopic eye. An independent t test was performed on the means to compare the monocular P1N2 amplitude (right eye and left eye) of the normal group and non-amblyopic eye in the amblyopic group and to compare the inter-ocular amplitude difference of the amblyopic and normal groups.

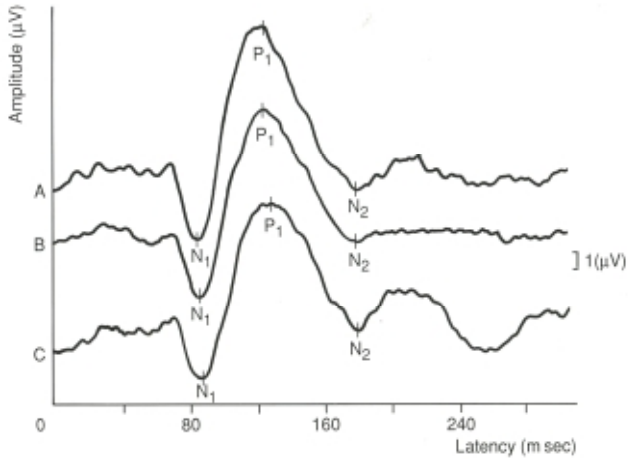

Fig 1: A typical set of three waves from an individual subject in the normal group (A) represents the wave from binocular viewing, (B) from the right eye and (C) from the left eye. The wave has been displaced vertically for clarity. The peaks and troughs of interest are as indicated by N1, P1 and N2.

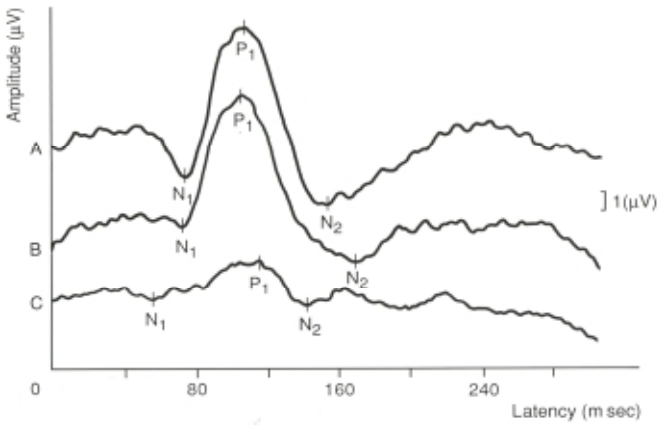

Fig 2: A typical set of averaged wave from an individual subject in the amblyopic group (A) is the wave from binocular viewing (B) from the non amblyopic and (C) from the amblyopic eye.

Results

Table 1 shows the mean and standard deviation of P1N2 amplitude and P100 latency for the right and left eyes and binocular states for 30 normal subjects. There was no significant difference on the means of the P1N2 amplitude of the right and left eyes (t= -1.2, p>0.05), but the difference was very significant for mean monocular versus binocular (t= 9.2, P<0.001). Table 1 also shows that there is no significant difference between P100 latency of the right and left eyes (t= -1.9 p>0.05). However, the latency of the binocular responses was shorter than the mean monocular responses (t = -2.08, P<0.05). Table 2 shows the mean and standard deviation of the non-amblyopic eyes, amblyopic eyes and binocular amplitude (P1N2) and P100 latency for 30 amblyopic groups. There was a statistically significant difference between the amplitude of the non-amblyopic and amblyopic eyes (t = 10.01, P<0.001). There was a statistically significant increase in the binocular amplitude for 30 subjects (t=-3.6, P<0.001). Table 2 also shows that there is a statistically significant difference between P100 latency of the non-amblyopic and amblyopic eyes (t= -7.18 p>0.001) with no significant difference between P100 latency of binocular states and the non-amblyopic eye (t= -1.17, P=0.24). There was no statistically significant difference on the means of the monocular P1N2 amplitude (right eye and left eye) of the normal group and non-amblyopic eye in the amblyopic group (t=-1.01 p>0.05).

The inter-ocular difference scores (RE-LE, non-amblyopic eye and amblyopic eye) were calculated for normal subjects and amblyopic groups for P1N2 amplitudes and P100 latencies. Table 3 shows that the mean inter-ocular P1N2 amplitude difference of the amblyopic group was greater than that of the corresponding normal group. There was a statistically significant difference on the means of the inter-ocular amplitude of the amblyopic and normal groups (t= 4.67, P<0.001). When the results of mean inter-ocular latency (P100) difference were analyzed in the same way, there was also a significant difference between the two groups (t= -5.35, P>0.001). Comparison of binocular P1N2 amplitude with the monocular non-amblyopic eye for ambyopics and with the mean monocular for the normal subjects showed binocular enhancement in both groups, but the increase was greater in the normal group. Regarding the type of amblyopia, the anisometropic group showed significantly greater binocular enhancement than the strabismic amblyopic group (t= 3.9, P<0.001).

Table 1: Mean and standard deviation P1N2 amplitudes and P100 latencies for right eye, left eye and binocular states for 30 normal subjects.

Eye	P1N2 amplitude (m V)	P100 latency (m sec)
Right eye	9.95±2.9	109.9±8.65
Left eye	9.30±3.2	111.76 ±7.24
Binocular	13.80±2.98	107.6±7.70

Table 2: Mean and standard deviation of P1N2 amplitude and P100 latency for non amblyopic and amblyopic eyes and binocular states for 30 amblyopic subjects.

Eye	P1N2 amplitude (m V)	P100 latency (m sec)
Non-amblyopic eyes	9.47±2.6	114.13±8.6
Amblyopic eyes	5.82±2.13	126.76±10.75
Binocular	10.90±3.07	116.3±6.83

Table 3: Mean and standard deviation of interocular difference of VEP scores RE - LE, non amblyopic – amblyopic eye for normal and amblyopic groups.

	Interocular amplitude difference	Interocular latency difference
Group	P1N 2 (μ v)	P100 (m sec)
Amblyopic eyes	3.64±1.99	-12.6±9.6
Normal eyes	0.64±2.9	-1.8±5.3
	T=4.67, P<0.001	T=-5.35, P<0.001

Discussion

The results showed that the VEP responses were significantly reduced in amplitude and prolonged in latency in amblyopic eyes. This is in general agreement with the data of previous investigations.[7-10] Holopigian et al,[10] showed that the VEP evoked by reversal checkerboard or grating patterns is often smaller when the amblyopic eye is stimulated than when the fellow non-amblyopic eye is stimulated. Our findings also showed that intra-ocular amplitude difference of the amblyopic group was greater than the corresponding normal group, which is similar to the findings of other VEP studies.[11,12] Geer and Westall,[12] suggested that the VEP response give the most accurate assessment of inter-ocular difference. They measured visual function using VEPs, the Cardiff test and the Bailey–Lovie chart in 21 visually normal children and 12 children with amblyopia. They reported that inter-ocular VEP latency differences identified eight of the 12 children with amblyopia and inter-ocular VEP amplitudes correctly identified 9 ones. On binocular viewing, our results indicate that the amount of VEP amplitude was significantly greater in normal control subjects than in both amblyopic groups. This is in agreement with the findings of others in binocular VEP studies.[13-15] Heravian et al,[15] using a 5.5 min arc check with a reversal rate of 3 Hz, showed that the binocular VEP is 26% larger than the mean monocular VEP amplitude. They suggested that the binocular enhancement of the VEP over the mean monocular amplitude could be the evidence of binocular integration of visual sensory input. When the results of the anisometropic and strabismic amblyopes were compared, the present study showed that the mean binocular amplitude was significantly greater for anisometropic group, which suggests the presence of binocular summation. This implies that there is a certain amount of cortical integration of the input from both eyes.[16]

A number of studies found features of visual structure and function that differred based upon the etiology of the amblyopia.[17] Some studies suggested distinctly different underlying visual pathway mechanisms between strabismic and anisometropic amblyopia whereas others found more similar features.[18] It follows that because anisometropia generates an inter-ocular discrepancy in form vision and also strabismus generates a discrepancy in spatial localization, different processing pathways may be affected or preserved.[7] Further studies that have induced visual loss by deprivation (e.g. lid closure, corneal scarring) may identify totally different alteration in visual function.[19,20]

One could argue that the binocular reduction in VEP responses found in our strabismic amblyopes (compared to that of the anisometropic group) might be attributed to suppression or inhibition in binocular vision which was not measured in this study. Earlier single unit studies of the effects of visual deprivation in the visual cortex of cats and monkeys showed that neural organization and function of binocular neurons is highly dependent upon normal binocular experience during the early sensitive periods of development.[18] Deprivation paradigms which obstruct normal binocular input such as artificially induced strabismus result in a substantial loss of binocularly driven cortical neurons.[19] These findings led to the suggestion that humans with abnormal binocular experience of

early onset have a reduced complement of binocular neurons.[21] Evidence for this suggestion came from the abnormal performance of these individuals on certain tasks which test binocular function. These subjects, for example, often show reduced or no streopsis, fail to show binocular summation on visual tasks retain eye of origin information under conditions in which normal observers are able to make reliable distinctions, and display reduced inter-ocular transfer of certain visual after–effects.[21] However, some psychophysical studies suggest that individuals with abnormal binocular disorders, such as strabismic amblyopia, may in fact exhibit normal binocular function under the appropriate stimulus conditions.[22] Further evidence for the importance of the optimum stimulus and test conditions in obtaining functional binocularity in monocularly deprived cats has also been observed in the cortical response from area 17 and area 18 and in the behavioral responses of cats reared with alternating monocular exposure.[23] These results, along with the normal binocular summation reported here, suggest that cortical binocular function be preserved to a substantial degree in certain amblyopic observers. The fact that these observers exhibit abnormal binocular function, particularly on threshold tasks, suggests that under conditions of weak stimulation, the binocular mechanisms are suppressed or deactivated because of the strabismic and/or amblyopic process. Binocular activation requires supra-threshold stimulation, once activated. However, the resultant binocular response exhibits apparently normal features.[24] The conditions of the test stimulus in the present study which used a check size of 15 min arc and a high contrast of 82% and a mean luminance of 89 cd/m^2 may have been of sufficient strength and specificity to activate the binocular mechanisms of the amblyopics.

It is concluded that in both amblyopic groups, the VEP responses were significantly reduced in amplitude and prolonged in latency. The intraocular amplitude difference of amblyopic groups was greater than that in the corresponding normal groups. In binocular viewing, the amount of VEP amplitude was greater in normal subjects than that in both amblyopic groups. The mean binocular amplitude was significantly greater in the anisometropic group than in the strabismic group.

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References

1 Von Noorden GK. Binocular vision and ocular motility: Theory and management of strabismus, 4th edn. The C.V. Mosby Co., St Louis,1990.

2 Simon JW, Seigfried JB, Mills MD, Cathoun JH, Gurland JE. A new visual evoked potential system for vision screening in infants and young children. *JAAPS* 2004; **8:**549-554.

3 Oner A, Coskun M, Everklioglu C, Dogan H. Pattern VEP is a useful technique in monitoring the effectiveness of occlusion therapy amblyopic eyes under occlusion therapy. *Doc Ophthalmol* 2004;**109(3):** 223-27.

4 Zhang W, Zhao K. Multifocal VEP difference between Early–and Late–onset strabismus amblyopia. *Doc Ophthalmol* 2005;**110:**173-180.

5 Skarf B, Eizenman M, Katz LM, Bachynski B, Klein R. A new VEP system for studing binocular single vision in human infants. *J Pediatr Ophthalmol Strabismus (JPOS)* 1993;**30:**237-242.

6 Holmes JM, Repka MX, Kraker RT, Clarke MP. The treatment of amblyopia. *Strabismus* 2006;**14:**37-42.

7 Yu M, Brown B, Edwards MH. Investigation of multifocal visual evoked potential in anismoetropic and esotropic amblyopes. *Invest Ophthalmol J Vis Sci* 1998;**39:**2033-2040.

8 Kelly JP, Weiss AH. Spatial-frequency-Dependent changes in cortical activation before and after patching in Amblyopic children. *Invest Ophtalmol J Vis Sci* 2004; **45:**3531-3537.

9 Heravian JS, Douthwaite WA, Jenkins TCA. Acuity predictions from visually evoked potential (VEP) to checker board pattern reversal stimuli: the effect of reversal rate and field size. *Clin Exp Optom* 1999;**82:**244-249.

10 Holopigian K, Seiple W, Kupersmith M. VEP threshold and suprathreshold deficits in amblyopia. *Clin Vision Sci* 1991;**6:**109-117.

11 Petrinovic HL, Deban N, Gabric N, Petrinovic J. Prognostic value of visual evoked responds in children amblyopia, *Eur Ophthalmol* 1993; **3:**114-120.

12 Geer I, Westall CA. A comparison of tests to determine acuity deficit in children with amblyopia. *Ophthalmol Physiol Opt* 1996;**16(5):**367-74.

13 Fawcett SL, Brich EE. Motion VEPs Stereopsis, and bifoveal fusion in children with strabismus. *Invest Ophthalmol J Vis Sci* 2000;**41:**411-416.

14 Odom JV, Bach M, Barber C, Brigell M, Marmor MF, Tormene AP, Holder G, Vaegan N. Visual evoked potentials standard. *Doc Ophthalmol* 2004;**108:**115-123.

15 Heravian JS, Jenkins TCA, Douthwaite WA. Binocular summation in visually evoked responses and visual acuity. *Ophthal Physiol Opt* 1990;**10:**257-261.

16 Suter S, Suter PS, Perrier DT, Parker KL, Fax JA, Rossler JS, Differentiation of VEP intermodulation and second harmonic component by dichoptic, Monocular, and binocular stimulation. *Visual Neuroscience* 1996;**13:**1157-1166.

17 Johansson B, Jakobsson P. Fourier–analysed steady–state VEPs in pre-school children with and without normal binocularity. *Doc Ophthalmol* 2006;**112:**13-22.

18 Crawford MLJ, Harwerth RS, Chino YM, Smith EL. Binocularity in prism-reared monkeys. *Eye* 1996;**10:**61–166.

19 Kiorpes L, Kiper DC, O'keefe LP, Cavanaugh JR, Movshon JA. Neuronal correlates of amblyopia in the visual cortex of macaque monkeys with experimental strabismus and anisometropia. *J Neuroscience* 1998;**18:**6411-6424.

20 Barnes GR, Hess RF, Doumoulin SO, Achtman RL, Pike GB. The cortical deficit in humans with stabismi amblyopia. *J Physiol* 2001;**533:**281-297.

21 Marshall WE, Dawson E, Neveu MM, Morgan MJ, Sloper JJ. Increased binocular enhancement of contrast sensitivity and reduced stereoacuity in Daune syndrome. *Invest Ophthal J Vis Sci* 2001; **42:**2821-2825.

22 Truchard AM, Ohzawa I, Freeman RD. Contrast gain control in the visual cortex : Monocular vs. binocular mechanisms. *J Neurosci* 2000;**20:** 3017-3032.

23 Walker GA, Ohzawa I, Freeman RD. Binocular cross- orientation suppression in the cat's striate cortex. *J Neurophysiol* 1998;**79:**227-239.

24 Polonsky A, Blake R, Braun J, Heeger DJ. Neural activity in human primary visual cortex correlates with perception during binocular rivalry. *Nature Neuroscience* 2000;**3:**1153-1159.