The impact of visual experience on the development of stereopsis

Ph.D. thesis

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Pécs, 2014

I. Introduction

We are all born with a genetically determined developmental program, which can be modified by experience and learning. Both the genetic endowment („nature") and environmental factors („nurture") influence the development of an individual. Although there is a great deal of knowledge regarding the phylo- and ontogenetic plasticity of the neocortex, the precise nature of environmental impact on the newborn human brain is still one of the most controversial issues of neuroscience. . Here, we introduce a developmental model that directly compares preterm and full-term infants with respect to the onset of a particular function. Studying preterm infants helps to clarify the nature of developmental processes that ignite the onset of a function. Preprogrammed processes are indicated by an equivalent time of onset in preterm and in full-term infants, as expressed in adjusted age, whereas a delayed onset time is expected in preterm compared with full-term infants on a postnatal scale. Experience-dependent processes are indicated by a shorter onset time in preterm vs. full-term infants, as expressed in adjusted age, whereas an equivalent time of onset in preterm and in full-term infants is expected as expressed in postnatal age. A diplomatic balance between preprogrammed and experience-dependent processes would naturally fall in between these options.

Plasticity is the functional and structural reorganization ability of the nervous system that is an important physiological mechanism in normal development as well as in recovery after neural injury. During the ontogenesis there are time windows, when our brain develops certain functions and it is extremely susceptible to environmental stimuli and lack of appropriate stimulation (i.e. deprivation) at the same time. This time window is called critical period.

The leading model–system of experience-dependent brain development is binocular vision, also called stereopsis. Stereopsis provides accurate depth perception by aligning the views of the two eyes in some of the rodents and in most carnivores, primates, and humans. The binocular system is unique among other cognitive capacities because it is alike across a large number of species; therefore, a remarkable collection of molecular, cellular, network, and functional data is available to advance the understanding of human development ((Hubel, Wiesel et al. 1977; Crowley and Katz 2000) This system is also unique in its relatively abrupt onset during ontogeny. The onset of binocular function follows the emergence of eye-specific organization of the visual cortex into ocular dominance columns, which seem to develop with the initial guidance of intrinsic molecular and electrical signals (Crowley and Katz 2000; Huberman 2007). Later on, in a distinct phase of development called the "critical period", the ocular dominance columns become particularly open to alteration by extrinsic environmental signals (Hubel, Wiesel et al. 1977). The well-defined timeline of developmental events is another valuable characteristic of binocular vision (Sengpiel and Kind 2002), persistently bringing it into the limelight of studies on cortical plasticity.

To address the origin of early plasticity of the binocular system in humans, we studied preterm human neonates compared with full term infants. We asked whether (1) early additional postnatal experience, during which preterm infants have an about 2 moths of extra environmental stimulation and self-generated movement, leads to a change in the developmental timing of binocular function. (2) age dependent maturation of DRDC-VEPs, which is similar to the maturation of P1 latency. In a longitudinal study, we performed almost 700 examinations with visual electrophysiological methods in infants and toddlers between 2005 and 2012.

Visual evoked potentials

Visual evoked potentials (VEPs) are brain electrical responses recorded over the occipital cortex and evoked by using various repeated stimuli. VEPs are used in both the basic research and clinical practice. VEPs require relatively little or no cooperation from the patient and it is a noninvasive and painless technique, therefore it is appropriate for the examination of infants. The VEP protocol is useful to avoid difficulties and artifacts arising from behavioral estimation of onset times in a preverbal population, such as infants. VEPs can be used in various experimental paradigms depending on the aim of the study.

Based on the temporal frequency of the stimulation and characteristics of the response, there are two major types of VEPs: (1) steady-state and (2) transient. *Steady-state VEP responses* can be registered to periodic stimuli at relatively higher repetition rate. The response consists of series of identical sinusoid waveforms; the amplitude and phase of the harmonic frequency components are approximately constant over time (Regan 1977; Regan 1979). In *transient VEPs* the stimulus frequency is relatively low (i.e., less than 4 Hz) and the stimuli evoked neural response returns to the baseline before the next repetition comes. The wave morphology is usually complex and cannot be modeled by a single sine wave or set of a few sine waves.

During our VEP-study we applied: (1) checkerboard reversal and (2) dynamic random dot correlograms.

II. Our examinations

In the following section I describe two studies. Since the methods in the two studies were very similar including the subject selection, I describe subjects and methods together and then I go into details of the study specific issues.

1. Subjects

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. To avoid confounding factors from retinal or neurologic injury of the premature visual system, we only included “low-risk” premature infants, who were not affected by the consequences of long-term respiratory treatment or reanimation and did not have major disabilities resulting from, e.g., cerebral lesions.

Beyond the VEP-examination we also performed some simple orthoptic tests at the time of each experimental session. According to our protocol, children were examined regularly on a monthly basis from the age of 2 to 3 months until the onset of DRDC-VEP-s or beyond. In total, 656 examinations were performed on 341 children, 40% on preterm and 60% on term infants. 8.5% of the sessions (56 sessions) were excluded due to the lack of cooperation from the infants (due to sleep or refusal of wearing goggles). In those cases testing was repeated a few days later. In 6% of experimental sessions (n=40) some sort of pathology was noted in the history or was found during examination, therefore these data were excluded from the final analysis. The detailed inclusion criteria and the accurate number of included subjects are described later at the two studies.

1.a Age Terminology

Age terminology was used according to the recommendation of the American Academy of Pediatrics. (Engle 2004)
Gestational age is the time intervening between the first day of the last menstrual period and the day of birth, conventionally expressed as completed weeks.
Postnatal age (also called chronological age) is the time elapsed after birth, described in days, weeks, or months.
Adjusted age is used to describe preterm children up to the age of 3 years, and expresses the age of the infant from the expected date of birth in days.

2. Methods

2.a Visual stimuli

Stimuli were generated on standard personal computer and presented on three 19-inch (30x40°) cathode ray tube (CRT) computer monitor (Samsung Model 957 MB; Samsung Electronics Slovakia Ltd., Galanta, Slovakia). Spatial resolution of the monitor was 320 x 240 dots and the temporal resolution was 60 Hz.

2.a.a Dynamic random dot correlogram (DRDC)

To determine the onset age of binocular function, we used a visual evoked potential (VEP) protocol with dynamic random dot correlograms (DRDC) as stimuli. For dichoptic viewing, R26 low-pass (red) and YG09 band-pass (green) gelatin filters (Tobias Optic) were used. The schematic representation of the DRDC stimulus and representative averaged DRDC-VEP responses are shown on Figure 1. DRDCs alternated at 1.875 Hz between binocularly correlated and anticorrelated phases, resulting in a pulsating percept. In the anti-correlated phase, images are composed of 50% red and 50% green dots; therefore, dark dots in the green channel correspond to every bright dot in the red and vice versa. One dot in the image subtended 15 min of arc, the luminance of the bright dots through the filters was 5.85 ± 0.33 cd/m2, and the contrast was about 80%. (Marko, Kiss et al. 2009) DRDC stimulus, as opposed to stereograms contains no hidden cyclopean image. The percept of a correlated phase is a noisy surface in the plane of the monitor, a sort of “snowstorm” while during anti-correlated frames “woolly” depth can be perceived (Julesz, Kropfl et al. 1980). Subjects with functional binocularity perceived a 1.875 Hz pulsation; in case of monocular viewing or without binocularity, only a 30 Hz noise was visible. Alternation between the two phases can only be detected by a person who has functional binocularity. Random dot images were updated 60 times per second. The image change was synchronized to the monitor refresh cycle. Subjects with functional binocularity perceived a 1.875 Hz pulsation; in case of monocular viewing or without binocularity, only a 30 Hz noise was visible. (Jando, Miko-Barath et al. 2012).

2.a.b Pattern reversal (PR)

To assess the integrity of the visual pathway in the studied infants, we also measured the latency of the visual evoked response to pattern reversal stimuli (PR-VEP). Check size was 120 min of arc, and stimulation frequency was 1.875 Hz (3.75 rev/sec). This frequency was

identical to the one used during DRDC stimulation. The contrast was 95%, and the luminance of the white checks was 106 ± 5.04 cd/m^2. During data analysis the P1 latency was estimated.

2.b Experimental procedure

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. Gold-plated electrodes were placed over the Oz (active electrode) and Fz (reference electrode), according to the International 10-20 System for electrode placement (Odom, Bach et al. 2009), with Ten20 conductive paste. An electrode at Cz served as ground. 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 the monitor. In the darkened room the screens were the only light sources. To attract and maintain attention, a steady transparent monocularly visible image served as a fixation object at the center of the screen. Data acquisition was suspended during agitated or inattentive behavioral phases. 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. To notice recording false DRDC-VEPs, monocular control trials were also included in the protocol if the subject tolerated monocular covering.

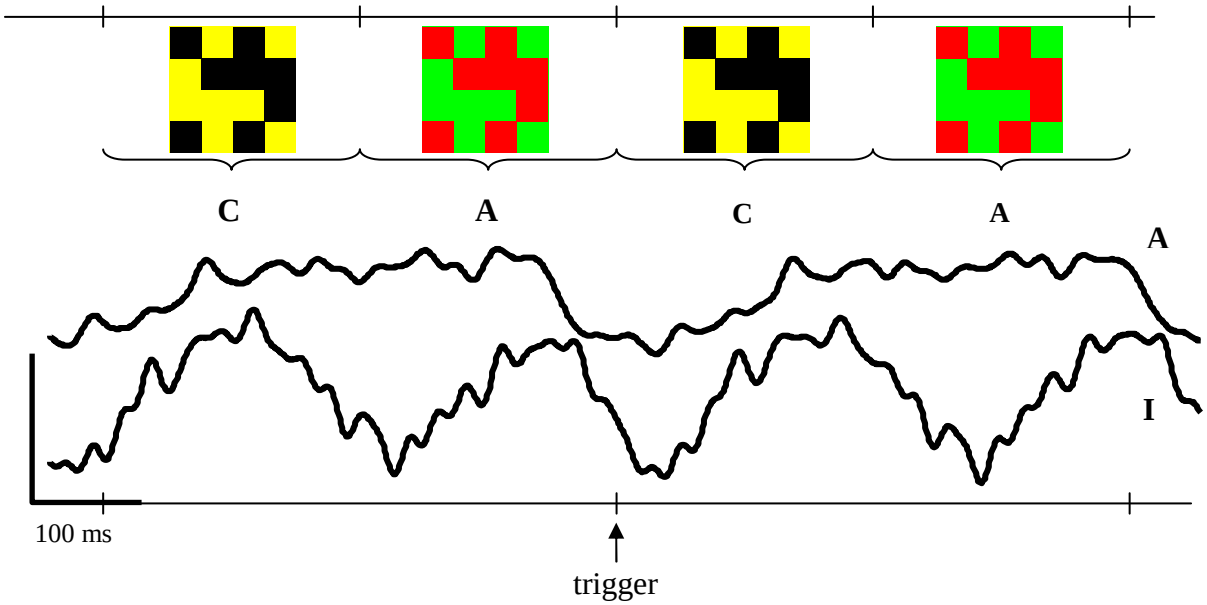

Figure 1. The generation of DRDC stimulus and representative averaged DRDC-VEP responses obtained from an adult (A) and an infant (I) using the same stimulus parameters. Steady state responses can be registered in both subjects; the frequency of the sine-wave like response shows an obvious doubling in infant, compared to that of adult.

2.c Data analysis

2.c.a DRDC-VEP

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 non-overlapping 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. This algorithm efficiently rejected the eye blink and other movement artifacts. If less than 10 epochs remained in the row data ranging between 70-200 ms after artifact rejection, data were categorized as not available.
Reliability of the records and detection of cortical binocularity was assessed by T^2circ statistics T^2circ is a statistical method designed to analyze repeating signals in the VEP records. The T^2circ 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. Although DRDC-VEP responses in adults at 1.875-Hz stimulus frequency are dominated by the first harmonic component, in infants the significant component is typically found at the second harmonic frequency. (Birch and Petrig 1996).
The level of significance for the T^2 circ statistic was established at $P < 0,01$ (Victor and Mast 1991). T^2_{circ} values are useful measure of response reliability: higher values represent more reliability (i.e., clearer correlation between signal and response). Failure of T^2circ to find statistical significance indicates that binocular visual stimulation is independent of brain activity.
The DRDC-VEP amplitude was defined as the double of the size of the Fourier vector at the fundamental frequency. This amplitude value corresponds to the peak to peak amplitude of the DRDC-VEP in the time domain. Phases of DRDC-VEPs were calculated from the real and imaginary part of the corresponding Fourier component of the DRDC-frequency as follows:

$$\text{PHASE } \Phi(\text{rad})=\arctan(x+iy);$$

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'. (Miko-Barath, Marko et al. 2014)

2.c.b PR-VEP

We carried out a similar analysis for PR-VEPs; however, 1.066 s epochs were used and the reversal rate (i.e., 3.75 Hz) was considered the fundamental frequency. Signal reliability test provided by T2circ was followed by a manual determination of the P1 peak latency. Records not passing the T2circ test were excluded from further analysis.

2.d Modelling the data

We used a least square algorithm to fit logistic functions to PR-VEPP1 latencies as a function of age, described by McCulloch at al. (McCulloch, Orbach et al. 1999). The logistic function was also used to fit the cumulative distribution of DRDC-VEP onset ages. 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.

II/A. The comparison of onset ages of cortical binocularity in preterm and full term infants

1. The objective of the study

The idea of testing preterm human infants in the DRDC-VEP protocol came from the late Bela Julesz, the inventor of random dot stereograms. Julesz and colleagues initiated the DRDC-VEP protocol in adults and infants in the 1980s (Braddick, Atkinson et al. 1980); however, the preterm study remained a plan until now. As stereopsis has an abrupt onset, this function is optimal for the examination of nature-nurture debate.
We asked whether early additional postnatal experience, during which preterm infants have an about 2 months of extra environmental stimulation and self-generated movement, leads to a change in the developmental timing of binocular function.

2. Calculation of the onset age

Infants were tested repeatedly, normally once in every month, Onset age of cortical binocularity was defined as the mean age between the last testing day without and the first testing day with the DRDC-VEP response. Onset ages were calculated both in postnatal and adjusted age. Using this approach the onset ages could be determined with about 1 month accuracy.

3. Definition of the preterm and full term groups

Fifteen healthy full-term (mean birth age, 39.07 ±1.33 wk; range, 37–40 wk; mean birth weight, 3,435 ± 494 g) and 15 healthy preterm (mean birth age, 31.27 ±3.03 week; range, 27–34 week; mean birth weight, 1,752 ± 683 g) infants were involved in our study. The postnatal age of infants at the first session was 10.73±1.47 and 11.66± 1.09 wk for the full term and preterm infants, respectively. Infants were tested repeatedly, normally once in every month (average repetition rate was: 4.92 ± 0.52 wk).

4. Results

4.a DRDC-VEP

Onset ages of binocular function based on DRDC-VEP responses are shown in Fig. 3. On the adjusted age scale, the two developmental curves are non-overlapping. Onset time is 1.99 mo for preterm and 3.50 for full-term infants [Student $t(28) = 4.46$, $P < 0.001$; Kolmogorov–Smirnov (KS) test: $P=0.0011$]. As expressed in PNA, preterm and full-term groups have overlapping developmental functions, and onset times are 4.07 mo for preterm and 3.78 mo for full-term infants [Student $t(28) = 0.578$, $P = 0.57$; KS test: $P = 0.5886$, not significant]. This pattern of results clearly indicates that the developmental timing of the onset of the DRDC-VEP response is experience-dependent and not preprogrammed in the tested age ranges. Preterm infants make almost full use of the extra stimulation time, and the evoked response to binocular correlation appears at around the same time after birth as in full-term infants. Since the first, or higher than second harmonic components rarely showed significance, we considered and accepted the existence of the second harmonic component as an ultimate marker of DRDC positive response (i.e., existence of cortical binocularity). The phases for full terms and preterms were significantly different from each other [$F(2,3098) = 34.36$; $P < 0.001$] at the onset of DRDC responses, suggesting an age-dependent processing

time of DRDC-VEPs. This suggests an age dependent maturation of DRDC responses similar to that of PR-VEPs.

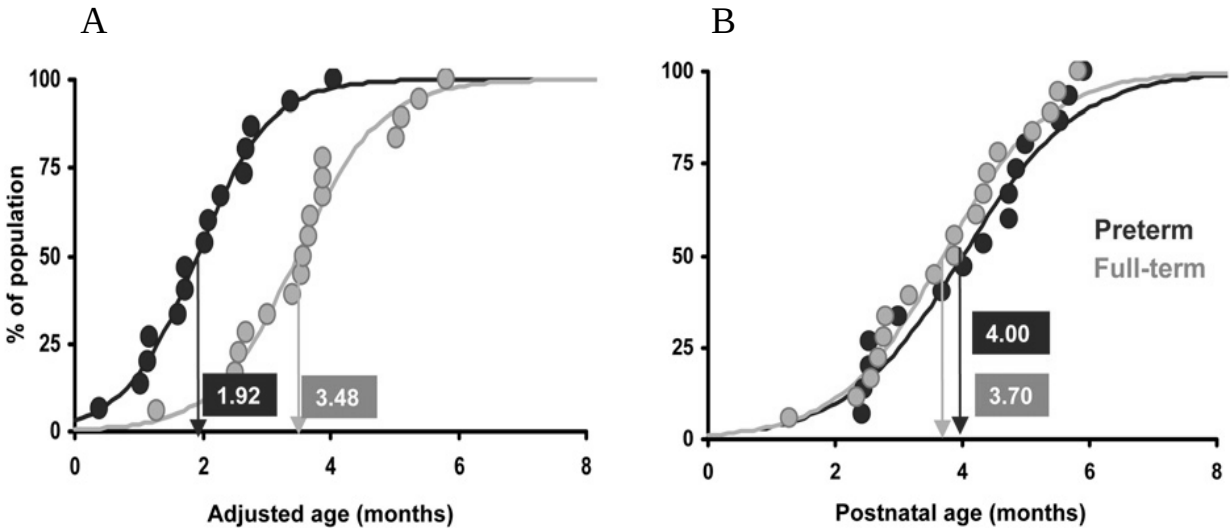

Figure 2. Results of the DRDC-VEP experiment. (A) Cumulative distribution of the onset times of DRDC evoked VEP responses in preterm (dark grey coloring) and full-term (light grey coloring) infants on an adjusted age scale. Dots represent the percentage of the population presenting DRDC response at a particular age, with a logistic curve fitting. Onset age of each population is estimated by the age at which 50%of the infants are responding to DRDCs. The preterm population has an earlier onset on this scale. (B) Data represented on a PNA scale. Estimated onset age is alike for preterm and full-term infants. This pattern of results clearly indicates experience-dependent development of cortical binocularity. (Jando, Miko-Barath et al. 2012)

4.b PR-VEP

Maturational curves for P1 latency in the PR-VEP response are shown in Fig. 4.

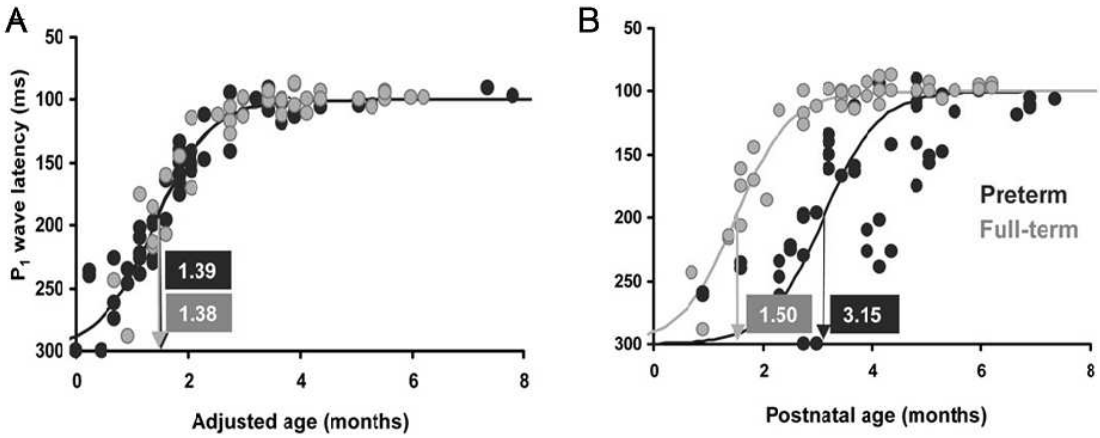

Figure 3. Results of the PR-VEP experiment. (A) Distribution of P1 wave latencies as a function of adjusted age. Dots represent individuals measured at different ages, with a logistic curve fitting. The greatest change in development (steepest part of the curve) occurs at the same age in preterm (dark grey) and full-term (light grey) infants. B. Data represented on a postnatal age scale: the maturation of preterm infants is delayed. This pattern of results clearly indicates preprogrammed development of the PR-VEP response.

On the adjusted age scale, the two curves fully overlap, and the most rapid change occurs at 1.52 months for preterm and at 1.50 mo for full-term infants [$F(80)=0.0159$; $P=0.9$, not significant]. On the postnatal age scale, preterm and full-term groups have non overlapping curves, with the most rapid change at 3.40 mo for preterm and at 1.62 mo for full term infants [$F(80)=56.1$; $P < 0.0001$], with a 1.78 mo difference between groups, which corresponds to the mean gestational age difference (1.79 mo) between our preterm and full-term groups. This pattern of results is exactly the opposite of the one for DRDC-VEP and indicates that P1 latency in the PR-VEP response is not determined by experience; it is fully preprogrammed. The timing of cell maturation and myelination of the visual pathways, as indicated by this response latency, is not advanced by the extra stimulation time in preterm infants. The results are in agreement with the literature, and clearly demonstrate that VEP latencies are independent of visual experience. (Roy, Barsoum-Homsy et al. 1995)

II/B. The post-onset maturation of DRDC-VEP in preterm and full term infants

1. The objective of the study

In our previous study we 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. To study the nature of this maturation we examined the phase of DRDC-VEP in a retrograde manner on our data recorded between 2007 and 2012.
The objectives of the present study were:
(1) to examine 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.

2. Definition of the preterm and full term groups

From the data of approximately 650 sessions, data were chosen according to the following inclusion criteria:
(1) Presence of statistically significant DRDC-VEP and PR-VEP responses.
(2) Lack of major internal, neurological, or organic ophthalmologic symptoms. For the preterm group, no or at most stage II retinopathy of prematurity. No history of intraventricular hemorrhage or periventricular leukomalacia.
Most of the first visits were scheduled between the second and sixth postnatal months. After the first year, some of these infants were examined yearly and followed up to 5 years of age.
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.

3. 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 adjusted age). 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. In total, 86 and 156 measurement sessions were included in the final analysis in preterm and full term infants, respectively.

Figure 4 shows representative averaged DRDC-VEP of an adult and a preterm infant. The first nine traces on the left panel 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. 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 5. 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 around 25-30 adjusted weeks. When preterm and full-term DRDC-VEP phases are plotted as a function of adjusted age 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 postnatal age (Fig. 3, top left). In order to explore age related changes in detail, linear and non-linear 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 (adjusted and postnatal ages). The regression coefficients (R^2) were slightly higher for preterm infants but did not exceed 0.24 in any group vs. 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 adjusted ages (R^2=0.68) or postnatal ages (R^2=0.52) were used as independent variables, which is a significant improvement compared to the linear model. For full-term infants the nonlinear approximation did not show significant improvement (R^2=0.12 for adjusted and R^2=0.11 for postnatal ages). When preterm and full-term infant data was modeled together, a common logistic fit could be established as a function of adjusted (R^2=0.5). The overall maturation process of P1 peak latency can be seen in Figure 5 bottom two panels, which show the very same data set in the two complementary, postnatal and adjusted 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 adjusted weeks (i.e., immature state). The P1 peak latency decreased gradually until 15 to 16 adjusted 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 adjusted scale was used ($F_{1,357}$=.08, P=0.2996, R^2 =0.9195) and a common model could not be established if data were plotted on the postnatal age scale ($F_{1,357}$=148.84, P < 10_25, R^2= 0.5542). The inflection point of the logistic function, which corresponds to the developmental window center, was given at 7.22 adjusted weeks. These results are compatible with the literature.

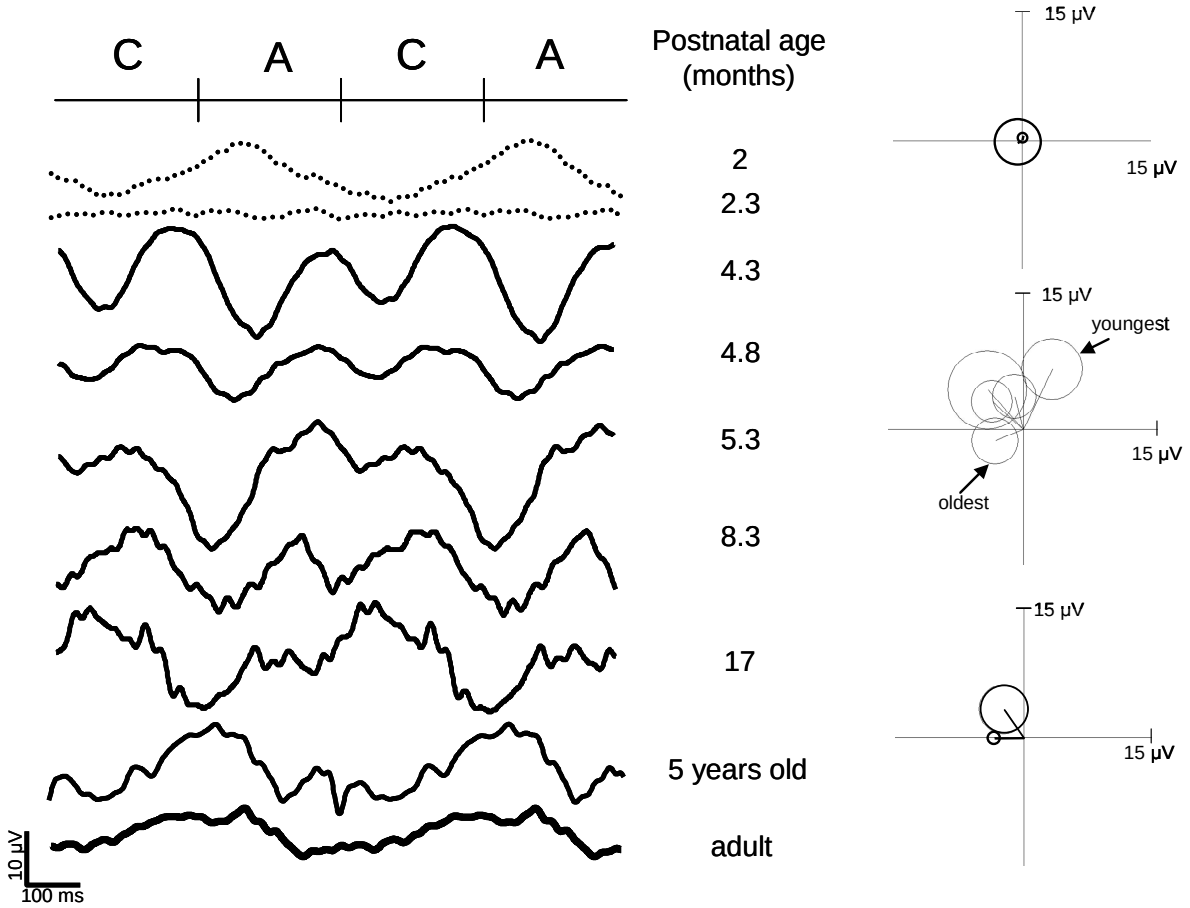

Figure 4.Representative averaged DRDC-VEP responses. Data were obtained at different ages from preterm infant and an adult. *Left:* Averaged DRDC-VEP traces. Letters ‘‘A’’ and ‘‘C’’ mark the anticorrelated and correlated phases of the DRDC stimulus, respectively. The alternation rate of the two phases (i.e., stimulus frequency) was 1.875 Hz. Postnatal 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 2, 2.3, 4.3, 4.8, 5.3, 8.3, and 17 months were recorded from preterm. *The right panel* shows the vectographic representation of the DRDC-VEP records seen on the left. 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. First panel: 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. Second panel: The second harmonic components of preterm infant’s VEPs (4.3–17). 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 (4.3 months) to the oldest age (17 months). Third panel: First harmonic Fourier component in the 5-year-old preterm child’s and adult’s control DRDC-VEPs.

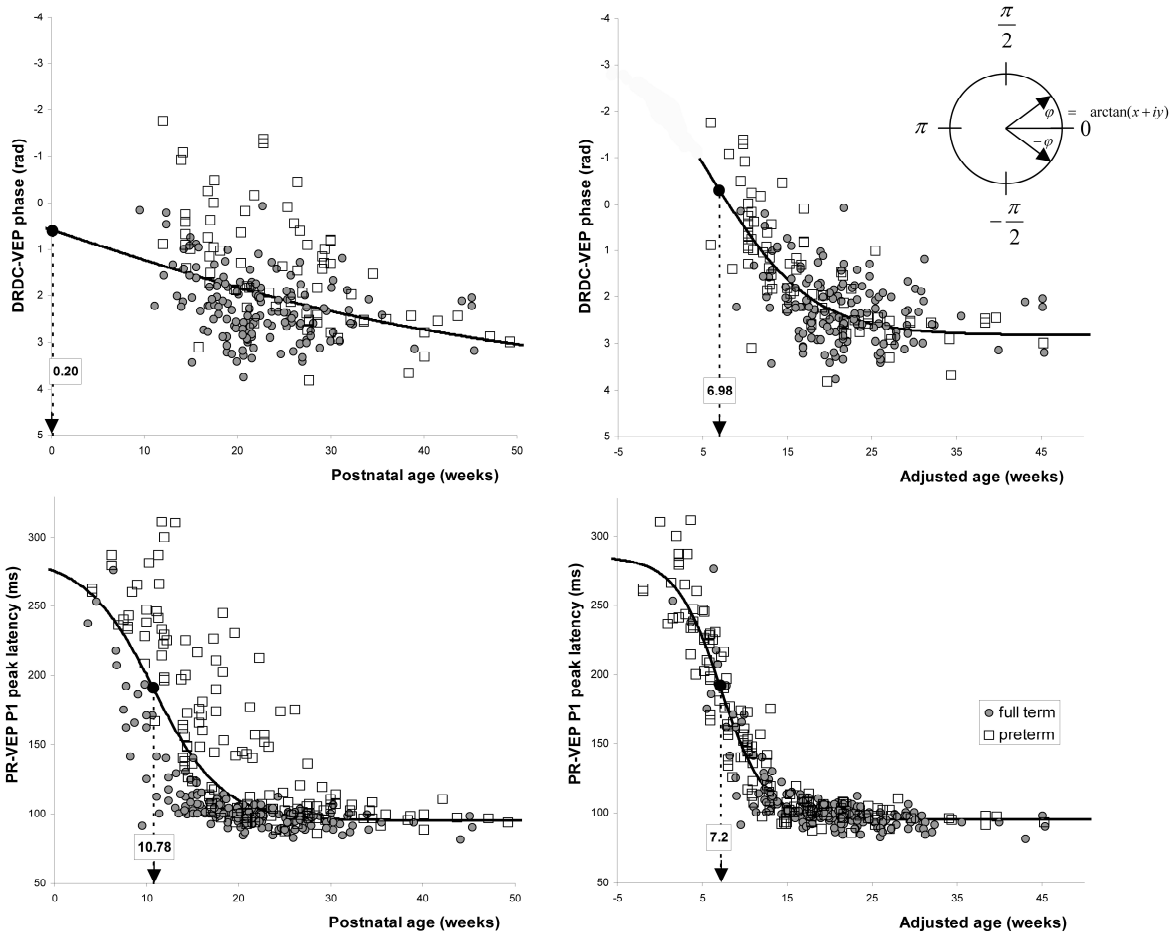

Figure 5. *Top panels:* The relationship between age and DRDC-VEP phases. DRDC-VEP phases of the 2nd harmonic Fourier components (i.e., 3.75 Hz) of the DRDC fundamental frequency (i.e., 1.875 Hz) are plotted in rads as a function of adjusted and postnatal ages in weeks. *Bottom panels:* The relationship between age and PR-VEP P1 peak latencies. Squares represent preterm, while 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 adjusted age scale was used. Dashed line arrows project to the most intense point of the development (the so called *developmental windows centers*) to the age scale. The framed values above the arrows show the exact values for the developmental windows centers in weeks.

According to Figure 6, a linear correlation exists between P1 latencies and DRDC-VEP phases (R^2=0.45; F(1,240)=172.1; p<0.0001). The regression equation can be seen in Figure 6.

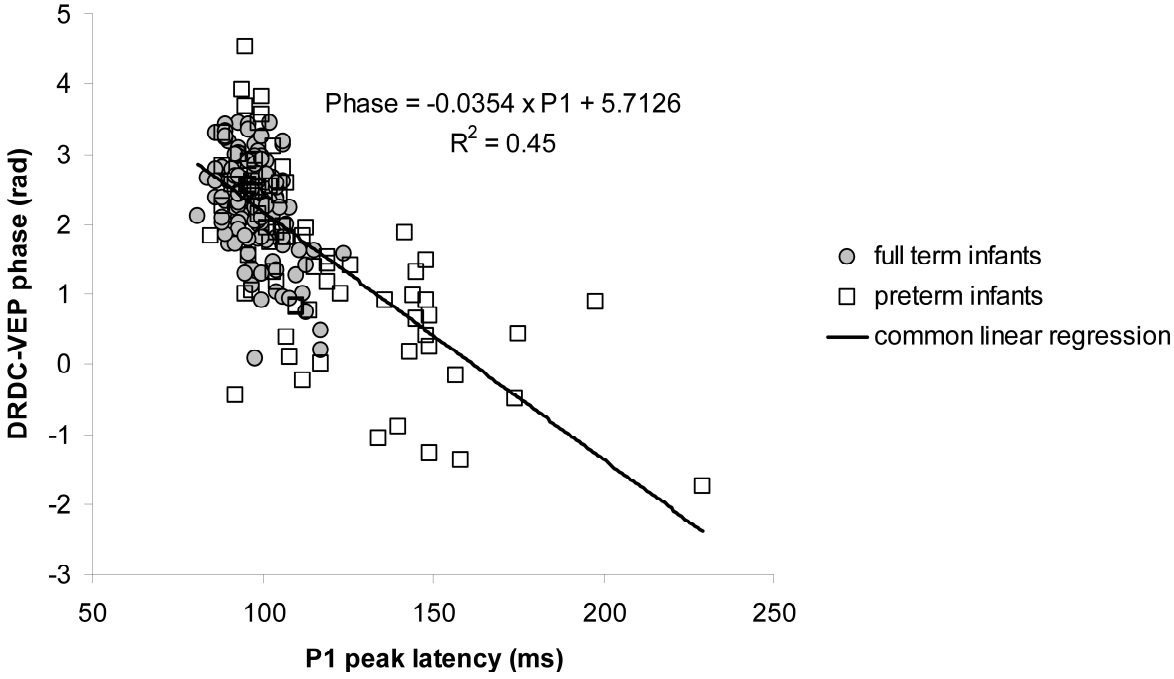

Figure 6. The correlation between P1-peak latency and DRDC-VEP phases. The scatter plot includes all preterm and full-term subjects where a DRDC-VEP response and PR-VEP response were recorded simultaneously in the same session. DRDC-VEP phase is plotted as a function of P1 latencies. The squares represent preterm, whereas the circles represent full-term infants. The line indicates a common linear regression line fit to the data set. (R^2=0.45; F(1,240)=172.1; p<0.0001).

III. Discussion

A. Effect of precocious visual experience in preterm infants

We demonstrated that two indicators of normal visual development present widely different patterns in response to extra stimulation time in human infants born approximately 2 months before term. The onset age of binocular function, as measured by the visual evoked response to dynamic random dot correlograms (DRDC-VEP), appears to be at around the same time after birth in preterm (4.07 months) and full-term (3.78 months) infants. PR-VEP latency is not affected by premature birth, demonstrating that the maturation of the visual pathway follows a preprogrammed developmental course. Despite the immaturity of the visual pathway, binocular function, involving cortical processing, seems to be open for experience-dependent changes right after birth even in premature infants.

Past work on the visual development of preterm infants (Weinacht, Kind et al. 1999) has not demonstrated experience-dependent cortical development so clearly. The lack of conclusiveness in earlier studies is mainly attributable to the less abrupt onset of the previously studied mechanisms, which makes conclusions more difficult to be drawn, although indications that development is affected by variations in visual experience exist. With respect to the development of binocular function in other vertebrates, experience dependency is rarely tested under normal stimulation circumstances, such as in our study.

Preterm studies are not reasonable to consider in those species that are born with closed eyes and have a relatively short gestational period (e.g., ferrets, cats). The most commonly used experimental manipulations, mimicking naturally occurring human clinical conditions, are dark rearing, monocular form deprivation (by limiting the view of one eye), or induced misalignment of the two eyes. These usually lead to reversible reorganization of cortical ocular dominance columns in the critical period (Hubel, Wiesel et al. 1977; Crowley and Katz 2000; Sengpiel and Kind 2002; Huberman 2007)

It is assumed that the numerous molecular mechanisms uncovered with the above manipulations reveal processes that normally establish (modify and stabilize) synaptic connections in the visual cortex. Although ocular dominance columns may not directly be linked to binocular function (Cumming and Parker 1997), column formation generally precedes the onset of the critical period and stereopsis in those species where the columns exist (Hubel, Wiesel et al. 1977; LeVay, Wiesel et al. 1980; Crowley and Katz 2000; Huberman 2007). Both classic and modern studies support the view that neural activity driven by visual experience is essential for transforming the early rudimentary cortical connectivity patterns into a mature network in all of the studied vertebrate species (Sengpiel and Kind 2002). The development of human ocular dominance column formation is not known; however, our results indicate that the mechanisms turning on the critical period and stereopsis are flexibly timed by external stimulation.

It is remarkable that the available 2 months of extra stimulation in preterm human infants lead to a clear advantage in cortical detection of binocular correlation. Despite the immaturity of the visual pathways, which is demonstrated by the stimulation independent P1 latency in our study, the visual cortex is ready to accept environmental stimulation right after birth. The results suggest that the developmental processes preceding the onset of binocular function are not preprogrammed and that the mechanisms turning on stereopsis are experience-dependent in humans.

The onset age of binocular function, as measured by the visual evoked response to dynamic random dot correlograms (DRDC-VEP), appears to be at around the same time after birth in preterm (4.07 months) and full-term (3.78 months) infants. PR-VEP latency is not affected by premature birth, demonstrating that the maturation of the visual pathway follows a preprogrammed developmental course. Despite the immaturity of the visual pathway, clearly demonstrated by the PR-VEP latencies, our DRDC-VEP data show that the visual cortex is remarkably ready to accept environmental stimulation right after birth. This early plasticity makes full use of the available extra stimulation time in preterm human infants and results in an early onset of cortical binocularity. According to our data, the developmental processes preceding the onset of binocular function are not preprogrammed, and the mechanisms turning on stereopsis are extremely experience-dependent in humans.

B. The post-onset maturation of DRDC-VEP in preterm and full term infants

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, in infants the significant component is typically found at the second harmonic frequency; first and fourth harmonic components are never present before 6 months of adjusted age. 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 adjusted age-related VEP phases in the merged preterm and full-term infant groups, but the common model failed for postnatal age 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 adjusted age (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 developmental window.
(5) Finally, the correlation between the P1 peak latency and DRCD-VEP phase suggests a common underlying developmental mechanism.

1. Development in preterm versus full-term infants

Comparison of the development in preterm and full-term infants is a basic experimental model which 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 is plotted as a function of adjusted age. Conversely, development of an extremely *experience dependent* function shows overlap when its parameter is plotted as a function of postnatal age, and shows diversity when adjusted age is used. (Jando, Miko et al. 2012, Roy et al. 1994, Bosworth, Dobkins 2008, Bosworth, Dobkins 2009)

2. Experience dependent and independent visual development

In the present study we report a counter clockwise shift of DRDC-VEP phase in preterm infants after the onset ages of cortical binocularity. Phase data show a better overlap between preterm and full-term infants when adjusted age 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 adjusted age, very similarly to the phase data. The results regarding the P1 maturation are in accord with previous findings (Roy, Barsoum-Homsy et al. 1995; Jando, Miko-Barath et al. 2012), 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 of DRDC-VEP phase and P1 peak latency maturation suggest a correlation between the two parameters.

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

3. DRDC-VEP phase, P1 peak latency and response time

There is a general agreement that a decrease in transient P1 peak latency or an analogous shift in steady state VEP phase can be explained by shorter response time and/or faster retino-cortical processing of the visual information. (Regan 1988) In the present study, we found an opposite (i.e., counter clockwise) 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 (Huxley and Stämpeli 1949); thus myelination during development presumably accelerates signal transmission and reduces response time (Atkinson 1984). 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 (Magoon and Robb 1981; Brecelj 2003). The process of myelination begins at around the 28-32th gestational week and is terminated between 1 and 2 years of age ((Tsuneishi and Casaer 1997; Brecelj 2003; Madan, Jan et al. 2005).

Myelination is less intense at the beginning, but becomes rapid at around the 38th gestational week (Huppi, Warfield et al. 1998); resulting in nearly adult-like P1 latencies at around the 15th adjusted age week, followed by a long-drawn-out latency decrease (Roy, Barsoum-Homsy et al. 1995). Besides myelination, several other factors add to the maturation of P1 including retinal development, synaptogenesis and development of synapses (Magoon and Robb 1981; Roy, Barsoum-Homsy et al. 1995).

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 adjusted ages, 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.

IV. Conclusions

The onset age of binocular function, as measured by the visual evoked response to dynamic random dot correlograms (DRDC-VEP), appears to be at around the same time after birth in preterm (4.07 months) and full-term (3.78 months) infants. PR-VEP latency is not affected by premature birth, demonstrating that the maturation of the visual pathway follows a preprogrammed developmental course. Despite the immaturity of the visual pathway, clearly demonstrated by the PR-VEP latencies, our DRCD-VEP data show that the visual cortex is remarkably ready to accept environmental stimulation right after birth. This early plasticity makes full use of the available extra stimulation time in preterm human infants and results in an early onset of cortical binocularity. According to our data, the developmental processes preceding the onset of binocular function are not preprogrammed, and the mechanisms turning on stereopsis are extremely experience-dependent in humans.

According to the literature, the onset ages of binocularity coincides with the beginning of the critical period, therefore premature birth presumably shifts the critical period to younger ages. (Birch 2012) The stimulating effect of extra visual input underlines the necessity of early visual intervention in cases of amblyopia and other visual impairments to reduce the duration of abnormal visual experience. Our findings also suggest that the intervention should be timed to adjusted, rather than post natal age in preterm infants.

The counter clockwise 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., adjusted) 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 16-18 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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