Maturation of Cyclopean Visual Evoked Potential Phase in Preterm and Full-Term Infants

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Purpose. P1 is the major positive component of pattern-reversal visual evoked potentials (PR-VEPs). The rapid decrease of its latency correlates with the progressive myelination in the developing infant brain, which affects signal transmission in the visual system. An age-dependent phase shift, analogous to P1 peak latency, can be observed in dynamic random dot correlogram (DRDC)-evoked VEPs (DRDC-VEPs), a method used to assess binocular function. Our goal was to study the relationship between cyclopean DRDC-VEP phases and PR-VEP P1 latencies in full-term and preterm infants so as to further explore the experience dependence of early binocular developmental processes.

Methods. DRDC-VEPs and PR-VEPs were recorded in 128 full-term and 47 preterm healthy infants and toddlers. DRDC stimuli were presented on the red and green channels of a CRT monitor while infants wore red-green goggles for dichoptic viewing. Reliability of VEP responses was assessed by the T^2_{circ} statistic. Logistic function was fit to the phase and latency data as a function of age, and goodness of fit was assessed by analysis of residuals.

Results. The phase shift of DRDC-VEPs and the rapid decrease of P1 latencies occur at identical postconceptual ages. A correlation also was found between P1 latencies and DRDC-VEP phases.

Conclusions. Although development of binocularity is an extremely experience-dependent process, our data suggest that DRDC-VEP phase and P1 latency mature independently from visual experience. We propose that both the phase shift and decreasing P1 latency are indicators of myelination and increasingly faster signal transmission in the developing visual system.

Keywords: stereopsis, binocular vision, VEP, visual development, binocular correlation

Stereopsis provides the most accurate depth perception in front-eyed animals and humans. According to the classic view, the development of binocular vision requires appropriate visual input that sculpts the neuronal organization in the visual cortex and leads to the development of orientation-selective and ocular dominance columns.[1–5] Hubel and Wiesel[1,4,6] demonstrated in a series of cat experiments that visual deprivation in one eye results in an abnormal neuronal connectivity of the affected eye in the cortex. This abnormal synaptic organization, due to the lack of appropriate visual input, prevents the development of binocular vision.[1,4,6] Since the seminal work of Hubel and Wiesel,[1,4,6] binocularity has become a widely accepted model of experience-dependent visual development.[6–9] Recently, Jandó et al.[10] demonstrated the accelerating effect of additional visual experience in healthy preterm infants; earlier onset of visual experience resulted in earlier maturation of binocular vision. These data clearly show that the human brain is ready to accept and use environmental stimuli 2 to 3 months before birth, and the neuronal plasticity mechanisms are geared up at this early stage for structural reorganization. This further emphasizes the quintessential role of visual experience in the formation of binocular neuronal organization in the visual cortex.[10]

The early postnatal development of vision has been extensively studied by using visual evoked potentials (VEPs).[11–17] Several studies have shown that the peak latency of the major positive wave component of pattern reversal VEPs (PR-VEPs), called P1, is a reliable indicator of the general maturation of the visual system.[12,13,18–21] In full-term infants, there is a rapid decrease in P1 peak latency from approximately 260–300 ms to the adult-like 100 ms in the first 15 postnatal weeks for large (120 minutes of arc) check sizes.[10,16,22,23] Numerous VEP experiments have demonstrated that maturation of P1 peak latency is not affected by visual experience (i.e., additional visual experience in preterm infants does not accelerate the maturation of P1 peak latency).[10,24] Experience-independence suggests that this development is driven by intrinsic molecular and neuronal processes and most likely is associated with retinal development, synaptogenesis, development of synapses, and myelination of the nerve fibers in the visual pathways and elsewhere in the brain.[25–27]

The binocular visual system can be selectively activated by cyclopean stimuli that are composed of random dots and can be perceived only if each eye receives the appropriate image simultaneously and the subject has mature and intact stereovision.[28,29] For VEP recording, Julesz and colleagues[30,31] invented two types of cyclopean stimuli: dynamic random dot

stereogram (DRDS) and dynamic random dot correlogram (DRDC). Both types of stimuli have two alternating phases, which evoke a binocular neuronal response and the accompanying electrical activity can be recorded over the occipital cortex. With a lack of stereopsis, no electrical response can be recorded.

Because DRDC-VEPs can be evoked solely after the onset of binocularity, DRDC-VEP has become an important indicator of binocular function in developmental studies.[32–34] Although there is some variance between studies regarding the onset age of cortical binocularity (i.e., the age when the infant suddenly becomes susceptible for binocular stimulation), it is generally accepted that binocularity appears between the second and sixth postnatal months in full-term infants without visual abnormalities.[10,32,34,35] Although Jandó et al.[10] essentially confirmed these results in preterm infants, it was also noted that the DRDC-VEP phase at the onset ages of binocularity are not the same for preterm and full-term infants, suggesting age-dependent maturation of the DRDC-VEP phase.

The objectives of the present study were (1) examination of DRDC-VEP phases in preterm and full-term infants as a function of age after the onset age of binocularity; (2) to determine whether DRDC-VEP phases depend on visual experience or are an experience-independent developmental process; and (3) to study the relationship between DRDC-VEP phases and PR-VEP P1 peak latencies.

Subjects and Methods

Subjects

A total of 128 healthy full-term (mean birth age 39.3 ± 1.21 weeks; range, 37–41 weeks; mean birth weight: 3419.2 ± 532 g), and 47 healthy preterm (mean birth age 32.2 ± 3.33 weeks; range, 25–36 weeks; mean birth weight: 1713.8 ± 638.1 g) infants and toddlers participated in the present study, which can be regarded as an independent source of samples. Selection of infants is based on our measurements and the infants' medical records. Inclusion criteria were as follows: (1) Presence of a significant PR-VEP response. (2) Presence of a significant DRDC-VEP response (i.e., development of cortical binocularity) until the sixth postnatal month. Those who came at older than 6 months had to have a significant DRDC-VEP response on the first visit, otherwise the subject was not included. (3) No history of intraventricular hemorrhage or periventricular leukomalacia. (4) Lack of major internal, neurological, or organic ophthalmologic symptoms. For the preterm group, no or at most stage II retinopathy of prematurity. Infants were recruited by contacting the parents via local midwiferies or the Department of Ophthalmology at the University of Pécs. Parents were fully informed about the nature of the study. For each subject, one of the parents was required to sign a consent form before the experiments. One adult subject with intact binocularity was also involved in the study as a control, who was a member of our research team. The recruitment and experimental protocols were in accord with local legislations and the Declaration of Helsinki, and approved by the Regional and Local Research Ethics Committee at the University of Pécs.

Adjusted and Postnatal Ages. For age terminology, the recommendations of the American Academy of Pediatrics were followed.[36] Postnatal age (PNA) is simply the time counted from birth. Although postmenstrual (or postconceptual) age (PMA) is an appropriate term to measure the time elapsed from conception, adjusted age (ADJ) is a convenient scale to avoid large differences between the PNA and PMA. Adjusted age is defined as PMA_{DAY} minus 280. It is negative for preterm infants at birth and becomes positive as the due date is passed. To use weeks for data plotting and statistical analysis, ages were calculated primarily in days, then divided by 7 and rounded to two decimals.

The total number of data points, which represent the number of occasions infants produced a significant DRDC-VEP response for each age group, are presented in Table 1.

Developmental Window. Age-dependent developmental processes can be best characterized by the developmental window (DW). Within the DW, the developmental indicator changes in a sigmoid fashion. The sigmoid characteristic of a developmental time course can be interpreted as follows. Initially, the developmental indicator signals a fully immature state (i.e., immature asymptote). Within the DW, in which the developmental process occurs, the indicator reaches its fully mature state (i.e., mature asymptote). The highest slope of indicator change is in the middle of the DW (DW center), where development is the most rapid (i.e., inflection point of the logistic function). In the later phase of development, the indicator changes less rapidly and gradually reaches its mature asymptote. The comparison of developmental timing between preterm and full-term infants on two complementary age scales (i.e., PNA versus ADJ) permits study of the experience-dependence of a developmental process. Identical DW centers on the PNA scale and different DW centers on the ADJ scale suggest extreme experience-dependence. Identical DW centers on the ADJ scale and different DW centers on the PNA scale suggest the opposite (i.e., extremely experience-independent developmental process). The DWs and their centers were determined by logistic fit to the developmental indicators (i.e., peak latency or phase; for details see Modeling the Data and Statistical Evaluation).

Visual Stimuli

Stimuli were generated on an IBM compatible personal computer (Asustek Computer, Inc., Taipei, Taiwan) and presented on a 19-inch cathode ray tube (CRT) computer monitor (Samsung Model 957 MB; Samsung Electronics Slovakia Ltd., Galanta, Slovakia). Spatial resolution of the monitor was 320 × 240 dots and the temporal resolution was 60 Hz.

Dynamic Random Dot Correlogram. For channel separation, during DRDC-VEP recordings, R26 low-pass (red) and YG09 band-pass (green) gelatin filters (Tobias Optic, Ltd., Budapest, Hungary) were used. During correlated phase, random images consisted of 50% dark (black) and 50% bright (yellow) elements; these images appear exactly the same either through the red or the green filter. During anticorrelated phase, random dot images contained 50% red and 50% green elements; each dark element through the red filter corresponded to a bright element through the green filter and vice versa. Random dot images were updated at 30 Hz and synchronized to the monitor refresh cycle. The alternation rate of the two phases (i.e., stimulus frequency) was 1.875 Hz. Each element in the image subtended 15 minutes of arc, the luminance of the bright elements through the filters was 5.65 ± 0.32 cd/m^2, and the contrast was approximately 80%. Subjects with intact binocularity perceived a pulsation at 1.875 Hz. In case of monocular viewing condition or without functional binocularity, a 30-Hz noise was visible. For more details, see Marko et al.[37]

Checkerboard Pattern Reversal. As a control condition for DRDC-VEP, PR-VEP measurements were performed in each experimental session. The assessment of P1 latency also served as a measure of the integrity of visual pathways and the functionality of the recording apparatus. A single check size of 120 minutes of arc was used, the stimulus frequency was 1.875

Hz (i.e., the reversal rate [r/s] was 3.75 r/s), the same used during DRDC stimulation. The mean luminance of the white checks was 106 cd/m^2 and contrast was 95%.

Experimental Procedure

Most of the first visits were scheduled between the second and sixth postnatal months. In most infants, a significant PR-VEP response was recorded before the onset age of cortical binocularity. Typically, there were between one and four examinations, with approximately 4 to 8 weeks between measurements until binocularity became evident (i.e., significant DRDC-VEP could be recorded). For those subjects who had their first visit at older than 6 months of age, a significant DRDC-VEP response was a criterion for them to be included. In a few cases, the number of visits reached 12 sessions. After the first year, some of these infants were examined yearly and followed up to 5 years of age. Following electrode attachments, infants were placed in a comfortable child seat or in their parent's lap at a 0.5-m viewing distance from a 19-inch CRT monitor. The screen, which was the only light source in the darkened room, subtended approximately $30^\circ \times 40^\circ$ within the visual field of the infants. To attract and maintain attention, a steady transparent monocularly visible image (e.g., a smiling sun) served as a fixation object at the center of the screen. Their attention to the stimulus was facilitated also by sound-making toys held in front of the screen by the experimenter. Data acquisition was suspended during agitated or inattentive behavioral phases. PR-VEP recording preceded DRDC-VEP recording. Each DRDC-VEP recording block lasted at least for 70 to 100 seconds, or up to the limit of cooperation. Each combined PR- and DRDC-VEP session was usually shorter than 10 to 15 minutes. In those cases in which sleep or the refusal of wearing goggles prevented the completion of measurements, testing was repeated a few days later. To notice recording false DRDC-VEPs, monocular control trials were also included in the protocol if the subject tolerated monocular covering.

Recording and Data Analysis

Gold-plated electrodes were placed over the Oz (active electrode) and Fz (reference electrode), according to the International 10-20 System for electrode placement. An electrode at Cz served as ground. Brain electrical signals were amplified, band-pass filtered between 0.5 and 250 Hz, and sampled at 960 Hz. Signals were collected and processed with CED 1401 Power (Cambridge Electronic Design Limited, Cambridge, England) data acquisition equipment. For DRDC-VEPs, records were divided into 2.133-second nonoverlapping epochs. After fast Fourier transformation, the Fourier components of the first, second, and fourth harmonics of the stimulus fundamental frequency were used for artifact rejection. Fourier vectors greater than 30 μV were regarded as artifacts. Reliability of the records and detection of cortical binocularity was assessed by T^2_{circ} statistics.[38] T^2_{circ} is a statistical method designed to analyze repeating signals in the VEP records. The T^2_{circ} statistic essentially measures response reliability; higher values point out a clearer correlation between the stimulus and the brain response. The first (i.e., 1.875 Hz), second (i.e., 3.75 Hz), and fourth (i.e., 7.5 Hz) harmonics of DRDC frequency were analyzed. The level of significance for the T^2_{circ} statistic was established at $P = 0.01$. Failure of T^2_{circ} to find statistical significance indicates that binocular visual stimulation is independent of brain activity.

Phases of DRDC-VEPs were calculated from the real and imaginary part of the corresponding Fourier component of the DRDC frequency as follows:

$$\text{PHASE} = \arctan(x + iy), \quad (1)$$

where x is the real (i.e., cosine) and iy is the imaginary (i.e., sine) part of the Fourier component, whereas *arctan* refers to "arcus tangent."

We carried out a similar analysis for PR-VEPs; however, 1.066-second epochs were used and the reversal rate (i.e., 3.75 Hz) was considered the fundamental frequency. Signal reliability test provided by T^2_{circ} was followed by a manual determination of the P1 peak latency. Records not passing the T^2_{circ} test were excluded from further analysis. A more detailed description of the method can be found in Jandó et al.[10] and Markó et al.[37]

Modeling the Data and Statistical Evaluation

General linear correlation and regression model were used to decide whether DRDC-VEP phases have a statistically significant correlation with age or not. The linear correlation also was calculated for P1 peak latency. A nonlinear model also was tested assuming a similar developmental mechanism for both PR-VEP P1 peak latencies and DRDC-VEP phases. According to our null hypothesis, the DRDC-VEP phase changes in relation with age follow a logistic function similar to other developmental patterns. Levenberg-Marquardt's least square algorithm was used for fitting, a similar technique was used by McCulloch et al.[11] and Jandó et al.[10] The goodness of fit was evaluated by residual analysis after fitting the logistic function to the data set.

The general form of a logistic function is as follows:

$$f(x) = \frac{a}{1 + e^{-b(x+c)}} + d, \quad (2)$$

where a represents the difference between the mature and the immature asymptote of the developmental indicator, d represents the lowest indicator value, the horizontal location of the midpoint in the logistic function is defined by c, and b correlates with the slope at c. Because the calculated phases are limited in a $-\pi$ to $+\pi$ interval, the parameter a was fixed at $2 \times \pi$.

The goodness of fit was determined by residual analysis and also was used to decide if preterm and full-term data sets can be modeled by the same function or by two significantly different functions. Residuals and the goodness of fit were calculated as follows:

$$res_i = y_i - f(x_i) \quad (3)$$

$$SS_{tot} = \sum_i (y_i - \bar{y})^2 \quad (4)$$

$$SS_{res} = \sum_i (res_i)^2 \quad (5)$$

$$R^2 = 1 - \frac{ss_{res}}{ss_{tot}} \quad (6)$$

where y_i represents the actual data points, $f(x_i)$ is the function predicted y_i at x_i, SS_{res} is the summed squared error of the residuals, and SS_{tot} is the total error of the dependent variable. R^2 was used to describe the strength of correlation.

For testing the existence of a common model for preterm and full-term infants, the logistic function was fit to the merged preterm and full-term data set. Then, group residuals were compared by one-way ANOVA. When a common function could be fit to the data, both group residuals were distributed similarly around zero. When ANOVA tests did not show

Table 1. Age Distribution of DRDC-VEP Measurements

	Preterm Infants						Full-Term Infants					
	PNA			ADJ			PNA			ADJ		
Age, mo	sig	NA	NS	sig	NA	NS	sig	NA	NS	sig	NA	NS
0	0	0	0	0	2	2	0	0	0	0	0	0
1	0	0	2	0	2	21	0	2	1	0	2	2
2	0	4	7	4 (0)	2	26	0	1	12	0	1	13
3	2 (0)	1	20	25 (6)	0	9	5 (1)	1	12	9 (1)	1	16
4	15 (5)	0	19	15 (5)	0	5	22 (0)	0	9	27 (2)	1	9
5	11 (3)	1	13	13 (5)	5	2	55 (9)	2	15	55 (9)	1	12
6	11 (2)	4	4	8 (6)	3	0	33 (4)	1	5	31 (6)	1	3
7	22 (8)	0	0	6 (4)	2	0	24 (8)	2	0	17 (3)	2	0
8–12	16 (14)	12	0	6 (6)	5	0	15 (5)	5	0	15 (6)	5	0
13–24	3 (3)	4	0	5 (5)	3	0	1 (0)	2	0	1 (0)	2	0
25+	6 (4)	1	0	4 (2)	3	0	1 (1)	0	0	1 (1)	0	0

The "sig" column includes data points, which are plotted in the top panels of Figure 3; numbers are occasions when significant DRDC-VEP were recorded and their phases could be determined. The "NS" and "NA" columns represent the number of nonsignificant and unsuccessful DRDC-VEP recordings (i.e., not available), respectively. Numbers in brackets show nonindependent samples (i.e., occasions when subjects were recorded on more than one occasion). According to the table, for example, 25 3-month-old (ADJ) preterm and two 3-month-old (PNA) preterm infant data were included. Six of the 25 3-month-old (ADJ) preterm infant measurements were repetitions (i.e., nonindependent samples).

significant difference between the group residuals, the common function was accepted as an equally good model for both preterm and full-term populations. When residuals were different, we concluded that the two data sets could be modeled only by significantly different functions.

Results

Eighty-nine percent of infants successfully completed both DRDC- and PR-VEP recordings for the first time of each visit. Sessions were concluded as unsuccessful if no or poor-quality data could be recorded due to poor attention and crying (rather in infants older than 7 months) or sleepiness (infants younger than 2 months of ADJ). The success rate during our measurements was comparable to other VEP studies performed on infants.[12] Because the first, or higher than second, harmonic Fourier components became significant only in infants older than 6 to 7 months, we considered and accepted the existence of the significant second harmonic component as an ultimate marker of significant DRDC-VEP response (i.e., existence of cortical binocularity). For this reason, only the second harmonic was included in further data analysis, except in adults and children older than 1 year. Table 1 summarizes the number of all significant, nonsignificant, and unsuccessful DRDC-VEP measurements for all age groups. Most of the infants had at least one successful and significant PR-VEP P1 peak latency measurement before the onset age of cortical binocularity.

Figure 1 and Figure 2 show representative averaged DRDC-VEP and PR-VEP responses, respectively. The first nine traces on the left panel in Figure 1 show a preterm infant who was examined approximately once every 4 weeks for a year and then followed up yearly until the age of 5. According to the T^2_{circ} statistic, the DRDC stimulus had no effect on the EEG in the top two VEPs and in cases of monocular controls (dotted curves). The infant was presumably lacking binocularity at the youngest two ages. The statistically significant DRDC-VEP traces recorded in different ages are consistently reproducible (3.3–16 months), but show a gradually changing characteristic: there is an obvious counterclockwise phase shift, and the responses in the younger ages show an obvious frequency doubling. The frequency doubling of the response disappears at age 5, when the fundamental frequency of the stimulus dominates the electrical response of the brain, as in adulthood. Traces from 10 to 12, marked as 4.8, 6.3, and 7.8, were typical records from a full-term subject. The phase shift is modest and the frequency doubling is also present. All infant VEP responses were found significant for the second harmonic component except the 5-year trace, which showed significance for the first harmonic component, similar to adults. The bold curve represents a typical DRDC-VEP of an adult control subject with intact stereovision; the response was found significant for the first harmonic component (fundamental frequency) only.

Figure 3 top two panels summarize all DRDC-VEP phases as a function of age plotted with two complementary age scales. DRDC-VEP phase clearly changes with age from the onset ages of binocularity until it asymptotes at approximately 25 to 30 ADJ weeks. When preterm and full-term DRDC-VEP phases are plotted as a function of ADJ, there is a better overlap between preterm and full-term data points (Fig. 3, top right) in comparison with the plot as a function of PNA (Fig. 3, top left). To explore age-related changes in detail, linear and nonlinear models were applied. The general linear correlation and regression model showed statistically significant but poor linear correlation for each group (preterm and full-term infants) for both age calculation methods (ADJ and PNA). The result of the linear modeling can be seen in Table 2. The regression coefficients (R^2) were slightly higher for preterm infants but did not exceed 0.24 in any group versus age combinations, indicating that the linear model insufficiently describes the relationship between ages and phases. Conversely, nonlinear models performed much better. The best logistic fits were achieved for preterm infants when ADJs ($R^2 = 0.68$) or PNAs ($R^2 = 0.52$) were used as independent variables, which is a significant improvement compared with the linear model. For full-term infants, the nonlinear approximation did not show significant improvement ($R^2 = 0.12$ for ADJ and $R^2 = 0.11$ for PNA); some parameters of the logistic function resulted in inadequate numbers because the confidence bounds were too large. When preterm and full-term infant data were modeled together, a common logistic fit could be established as a function of ADJ ($R^2 = 0.5$). The difference can be noticed in Figure 3. To explore the role of visual experience, residual analysis was performed after logistic fit. Analysis of residuals supported the common model for ADJs ($F_{1,240} = 1.03$, $P =$

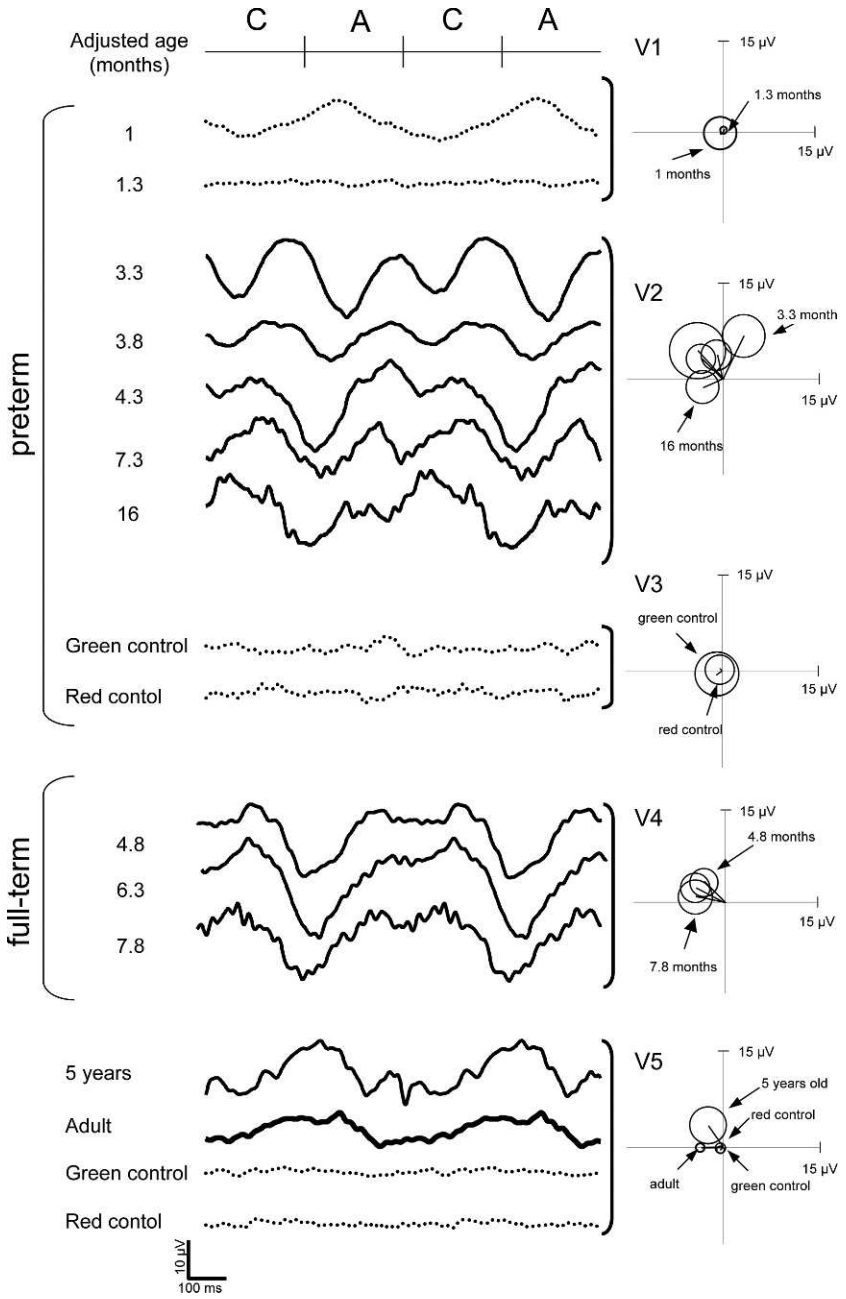

Figure 1. Representative averaged DRDC-VEP responses. Data were obtained at different ages from preterm infant (L.W.), full-term infant (E.G.), and adult. *Left*: Averaged DRDC-VEP traces. Letters "A" and "C" mark the anticorrelated and correlated phases of the DRDC stimulus, respectively. The alternation rate of the two phases (i.e., stimulus frequency) was 1.875 Hz. Adjusted ages are marked on the *left side* for the traces. *Dotted traces*: T^2_{circ} statistic showed no significance (i.e., no binocularity) or the response was recorded during monocular viewing as a control. *Solid traces*: T^2_{circ} statistic shows significant phase-lock to the stimulus (i.e., binocularity exists). In all solid traces, the second harmonic component of the stimulus (i.e., 3.75 Hz) was significant, except at the age of 5 and in the case of an adult, where the first harmonic (i.e., 1.875 Hz) was significant. *Bold trace*: Normal adult control DRDC-VEP response. Traces marked as 1, 1.3, 3.3, 3.8, 4.3, 7.3, and 16 months were recorded from preterm, whereas 4.8, 6.3, and 7.8 were recorded from full-term subjects. The *right* shows the vectographic representation of the DRDC-VEP records seen on the *left*. Brackets group traces that belong to the vector charts on the *right*. The vectors are averaged Fourier vectors of the first or the second harmonic of the stimulus frequency derived from at least 30 epochs. The radii of the circles at the tip of the vectors represent the confidence intervals of the average vectors at $P = 0.99$, derived from the T^2_{circ} statistic. **(V1)** Vectographic plot of the second harmonic component of the first two *dotted VEP traces*. The average vectors are NULL vectors, showing that the stimulus has no significant effect on the response. **(V2)** The second harmonic components of a preterm infant (L.W.) VEPs (3.3–16). *Circles* do not contain the origin, therefore the DRDC-VEP is phase locked to the stimulus, and the second harmonic is significantly present in the response. We can observe a counterclockwise phase shift of the average vectors from the youngest age (3.3 months) to the oldest age (16 months). **(V3)** Vectographic plot of the second harmonic component of the *dotted VEP traces* recorded in a monocular viewing condition (one of the eyes was covered). Both average vectors are NULL vectors, showing that the stimulus has no significant effect on the responses in monocular conditions. These monocular controls belong to the 4.3 months' preterm record (L.W.). **(V4)** The second harmonic components of a full-term infant (E.G.) VEPs (4.8–7.8). *Circles* do not contain the origin, therefore the DRDC-VEP is phase-locked to the stimulus, and the second harmonic is significantly present in the response. We can observe a modest counterclockwise phase shift of the average vectors from the youngest age (4.8 months) to the oldest age (7.8 months). **(V5)** First harmonic Fourier component in the 5-year-old preterm child's and adult's control DRDC-VEPs. Monocular controls for the adult records are also included, which resulted in NULL vectors.

Table 2. General Linear Correlation and Regression Model

	General Linear Model Parameters		Statistical Analysis		
Group	Slope	Intercept	R^2	F	P
ADJ PRE	0.015 (0.0094–0.0212)	1.23 (0.92–1.54)	0.24	26.46	1.7×10^{-6}
ADJ FULL	0.016 (0.01–0.027)	1.83 (1.61–2.06)	0.11	18.56	2.9×10^{-5}
PNA PRE	0.015 (0.009–0.021)	1.12 (0.78–1.46)	0.23	25.07	3.0×10^{-6}
PNA FULL	0.018 (0.0098–0.027)	1.82 (1.59–2.06)	0.10	17.86	4.1×10^{-5}

Values in parentheses are the 95% confidence bounds. FULL, full-term; PRE, preterm.

0.3112), but failed to prove it for the PNAs ($F_{1,240} = 62.37$, $P = 1.02 \times 10^{-13}$). Logistic curve fitting found the DW center at 6.98 ADJ weeks, which is very similar to the DW center calculated for PR-VEP P1 peak latency. Because independent samples and results from repeated measurements were mixed in ANOVA (see Table 1), we resampled our data in a Monte Carlo simulation to strictly follow the rule of independence, as if measurements were taken only once from each infant (i.e., only one randomly selected measurement was used in the statistical analysis for each infant who had repeated measurements). The results after 1000 simulations were essentially the same. The averages and SEs for the most important parameters were given ($F_{1,173} = 1.280 \pm 0.0285$, $P = 0.3322 \pm 0.00618$, DW center $= 7.37 \pm 0.0140$) and ($F_{1,173} = 52.74 \pm 0.213$, $P = 1.811 \times 10^{-10} \pm 2.07 \times 10^{-11}$, DW center $= 0.170 \pm 0.0148$) for ADJ and PNA scaled data, respectively.

Figure 2 shows representative averaged PR-VEP responses of a full-term infant subject (B.C.) recorded weekly between 7 and 16 PNA weeks. The P1 peak latency, indicated by dots on the figure, clearly shows a progressive decrease with age. The characteristic of PR-VEP responses also changes with age. At young ages, the response has a steady-state VEP (ssVEP) characteristic, which gradually becomes a transient VEP-like response. In adults, typical transient VEP responses can be obtained below 4 r/s, whereas ssVEPs can be recorded at higher than 4 r/s reversal rates. The overall maturation process of P1 peak latency can be seen in Figure 3 (bottom two panels), which shows the very same data set in the two complementary, PNA and ADJ, age scales just like in the top panels. The longest P1 peak latencies (260–318 ms) could be recorded in preterm or very young full-term infants between −1.8 and 3.0 ADJ weeks (i.e., immature state). The P1 peak latency decreased gradually until 15 to 16 ADJ weeks, when the latency reached the adult-like values at approximately 95 ms (i.e., mature state). Nonlinear logistic curve fitting and residual analysis confirmed that the maturation of this particular developmental index could be modeled by a single logistic function when the ADJ scale was used ($F_{1,357} = 1.08$, $P = 0.2996$, $R^2 = 0.9195$) and a common model could not be established if data were plotted on the PNA scale ($F_{1,357} = 148.84$, $P < 10^{-25}$, $R^2 = 0.5542$). The inflection point of the logistic function, which corresponds to the DW center, was given at 7.22 ADJ weeks. These results are compatible with the literature.

According to Figure 4, a linear correlation ($R^2 = 0.45$, $F_{1,240} = 172.1$, $P < 0.0001$) exists between P1 latencies and DRDC-VEP phases. The regression equation can be seen in Figure 4.

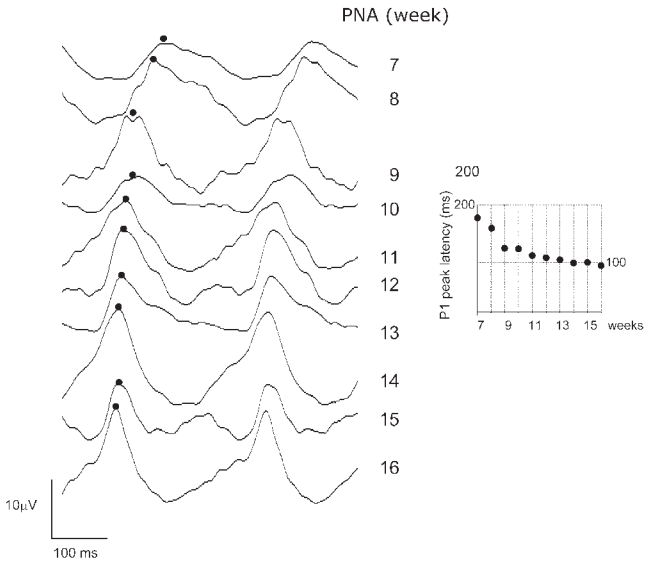

Figure 2. Representative averaged PR-VEP responses obtained from a full-term infant (B.C.) weekly. *Left*: Averaged RP-VEP traces. Two consecutive stimulation cycles are shown. The first P1 peaks of the two are indicated by *dots*. The stimulus frequency was 1.875 Hz (i.e., 3.75 r/s) and check size was 120 minutes of arc. PNAs (identical with ADJs in full-term infants) are marked on the *right side* of the traces. *Right*: The small inserted chart is a plot of the P1 peak latencies against ages in weeks for the records shown on the *left*.

Discussion

This is the first study describing age-dependent changes in the DRDC-VEP phases in infants after the onset ages of binocularity, implying acceleration in response timing. The most important new findings are as follows: (1) Although DRDC-VEP responses in adults at 1.875-Hz stimulus frequency are dominated by the first harmonic component,[30,34,37,39] in infants the significant component is typically found at the second harmonic frequency[10,34]; first and fourth harmonic components are never present before 6 months of ADJ. The first harmonic component becomes significant at older ages only. (2) The second harmonic component of the DRDC-VEP has a counterclockwise phase shift with age. The age effect is mild in full-term but robust in preterm infants. (3) Despite the weak correlation between age and VEP phases in full-term infants, curve fitting and analysis of residuals reveals that a common logistic function can model the ADJ-related VEP phases in the merged preterm and full-term infant groups, but the common model failed for PNA scale. This developmental pattern suggests that the marked counterclockwise phase shift in preterm infants is rather a preprogrammed developmental process, not influenced by extra visual experience. (4) The nearly identical DW centers on the ADJ scale (i.e., 6.98 and 7.22 weeks for the DRDC-VEP phase and P1 peak latencies, respectively) suggest that these two developmental indicators mature in the same DW. (5) Finally, the correlation between the P1 peak latency and DRCD-VEP phase suggests a common underlying developmental mechanism.

Development in Preterm Versus Full-Term Infants. Comparison of the development in preterm and full-term

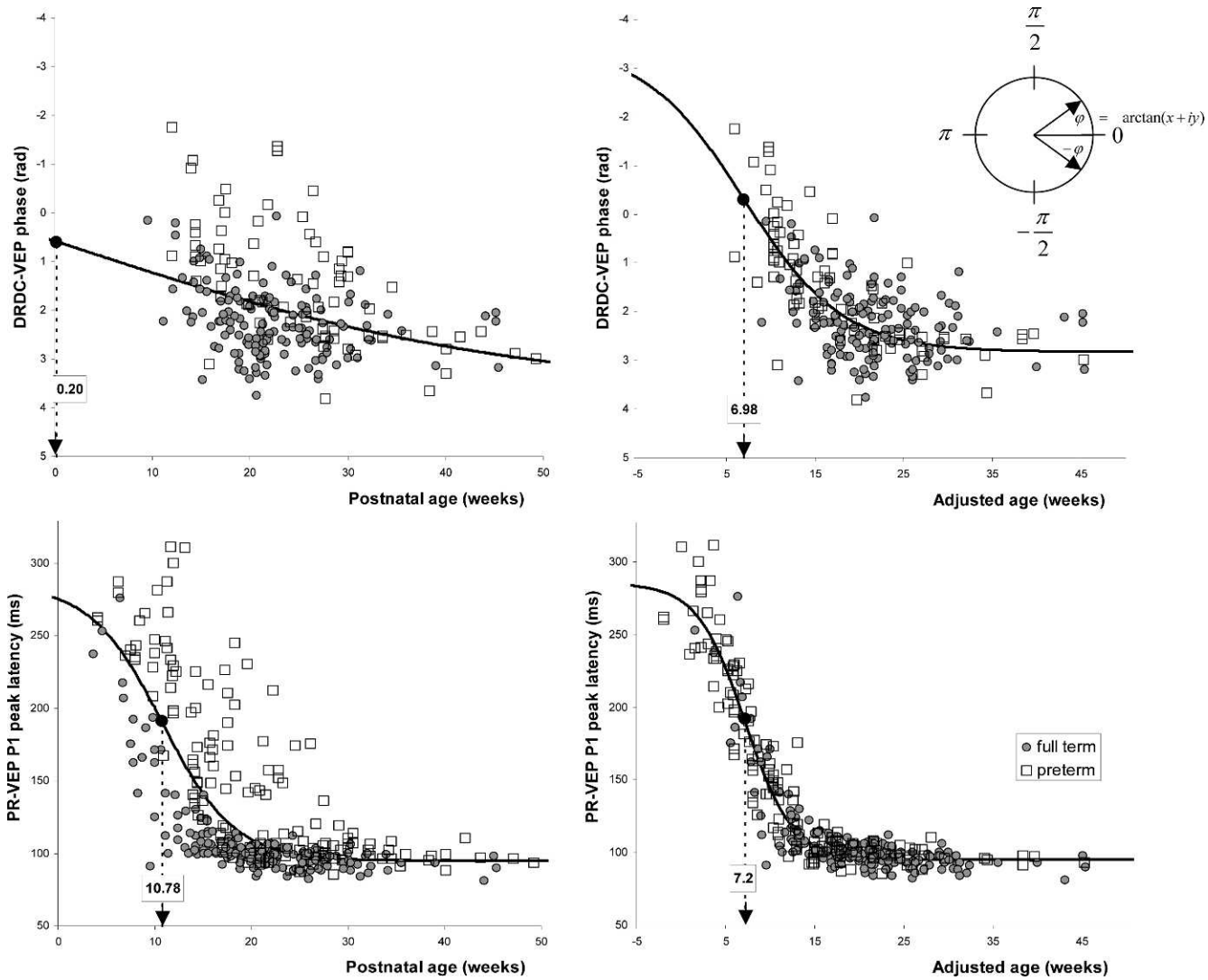

FIGURE 3. *Top*: The relationship between age and DRDC-VEP phases. DRDC-VEP phases of the second harmonic Fourier components (i.e., 3.75 Hz) of the DRDC fundamental frequency (i.e., 1.875 Hz) are plotted in rads as a function of ADJs and PNAs in weeks. *Bottom*: The relationship between age and PR-VEP P1 peak latencies. *Squares* represent preterm, whereas *circles* indicate full-term infants. The *solid curves* represent the common logistic fit to the merged preterm and full-term data set. For both DRDC-VEP phases and P1 peak latencies, common logistic fit could be established when the ADJ scale was used. *Dashed line arrows* project the DW centers (*large black dot* on the logistic function) to the age scale. The *framed values* above the *arrows* show the exact values for the DW centers in weeks, which are determined by the logistic fit parameter "c." Fitting the logistic curve in the very young age range where binocularity does not exist has theoretical (mathematical) meaning only; however, it clearly demonstrates the irrelevance of the calculated DW center when PNAs are used (*top left*).

infants is a basic experimental model that allows for the effect of experience-dependence of a visual function to be studied**.** Preterm birth may affect the structural and functional maturation of vision in many different ways; shorter intrauterine residence might delay or even deprive the development of the visual system, whereas earlier onset of visual experience may accelerate maturation of certain functions. When the development of a function is determined purely by ontogenetic factors, which are timed to the date of conception (i.e., the additional visual input has no impact), preterm infants are expected to show the same developmental pattern as full-term infants when data are plotted as a function of ADJ. Conversely, development of an extremely experience-dependent function shows overlap when its parameter is plotted as a function of PNA, and shows diversity when ADJ is used.[10,24,40–42]

Experience-Dependent and -Independent Visual Development. In a recent article, Jandó et al.[10] published clear-cut results about an experience-dependent visual development in human infants. The onset ages of DRDC-VEPs were very similar in the preterm and full-term infant groups when they were plotted as a function of PNA, indicating that the development of binocularity is notably influenced and accelerated by precocious exposure of visual experience due to earlier birth. At the onset of binocularity, differences in DRDC-VEP phases also were observed between preterm and full-term infants despite the same PNAs, which suggests an age-dependent maturation of these responses.[10]

Psychophysical and electrophysiological studies clarified that although visual experience is necessary, several visual functions develop without significant effects from visual experience.[10,24,42,43] The maturation of visual acuity, for instance, is dependent on the ADJ rather than on the PNA, so the additional visual experience does not accelerate it.[41,43–45]

In the present study, we report a counterclockwise shift of DRDC-VEP phase in preterm infants after the onset ages of

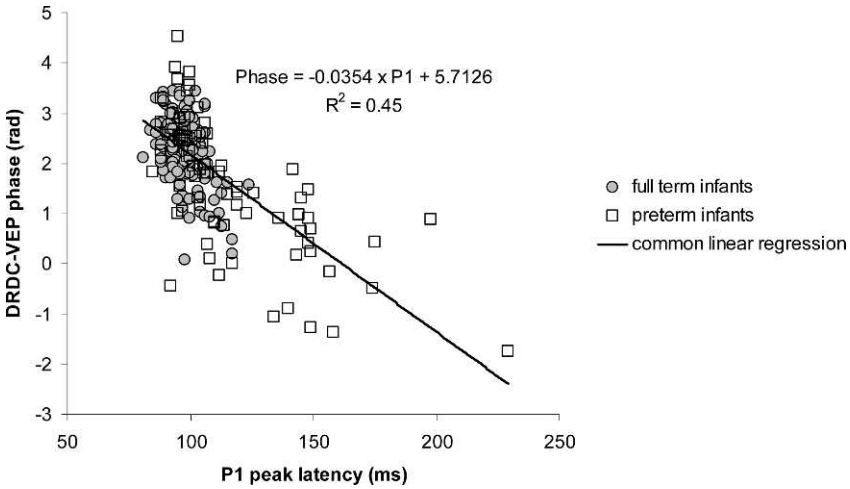

FIGURE 4. Correlation between P1 peak latency and DRDC-VEP phases. The *scatter plot* includes all preterm and full-term subjects where a DRDC-VEP response and PR-VEP response were recorded simultaneously in the same session. DRDC-VEP phase is plotted as a function of P1 latencies. The *squares* represent preterm, whereas the *circles* represent full-term infants. The *line* indicates a common linear regression line fit to the data set.

cortical binocularity. Phase data show a better overlap between preterm and full-term infants when ADJ was used. When comparing the P1 peak latency between preterm and full-term groups, a significant overlap is found when data were plotted as a function of ADJ, very similar to the phase data. The results regarding the P1 maturation are in accord with previous findings,[10,24] indicating that early decrease of P1 peak latency and DRDC-VEP phases are mainly determined by preprogrammed mechanisms and extra visual experience has no accelerating effect. The identical developmental pattern and the fact that DRDC-VEP phase and P1 peak latency maturation concur in the same DW suggest a correlation between the two parameters.

Indeed, we found close correlation between DRDC-VEP phases and P1 peak latency, which suggests that the changes of these developmental indicators may share common underlying neural mechanisms.

DRDC-VEP Phase, P1 Peak Latency, and Response Time. There is no agreement regarding the neuronal origin of P1; several authors concluded that the P1 VEP component has a striate and exrastriate generator.[46–49] Although P1 seems to be an index of relatively late visual processing stages, its peak time is closely correlated with the neuronal "response time" or "arrival time" of visual information in the cortex. There is a general agreement that a decrease in transient P1 peak latency or an analogous shift in ssVEP phase can be explained by shorter response time and/or faster retino-cortical processing of the visual information.[23,50,51] Decreased retinal illumination is one of the factors that increases P1 peak latency[39,52,53] and also introduces a clockwise shift in RP-VEP[51] and DRDC-VEP phases,[39] which will consequently elongate response time to the visual stimulus and slow down visual information processing in the visual system. In the present study, we found an opposite (i.e., counterclockwise) phase shift in DRDC-VEP phase and a decrease in P1 peak latency as a function of age, which suggests gradually shorter response time and faster retino-cortical and may be intracortical visual information processing in the brain during development.

It is known that the thickness of the myelin sheath highly affects the conduction velocity of the neuronal signals in nerves[54]; thus, myelination during development presumably accelerates signal transmission and reduces response time.[55] A number of anatomical and physiological studies demonstrated that myelination is not completed in the infant's brain at the time of birth and intense myelination takes place during early postnatal life.[26,27] The process of myelination begins at approximately the 28th to 32nd gestational week, and is terminated between 1 and 2 years of age.[20,22,56–58] Myelination is less intense at the beginning, but becomes rapid at approximately the 38th gestational week,[57] resulting in nearly adult-like P1 latencies at approximately the 15th ADJ week, followed by a long drawn-out latency decrease.[24] Besides myelination, several other factors add to the maturation of P1, including retinal development, synaptogenesis, and development of synapses.[25–27] The proportions of the contributing factors are still in question, however, with myelination probably being the most important.[55,59]

The difference in DRDC-VEP phases between preterm and full-term infants indicates that the binocular correlation processing system can work at different "speeds." In preterm infants, it works with slower response times at the same PNA in comparison with full-term infants. The marked acceleration of DRDC-VEP phases observed in the preterm infants in this study could be explained by the same factors that reduce P1 peak latency. The mild effect seen in full-term infants could be due to the later onset ages of binocularity. By the time the cortex becomes mature and susceptible for binocular stimulation (i.e., able to generate DRDC-VEP responses), the intense myelination period is already completed in full-term infants; therefore, the acceleration of the DRDC-VEP phases cannot be obviously detected. In preterm infants, the cortex becomes mature for binocular stimulation at earlier ADJs, when the intense myelination period is not yet complete. In this early stage, the binocular information processing system works with slower response timing, but as the myelination progresses, DRDC-VEP phases show marked acceleration that can be easily observed, as it was followed up in this study.

CONCLUSION

The counterclockwise phase shift of DRDC-VEPs and the rapid decrease of PR-VEP P1 peak latencies observed in this study occur at nearly identical postconceptual (i.e., ADJ) ages. This phase change is most probably due to the same developmental factors that result in the decrease of P1 peak latency. Both the phase shift and P1 peak latency are likely footprints of myelination and gradually faster retino-cortical (may be intracortical) processing of binocular information in the visual system. Both developmental indicators PR-VEP P1 peak latency

and DRDC-VEP phase show a developmental pattern that suggests an intrinsic, experience-independent developmental process in the background. The most important underlying mechanism is presumably the intense myelination of the optic nerves and tracts in the first 16 to 18 postnatal weeks. The phase change is robust in premature infants because of the earlier onset of binocularity. In most full-term infants, the phase shift cannot be detected because the binocularity appears when the early phase of the rapid myelination period is over.

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