

Alteration in pattern reversal visual evoked potential in pediatric population with amblyopia and spherical refractive errors

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Purpose: To study the effect of refractive errors on pattern visual evoked potential (VEP) recordings in the pediatric population. **Methods:** This cross-sectional observational study assessed 240 eyes of 120 participants attending the outpatient department of a tertiary care center in North India. Participants were between 8 and 18 years of age; 30 participants each were recruited into four groups, namely emmetropia, myopia, hypermetropia, and amblyopia. They were then subjected to pattern reversal VEP, with P-100 amplitude and latency recorded for each participant. **Results:** The emmetropic group in this study provided normal values of P-100 parameters, namely P-100 latency and P-100 amplitude with readings of 115.78 ± 10.19 ms and 11.11 ± 4.08 μ V, respectively. P-100 amplitude was significant compared to P-100 latency in detecting the presence or absence of a specific type of refractive error. It was found that there was a significant association between severity of myopia and P-100 latency (both unaided and aided) with $P < 0.05$. The severity of hypermetropia showed a significant association with P-100 amplitude (unaided) ($P < 0.05$). Receiver operating characteristics analysis revealed P-100 amplitude to be a good predictor of refractive error and the cut-offs were calculated. **Conclusion:** The P-100 parameters of the pediatric Indian population were comparatively higher than conventional values. P-100 latency seemed to better correlate with myopia, while hypermetropia correlated with P-100 amplitude. P-100 amplitude appears to be the most significant predictor of the presence of refractive error in an individual.

Key words: Amblyopia, hypermetropia, myopia, P-100, pediatric, refractive error, visual evoked potential

Visual evoked potentials (VEPs) reflect electrical phenomena occurring during the visual processing and are a graphic illustration of the cerebral electrical potentials generated by the occipital cortex evoked by a defined visual stimulus.^[1] VEP is affected by factors such as pupil diameter, refractive errors (REs), type of stimulus, age and sex, electrode position, and anatomical variations.^[2] It is believed that RE causes defocus, which may, in turn, show changes in VEP and if allowed to persist may lead to corresponding neurological changes. Few studies have been conducted on the effect of refractive errors on pattern VEP recordings, especially in pediatric patients. This study attempts to explore the changes in pattern reversal VEP in pediatric participants with amblyopia, myopia, and hypermetropia. The study also investigates the changes in pattern VEP, with special emphasis on P100 amplitude and latency in participants with amblyopia and spherical refractive errors. The characteristics of pattern VEP between participants with spherical refractive errors and controls are also compared and analyzed.

Methods

Study population

The study design was a cross-sectional observational study, and 120 participants were recruited for the study by randomly

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selecting from the out-patient department of a tertiary care center in North India and had to meet the following inclusion criteria: aged between 8 and 18 years and refractive status being emmetropia, myopia, hypermetropia, or amblyopia (strabismic and anisometropic). The participants were divided into four groups, namely A, B, C, and D consisting of emmetropia, myopia, hypermetropia, and amblyopia, respectively, with each group consisting of 30 participants each. Group A with emmetropic individuals consisted of age-matched individuals. The exclusion criteria were if any participants were suffering from pathological myopia, astigmatism, visual deprivation, or organic amblyopia. Any participant with a history of intraocular disease, surgery, ocular anomaly, and/or any central nervous system disorder was also excluded from the study. The project was approved by the institutional research ethics board. The research followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Data collection

After obtaining written, informed consent from the guardians of the pediatric participants, a thorough ophthalmological examination was performed, which included LogMAR visual

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acuity (aided and unaided), cycloplegic refraction, ocular motility, and funduscopy. The group B and C participants consisting of myopia and hypermetropia were further subclassified into mild, moderate, and severe myopia and hypermetropia, respectively. The classification followed for myopia was mild myopia: less than -3.00 D, moderate myopia: between -3.00 D and -6.00 D, and high myopia: more than -6.00 D. Hypermetropia was classified as mild hypermetropia: +2.00 D or less, moderate hypermetropia: +2.25 D to +5.00 D, and high hypermetropia: more than +5.00 D.^[3,4] Group D participants with amblyopia were subclassified into anisometropic and strabismic amblyopia.

VEP was recorded using a PC-based, 2-channel, Nihon Kohden Neuropack MEB -9400 (N.K. Corp., Tokyo, Japan) machine and standard silver-silver chloride disc electrodes. Pattern reversal protocol was used for VEP recording as per the guidelines of International Society for Clinical Electrophysiology of Vision (ISCEV).^[5] The scalp electrodes were placed relative to bony landmarks in proportion to the size of the head according to the international 10/20 system. The active electrode was placed at Oz, which is the highest point of the occiput, which lies over the visual cortex. The reference and ground electrodes were placed at Fz and Cz (vertex), respectively. The recording was done in a dark room with quiet surroundings. Visual stimulation was done with a checkerboard pattern generated on the monitor by using the software installed, which consisted of black and white checks whose phase was reversed (black to white and white to black) at a fixed rate of two reversals per second. The subject was seated at a fixed distance of 100 cm from the screen and was asked to fixate at the center of the screen. Monocular stimulation was given to both eyes separately. A sweep length of 250 ms was done, and more than 200 responses were averaged. An amplification range of 20,000–1,00,000 was used. To ensure reproducibility, the waveform was recorded twice. The electrode impedance was kept at less than 5 k Ω . The P100 latency (measured from 0 ms to the highest point of the peak of P100) and the P100 amplitude (measured from N75 to P100) were measured from the VEP recordings obtained. All recordings of participants in groups B, C, and D were carried out with both unaided visual acuity and best-corrected visual acuity. The recordings of group A were duplicated under two subgroup headings—aided and unaided—for ease of statistical analysis.

Statistical analysis

The data obtained were entered into Microsoft Excel software, and analysis was performed using statistical software package (SPSS for Windows, version 23, SPSS, Chicago, Illinois, U.S.A.); 240 eyes of 120 participants were considered for analysis. To prevent violation of independence of observations, a linear mixed-effects regression analysis was performed to circumvent the fact that two eyes came from the same patient. Descriptive statistics were elaborated in the form of means/standard deviations and medians/IQRs for continuous variables, and frequencies and percentages for categorical variables. Data were presented in a graphical manner wherever appropriate for data visualization by using histograms/box-and-whisker plots/column charts for continuous data and bar charts/pie charts for categorical data. Group comparisons for continuously distributed data were made using independent sample *t* test when comparing two groups. If data were found to be

non-normally distributed, appropriate non-parametric tests in the form of Wilcoxon Test were used. Chi-squared test was used for group comparisons for categorical data. In case the expected frequency in the contingency tables was found to be <5 for >25% of the cells, Fisher's exact test was used instead. Linear correlation between two continuous variables was explored using Pearson's correlation (if the data were normally distributed) and Spearman's correlation (for non-normally distributed data). Statistical significance was kept at *P* < 0.05. The primary outcome of this study is P-100 latency and amplitude. All four groups were compared and post-hoc pairwise analysis was performed in terms of the primary outcome. The primary outcome was correlated with the severity of refractive error in groups B and C. The cut-off values for P-100 latency and amplitude between group A and other groups were also calculated.

Results

A total of 240 eyes belonging to 120 participants were analyzed; the distribution of these participants is given in Table 1. The mean values of P-100 parameters for every diagnosis were also calculated along with values if a diagnosis is present or absent as well [Table 2]. When the association between P-100 parameters and presence or absence of a refractive error was assessed, it was found that P-100 amplitude (unaided) showed significance in differentiating if hypermetropia is present or absent, while P-100 amplitude (aided) showed significance in differentiating if hypermetropia, myopia, and amblyopia is present or absent. The P-100 latency was insignificant in differentiating the presence or absence of any refractive error. The Wilcoxon-Mann-Whitney U Test and Kruskal-Wallis test and Fisher's exact test were done to assess the associations of severity and type of refractive error with P-100 parameters. It was found that there was a significant association between severity of myopia and P-100

Table 1: Mean and frequency of the parameters of the entire dataset assessed in the study

All Parameters	Mean \pm SD Frequency (%)
Age (Years)	12.91 \pm 3.07
Gender	
Male	128 (53.3%)
Female	112 (46.7%)
P100 Latency (Unaided)	116.67 \pm 12.51
P100 Latency (Aided)	116.66 \pm 12.32
P100 Amplitude (Unaided)	10.21 \pm 4.20
P100 Amplitude (Aided)	9.84 \pm 3.93
Severity of Myopia	
Mild	51 (85.0%)
Moderate	4 (6.7%)
Severe	5 (8.3%)
Severity of Hypermetropia	
Mild	50 (83.3%)
Moderate	1 (1.7%)
Severe	9 (15.0%)
Type of Amblyopia	
Anisometropic	54 (90.0%)
Strabismic	6 (10.0%)

Table 2: Based on the diagnosis each P-100 parameters' mean value and P

Parameters	P100 Latency (Unaided)	P100 Latency (Aided)	P100 Amplitude (Unaided)	P100 Amplitude (Aided)
Diagnosis				
Emmetropia	115.78±10.19	115.78±10.19	11.11±4.08	11.11±4.08
Myopia	118.18±14.07	118.20±13.24	10.50±4.07	9.37±3.83
Hypermetropia	115.08±12.00	115.28±10.90	9.01±3.09	9.24±2.64
Amblyopia	117.65±13.49	117.54±14.47	10.23±5.15	9.66±4.71
P	0.437 ³	0.675 ³	0.020 ³	0.019 ³
Myopia				
Present	118.18±14.07	118.20±13.24	10.50±4.07	9.37±3.83
Absent	115.78±10.19	115.78±10.19	11.11±4.08	11.11±4.08
P	0.472 ²	0.365 ²	0.248 ²	0.017 ⁴
Hypermetropia				
Present	115.08±12.00	115.28±10.90	9.01±3.09	9.24±2.64
Absent	115.78±10.19	115.78±10.19	11.11±4.08	11.11±4.08
P	0.242 ²	0.466 ²	0.002 ⁴	0.004 ⁴
Amblyopia				
Present	117.65±13.49	117.54±14.47	10.23±5.15	9.66±4.71
Absent	115.78±10.19	115.78±10.19	11.11±4.08	11.11±4.08
P	0.898 ²	0.887 ²	0.054 ²	0.017 ²
Severity of Myopia				
Mild	115.21±13.05	115.37±12.20	10.78±4.31	9.72±3.92
Moderate	134.21±2.93	136.12±4.16	8.47±0.77	6.95±0.96
Severe	135.69±5.59	132.72±4.95	9.32±2.24	7.70±3.48
P	0.001 ³	0.001 ³	0.417 ³	0.239 ³
Severity of Hypermetropia				
Mild	113.76±11.77	115.35±11.37	9.49±2.88	9.45±2.50
Moderate	107.95±0	109.90±0	9.90±0	12.00±0
Severe	123.17±11.03	115.46±8.98	6.21±3.01	7.73±3.08
P	0.067 ³	0.678 ³	0.037 ³	0.114 ³
Type of Amblyopia				
Anisometropic	117.10±12.19	117.56±14.42	10.61±5.20	9.99±4.81
Strabismic	122.66±23.22	117.40±16.33	6.86±3.23	6.61±2.17
P	0.739 ²	0.990 ²	0.089 ²	0.063 ²

Significant at P<0.05, 1: Spearman Correlation, 2: Wilcoxon-Mann-Whitney U Test, 3: Kruskal-Wallis Test

latency (both unaided and aided), with P < 0.05. The severity of hypermetropia showed a significant association with P-100 amplitude (unaided) (P < 0.05). Other P-100 parameters were insignificant in terms of severity of myopia and hypermetropia. There was no significant association between any of the P-100 parameters and the type of amblyopia.

A receiver operating characteristics (ROC) analysis was performed to predict the cut-offs of various P-100 parameters in identifying if a specific refractive error is present [Fig. 1]. It was found that a cut-off of P100 amplitude (aided) ≤9.8 predicted the presence of myopia significantly (P < 0.013) with a sensitivity of 60% and a specificity of 68%. The odds ratio (95% CI) for myopia: present when P100 amplitude (aided) is ≤9.8 was 3.02 (1.43–6.38). The relative risk (95% CI) for myopia: present when P100 amplitude (aided) is ≤9.8 was 1.71 (1.19–2.49). A cut-off of P100 amplitude (unaided) ≤11 and P100 amplitude (aided) ≤11.25, predicted the presence of hypermetropia significantly (P = 0.002 and P = 0.005, respectively) with a sensitivity of 78% and specificity of 57%,

and sensitivity of 77% and specificity of 53%, respectively. The odds ratio (95% CI) for hypermetropia: present when P100 amplitude (unaided) is ≤11 and when P100 amplitude (aided) is ≤11.25 was 4.73 (2.13–10.51) and 3.67 (1.69–7.96), respectively. The relative risk (95% CI) for hypermetropia: present when P100 amplitude (unaided) is ≤11 and when P100 amplitude (aided) is ≤11.25 was 2.33 (1.48–3.9) and 2 (1.31–3.23), respectively. Also, a cut-off of P100 amplitude (aided) ≤9.5 predicted the presence of amblyopia significantly (P = 0.017) with a sensitivity of 60% and a specificity of 68%. The odds ratio (95% CI) for amblyopia: present when P100 amplitude (aided) is ≤9.5 was 3.24 (1.53–6.85). The relative risk (95% CI) for amblyopia: present when P100 amplitude (aided) is ≤9.5 was 1.77 (1.23–2.6). ROC was also used to predict the cut-off for differentiating emmetropia and other refractive errors (myopia, hypermetropia, and amblyopia). A cut-off of P100 amplitude (unaided) ≤11 predicted the presence of a refractive error significantly (P = 0.011) with a sensitivity of 69% and a specificity of 57%, and a cut-off of P100 amplitude (aided) ≤11.2 predicted the presence of a refractive

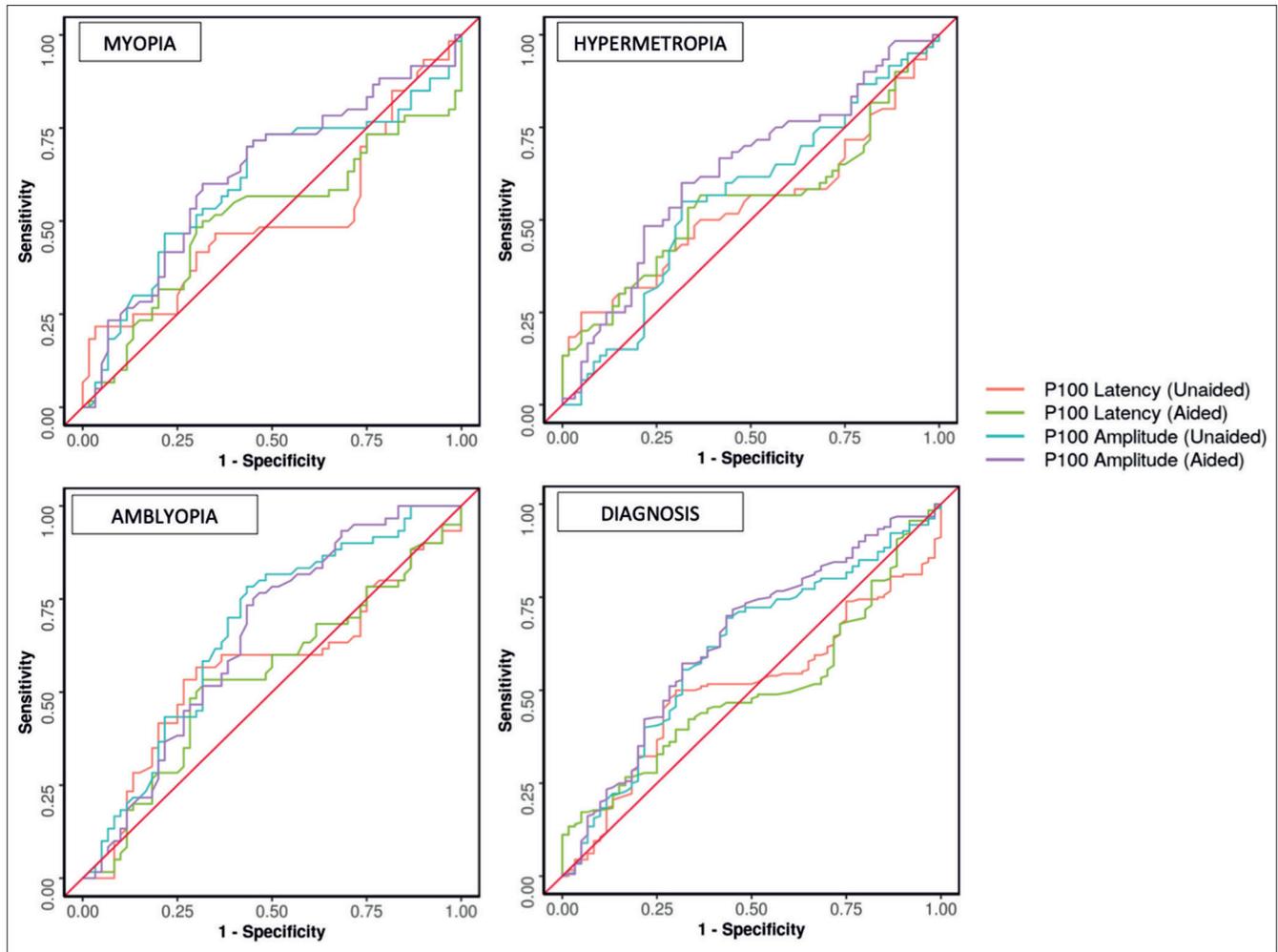


Figure 1: A receiver operating characteristics (ROC) analysis to predict the cut-offs of various P-100 parameters in identifying if a specific refractive error is present

error significantly ($P = 0.002$) with a sensitivity of 72% and a specificity of 55%. ROC analysis could not predict other parameters significantly, and all the ROC analyses stated above were found to have poor diagnostic performance.

Discussion

The emmetropic group in this study provided normal values of P-100 parameters, namely P-100 latency and P-100 amplitude with recordings of 115.78 ± 10.19 ms and 11.11 ± 4.08 μ V, respectively. Thus, according to our study, the normal P-100 latency value for the pediatric Indian population is almost 5 ms more than the conventional values given in earlier studies.^[6-9] When VEP P-100 parameters were used to detect the presence or absence of a specific type of refractive error, the P-100 amplitude was significant compared to P-100 latency. This observation is in agreement with a systematic relationship established by a study in which the amplitude was found to be decreased by 25% per diopter (D) of defocus and the effect was appreciable for 0.25 D.^[10] Refractive errors cause blurring of the stimulus and subsequently blurred vision, which has been shown to decrease the amplitude of the pattern reversal VEP.^[11]

In a recent study on an Indian population, pattern reversal VEP was performed on 50 hypermetropes and 50 myopes in

the age range of 18–40 years. There was a significant increase in P100 latency and the decrease in amplitude decreased with and without correction of myopic refractive error. However, no such significant change was recognized with hypermetropes.^[12] In our study population, the severity of myopia correlated with both aided and unaided P-100 latency readings similar to a study correlating refraction to P-100 latency in myopes. They had also found a significant negative correlation between refraction and P100 latency in myopia.^[13] The hypermetropic severity in our study correlated significantly with P-100 amplitude, notably the aided readings. A study group revealed that there is a consistently greater reduction in VEP amplitude for small amounts of plus lens defocus than for minus. They also showed that subjects partially accommodated for minus lenses. Also, a decrease in amplitude in non-cycloplegic refraction measurements seemed to occur more rapidly for plus lens than for minus, and it is thought to be due to the partial correction of defocus brought about by accommodative effort of the subject involved.^[14] The type of amblyopia assessed in this study, namely strabismic and anisometropic, had no significant correlation with P-100 parameters. However, there was a consistent trend of increased P-100 latency and reduced amplitude in all amblyopia subjects, with strabismic amblyopia showing the least mean value for P-100 amplitude (6.61 μ V) in the study.

The ROC analysis identified P-100 amplitude aided as the most important parameter in predicting the presence of a refractive error and not P-100 latency. Thus, this is an avenue that can be explored in future studies to assess if P-100 amplitude can be a more reliable predictor of underlying refractive error.

Conclusion

The P-100 parameters of the pediatric Indian population were comparatively higher than conventional values. There was a P-100 latency delay and amplitude reduction in patients with refractive error compared to emmetropes. P-100 latency seemed to better correlate with myopia, while hypermetropia correlated with P-100 amplitude. P-100 amplitude appears to be the most significant predictor of the presence of refractive error in an individual.

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Conflicts of interest

There are no conflicts of interest.

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