A novel way to make transient-VEPs a better predictor of human binocular integration
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To establish an electrophysiological marker of binocular vision, visual evoked potentials were recorded in normal observers for whom interocular refraction differences were induced with converging lenses under five dioptric conditions. Patterns of binocular interaction were categorized (facilitation, averaging or suppression) by comparing monocular and binocular responses. Quantitative and continuous indexes of binocular interaction were also calculated (binocular response minus the sum of monocular responses). Results indicated that patterns of interaction were not optimal to account for stereoscopic performance. The latter was, however, best explained by binocular integration indexes. This study shows evidence of predicting binocular vision based on a novel index that allows continuous quantification of binocular transient-visual evoked potential responses. NeuroReport 21:1023–1028 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Optimal binocular vision is associated with an enhancement of visual capacities, such as depth perception and stereopsis. The integration of binocular disparity underlying stereopsis is however compromised when one of the monocular inputs is altered by pathological conditions, such as strabismus or anisometropia.

Different approaches have been used to quantify binocular integration in humans. By comparing monocular and binocular responses, several psychophysical studies have observed binocular gain in reaction time and contrast threshold [1–3]. In the clinic, when binocular vision impairments need to be assessed, standardized stereo tests such as the Titmus and the Randot Stereotest are widely used. The main limitation of these behavioral assessments is the difficulty to test young or mentally-challenged individuals since motor and/or verbal skills are required. This is an important concern as binocular disorders are common in pediatric populations. To address this issue, electrophysiological testing can be used to assess the integrity of binocular vision.

Although the electrophysiological approach has been successful using non-standard steady-state visual evoked potentials (VEPs) (e.g. [4]), evidence from transient-VEPs are weaker. Three main patterns of binocular interaction have been reported by transient-VEPs studies [5–9]. First, the facilitation pattern, characterized by a binocular response higher than monocular responses, is often assumed to underlie the optimal binocular integration. The averaging pattern, on the other hand, is associated with no difference between the binocular response and the mean of monocular responses, where each eye contributes equally to binocular response formation. Finally, the suppression pattern refers to the inhibition of one eye (e.g. an anisometropic eye), which does not contribute to the binocular response. Although these patterns of binocular interaction are well defined conceptually, empirical data in humans is less convincing. Indeed, large response variability is typically observed, making the expected pattern not always obvious and predictable. This phenomenon has been linked to stimulus parameters such as temporal frequency and contrast level (e.g. [10]), although intra-individual and inter-individual variability is still present when those variables are kept constant [6,11,12]. This variability is particularly manifest for amplitude measurements, which explains why it is often ignored in transient-VEPs studies of binocular interaction. VEP latency, for its part, appears to reflect more typical patterns of binocular interaction [5,13,14] although it does not always reflect visual perception in a reliable manner (e.g. [15]).

In this study, we aimed at establishing a VEP marker to assess the binocular integration that would correlate with visual perception. To address this issue, we created an index of binocular integration inspired from multisensory studies [16] in which integration is reflected by the amplitude difference between the binocular response and the sum of monocular responses. To validate this metric in the context of binocular vision, monocular blurring was gradually induced to manipulate binocular integration, which was quantified electrophysiologically and behaviorally, and both the measures were compared.
Methods

Individuals

Twelve young adults (M_age = 24.7 ± 4.1 years; eight females) were recruited from psychology courses at the University of Montreal. All of the participants had normal or corrected visual acuity (20/20 or better on the Snellen chart) and normal stereopsis (at least 40′ of arc at the Randot Stereotest). One participant was excluded from the analysis because of technical data acquisition issues. The experimental protocol was approved by the CHU Sainte-Justine ethics board and informed consent was obtained from each participant.

Electrophysiological testing

A reversal checkerboard (spatial frequency: two cycles/degree; temporal frequency: 2 Hz; contrast: 96%; stimulation field: 15′) was controlled using Presentation software (Neurobehavioral Systems Inc., San Paolo, California, USA) and displayed on a View-Sonic P815 monitor located 57 cm from the individual. Participants were asked to maintain fixation on a cross located at the center of the monitor. Recordings were obtained using a V-Amp EEG system (Brain products GmbH, Munich, Germany) in accordance with the ISCEV standard [17]. In brief, the VEPs were recorded at Oz according to the 10/20 international system and referred at Fz. The ground electrode was placed on the forehead. The impedance of electrodes (Ag-AgCl) was kept below 5 kΩ. Signals were band-pass filtered at 0.1-100 Hz.

VEPs were obtained under binocular and monocular (one eye was occluded with a black patch) viewing conditions in a random order. Myopic anisometropia was induced by a convergent lens applied to one eye. Five refraction levels were arbitrarily induced to the left eye: 0, 2, 4, 6 and 8 dioptres (D). The interocular refraction conditions were randomly administered.

In each experimental condition, a typical triphasic waveform was obtained from 150 stimulus presentations. Peak-to-peak amplitude was used as recommended by the ISCEV committee [17] as this measure is associated with less variability in comparison to baseline-to-peak amplitude. The amplitude and latency of the N75, P100 and N150 VEP components were obtained and analyzed with Brain Vision Analyzer software (Brain products GmbH). Monocular responses were categorized compared to binocularly evoked responses according to facilitation, averaging and suppression binocular interaction patterns [5]. Furthermore, a binocular integration index was computed according to the following formula: [(right eye response + left eye response)−binocular response]/(right eye response + left eye response) + binocular response] × 100. The assumption underlying this index is the following: if any two neuron groups are independent of each other, the response to dual stimulation should be equal to the sum of responses when these two groups are stimulated separately [16]. Thus, any difference between the sum of the monocular responses and the binocular response is indicative of binocular integration.

Behavioral testing

Binocular stereoscopic vision was tested with the Randot Stereotest. This test allows the assessment of stereopsis threshold from 20 to 500′ of visual angle. The four subtests (random dot stereograms, animals, circles and suppression cross) were administered at each level of interocular refraction differences. If a participant failed identification at 500′, the fly stimulus of the Stereo Fly Test (3000′) was used to determine residual stereopsis. Each stereopsis score was normalized to fix stereoperception higher mean score between each experimental level as the optimal stereoperception. This optimal level was then taken as 100% and the other scores were determined by a ratio calculation.

Data analysis

Repeated two-way analysis of variances (ANOVAs) were used for each VEP component to test the patterns of binocular interaction [Viewing (right monocular, left monocular and binocular) × Refraction (0, 2, 4, 6 and 8 D)]. Follow-up analyses were performed to isolate simple effects. One-way repeated ANOVAs were used for each component to determine the effect of interocular refraction difference on VEP responses. Binocular integration from VEPs and behavioral testing were compared using data function fitting. Perceptual data was first best-fitted with TableCurve software (Systat, Chicago). The retained function was then applied to VEP integration and the explained variance was statistically compared with the perceptual data using an one-way repeated measures of ANOVA. Bonferroni correction was applied to all analyses to control for multiple comparisons.

Results

Electrophysiological testing

The effect of anisometropia on binocular interaction patterns was characterized for each interocular refraction difference. The latency of each VEP component was first analyzed. The N75 response analysis revealed main effects of viewing (left monocular, right monocular, binocular) and refraction (0, 2, 4, 6, 8 D). An interaction between these variables was also found [F(1.23,12.34) = 4.87, P < 0.05, R² = 0.33, see Fig. 1]. Follow-up analysis revealed no significant difference of viewing at 0 D and 2 D, indicating an averaging pattern. Only the 4 D level produced a significant interocular difference (P < 0.05), where the left (refracted) monocular response was significantly slower than the right (unrefracted) monocular response. As the latter was not significantly different from the binocular response, this pattern indicated a suppression effect. The left monocular responses were also slower than right monocular and
binocular responses at 6 D and 8 D but these effects did not reach the significance level ($P = 0.3$ and $0.07$, respectively).

Regarding the P100 latency, ANOVA revealed main effects of viewing and refraction in addition to a significant interaction between factors \( [F(1.51,15.13)= 22.10, P < 0.05, R^2 = 0.69, \text{see Fig. 1}] \). No significant interocular difference was found at 0 D. In addition, no latency difference was found between the binocular response and each monocular response. Such interocular interactions indicate the presence of averaging processes. An averaging pattern was also present at 2 D. From 4 D to 8 D, the binocular response differed significantly from the left monocular response, but not from the right monocular response. The equivalence of right monocular and binocular responses suggests that the refracted eye was suppressed by the normal eye.

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*Fig. 1*

Top, N75 latency; Middle, P100 latency (left) and N150 latency (right); Bottom, N75-P100 amplitude (left) and P100-N150 amplitude (right).
Main effects of viewing and refraction were found for the N150 latency. A significant interaction between viewing and refraction was also found [F(1.89,18.90) = 28.38, P < 0.05, R^2 = 0.74, see Fig. 1]. This component showed the same interocular pattern of binocular interaction than the P100. At 0 D and 2 D, the right monocular and left monocular responses did not significantly differ from each other or from the binocular response. These interactions indicate the averaging of monocular responses. A suppression pattern was present at 4 D, 6 D and 8 D; the left monocular response being significantly slower (P < 0.05) than the right monocular and binocular response (P < 0.05). The binocular response and right monocular responses did not differ significantly at those levels.

Amplitude analyses also revealed the binocular interaction patterns. For the N75-P100, main effects of viewing and refraction were found. Furthermore, the interaction between these variables was significant [F(2.95,29.49) = 24.34, P < 0.05, R^2 = 0.71, see Fig. 1]. At 0 D, the right monocular response and the left monocular response were significantly smaller (P < 0.05) than the binocular response, which indicates facilitation of the binocular response. At those levels, the left monocular response showed a significantly lower (P < 0.05) amplitude than the right monocular and binocular responses, suggesting a suppression pattern.

For the P100-N150, the data showed main effects of viewing and refraction, and a significant interaction between factors [F(3.48,34.80) = 37.14, P < 0.05, R^2 = 0.79, see Fig. 1]. When there was no or little refraction difference between the eyes (i.e. θ ≤ 2 D), no significant difference between viewing conditions was found. The three other levels (4, 6 and 8 D) showed suppression, that is, a significant difference (P < 0.05) between the left and right monocular responses as well as between the left monocular and binocular responses.

VEP amplitude was further examined using a binocular integration index. ANOVA showed an effect of refraction on the percentage of integration for the N75-P100 complex [F(4,40) = 22.95, P < 0.05, R^2 = 0.68, see Fig. 2a]. In particular, no difference was found between 0 D and 2 D, but a significant reduction (P < 0.05) of binocular integration was found between 2 D and 4 D. After this reduction, the percentage of integration remained stable between refraction levels. As illustrated in Fig. 2b, the same trend for refraction on binocular integration was found for the P100-N150 complex [F(2.52,25.23) = 34.39, P < 0.05, R^2 = 0.78]. No difference was found between 0 D and 2 D, followed by a significant reduction (P < 0.05) between 2 D and 4 D and finally by a stabilization between 4 D, 6 D and 8 D.

**Behavioral correlates**

Levels of refraction 0 D and 2 D, associated with normal depth perception (disparity sensitivity of 20–40 s), were similar. These levels were followed by a reduction of stereopsis at 4 D level. This reduction was associated with the inability to see any of the 3 D perception tests (disparity sensitivity > 3000 s), which remained stable throughout the remaining levels (4 D and 6 D).

The curve fitting the analysis revealed that the perceptual data were best explained using a logistic equation for each individual (r^2 = 0.99, SD = 0.001) (see Fig. 2c). This function was then applied to the VEP integration individual data. It was found that 58% (SD = 0.13) of the variance of the N75-P100 response and 73% (SD = 0.10) of the P100-N150 was explained by the perceptual function. One-way ANOVA revealed a significant main effect of type of integration [F(2,18) = 5.36, P < 0.05, R^2 = 0.37]. Although the good explained variance of the N75-P100 fitting, it was lower...
than the perceptual fitting ($P < 0.05$). However, no statistical difference was found between the P100-N150 and stereopsis, confirming that both the variables followed the same mathematical function.

Discussion

This study aimed at providing an electrophysiological marker of binocular vision. Although different patterns of binocular interaction were found as a function of interocular refraction differences (facilitation, averaging and suppression), indexes of binocular integration provided a quantitative assessment of VEP responses and were better correlated with behavioral data. In particular, we found that both the VEP and perceptual data were explained by the same mathematical function.

Patterns of interaction observed in this study were consistent with earlier reports in which facilitation and averaging were described in normal vision and suppression in presence of interocular refraction differences [2,5–9]. In particular, latency and amplitude alterations of the P100 found in these studies suggest that binocular suppression begins between 2 and 4 D of differences in interocular refraction. We found similar suppression effects at these levels, including for the N150 component, although evidence of suppression for the early VEP response (N75) was less consistent. The suppression patterns revealed by the present VEP data were correlated with stereopsis. In accordance with these findings, the critical level of interocular refraction differences to induce suppression in amblyopic anisometropes was also found around 3 D [18–20]. Furthermore, significant impairments of stereocuity based on Titmus stereo test were observed at 3 D refraction difference and greater in untreated anisometropes [18]. This threshold, either in healthy observers or patients, is therefore associated with a cortical suppression of inputs coming from the refracted or amblyopic monocular pathway.

In this study, the facilitation and averaging categorical patterns of interaction were not clearly distinct in terms of stereopsis correlates. Thus, contrary to suppression, these patterns appear not reliably associated with a perceptual change. A large range of interaction patterns has been associated with normal vision [7,8,21–23]. This variability may only reflect the choice of stimulus conditions. For instance, Apkarian, Nakayama and Tyler [6] showed that the magnitude of binocular facilitation changes as a function of several stimulus parameters such as spatial frequency, temporal frequency or contrast. Furthermore, the lack of facilitation can be explained by the incapacity of VEPs to measure the specific subsets of neurons that share the same disparity, orientation and spatial frequency tuning. Thus, it remains an open question whether there is a functional difference between averaging and facilitation processes in normal binocular vision. To our knowledge, this has not been directly addressed empirically in humans, although facilitation is commonly associated with optimal vision [5,24] and stereopsis [6]. As such, categorical patterns of binocular interaction should be taken with caution as far as perception is concerned.

Alternative to the interaction pattern approach, we found a much better relationship between VEP and perception, either under optimal or defective binocular viewing conditions, using an electrophysiological integration index based on amplitude. In particular, the P100-N150 index was the best marker of binocular perception. The fact that the P100-N150 instead the N75-P100 was a better predictor of stereopsis is in agreement with earlier transient-VEP studies that show that the electrophysiological response related to stereopsis typically occurs between 100 and 200 ms (e.g. [25]).

Conclusion

The aim of this study was to establish an electrophysiological predictor of binocular integration. Our results suggest that categorical patterns of binocular interaction are not good predictors of binocular perception. Instead, indexes of binocular integration obtained by directly comparing monocular and binocular responses are more reliable metric of human stereoperception in both optimal and non-optimal viewing conditions.

References


