Supporting Information

Jandó et al. 10.1073/pnas.1203096109

SI Text

Age Terminology. Age terminology was used according to the recommendation of the American Academy of Pediatrics (1).

GA is the time intervening between the first day of the last menstrual period and the day of birth, conventionally expressed as completed weeks.

PNA (also called chronological age) is the time elapsed after birth, described in days, weeks, or months.

Adjusted age (ADJ) is used to describe preterm children up to the age of 3 y, and expresses the age of the infant from the expected date of birth in days, weeks or months, e.g., the adjusted age (ADJ) of a 6-mo-old (PNA) preterm infant born 1 mo earlier than expected is 5 mo (Table S1).

Inclusion Criteria and Follow-Up of Infant Subjects. Infants were enrolled according to the following inclusion criteria:

i) General health. To ensure that all subjects were healthy, and to avoid the risk of permanent impairments affecting visual function (i.e., hypoxic lesions, impaired cerebral circulation, retinopathy of prematurity), only preterm and full-term infants who did not have congenital abnormalities, perinatal asphyxia, or other perinatal complications were participated in the study. Screening for metabolic diseases, cranial and abdominal ultrasound, brainstem evoked response audiometry (BERA), and otoacoustic emission (OAE) and orthopedic screenings were performed in all infants. In preterm infants, cardiologic examination, including echocardiography and neurological and developmental follow-up, were also carried out. Only infants without abnormalities (potentially) affecting visual and neurological development were included in the study.

ii) Regular appearance. Infants were tested repeatedly, normally once in every month; however, because of unpredictable conditions, e.g., illness, inconvenient weather conditions, lack of cooperation from the infant, etc., the examination could not always be accomplished on the scheduled date. If more than 8 wk elapsed between two consecutive examinations, infants were excluded from the study because of the added uncertainty in determining onset ages for binocular function.

iii) Intact binocularity. To assess binocular vision and ocular motility, we used ophthalmologic screening methods (see below). Because the normal visual development of preterm and full-term infants was the subject of this study, if a binocular visual disorder or an ocular motility problem was suspected in a subject at the regular screenings, the data of the infant were excluded from the final analysis. Because the lack of the DRDC-VEP response after a certain age is a sign of ophthalmological abnormalities and abnormal binocular vision (2), we also excluded those infants in a post hoc manner whose DRDC-VEP did not appear until the 68th PMA week.

All enrolled preterm infants went through a monthly routine pediatric ophthalmoscopy, and all infants had a detailed ophthalmologic test between 6 mo and 3 y of age at the Department of Ophthalmology, University of Pécs (test of fixation and ocular motility and pupillary reactions; Brückner, Hirschberg, and cover test; ophthalmoscopy; and retinoscopy). Because of the careful preselection of the subjects, none of the enrolled 15 preterm and 15 full-term infants showed any sign of visual disturbance or visible morphological changes indicating pathological conditions. They all had intact vision and had reached normal binocular function by the end of their enrollment in the study.

Modeling the Data. We used a least square algorithm to fit logistic functions to PR-VEP P_1 latencies as a function of age, described by McCulloch at al. (3). The logistic function (Fig. S1) was also used to fit the cumulative distribution of DRDC-VEP onset ages, where a represents the difference between the highest and the lowest values, d represents the minimum value of the function. Location of the inflection point is defined by c, whereas b correlates with the slope at the inflection point. The same logistic function was applied for modeling P_1 latencies and the cumulative distribution of DRDC onset ages; however, there are slight differences in the interpretation of the parameters. For both P_1 latency and DRDC-VEP, c is the onset age and d is the mature asymptote latency or 0% for P_1 and cumulative distribution model, respectively. Parameter a represents the difference between the mature and immature asymptote for the P_1 latency model; therefore, the immature asymptote P_1 latency is calculated as $d + a$. In the cumulative distribution model, a indicates that 100% of the population shows significant DRDC-VEP response. Parameter c has a positive value in the cumulative distribution model, because an increasingly larger proportion of the population bears the function as time goes on, whereas it has a negative value in the P_1 latency model, because immature P_1 decreases until it becomes adult-like.

Statistical Analysis. Residual analysis was used to determine the goodness of fit and to see whether full-term and preterm data can be described by a common function or by two significantly different functions. Residuals and the goodness of fit were calculated as follows:

$$res_i = y_i - f(x_i)$$

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

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

$$R^2 = 1 - \frac{SS_{res}}{SS_{tot}}$$

where y_i are 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 goodness of fit.

In the case of the cumulative distribution function of the DRDC-VEP response onset times, Student t test and the KS test can be applied to see if the mean onset times are statistically different between the preterm and full-term populations. On the other hand, the PR-VEP latency is a function of time (age) and not a cumulative distribution function (such as DRDC-VEP onset ages); therefore, simple comparative statistics cannot be applied. In the case of the PR-VEP latency, we tested the existence of a common model for preterm and full-term infants. First, the logistic function was fit to the common preterm and full-term dataset. Next, group residuals were compared by one-way ANOVA and two-sample KS test. When a common function could be fit to the data, both group residuals were distributed similarly around zero. When ANOVA and KS tests did not show 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 datasets can only be modeled by significantly different functions.

Accurate determination of all four parameters of the logistic function, especially the mature and immature asymptotes of P_1 latency, requires more data than available in 30 subjects. The mature and immature asymptote has already been estimated previously (see Table S2). These analyses revealed that mature and immature asymptote latencies could be rounded to 95 and 285 ms, respectively. Because the goal was to determine the onset ages of adult like P_1 latency, asymptotes were preselected, a and d parameters were set at 95 and 190, respectively (the cumulative distribution a was fixed at 100% and *d* was set to 0%). Therefore, the number of free parameters in the model was restricted to two, i.e., *b* and *c*.

Detailed Data Analysis. ***DRDC-VEP measurements.*** After the onset of cortical binocularity, stimulus-synchronic modulation could be detected in the scalp recorded EEG responses. The phase-locking between stimulation frequency and EEG signals could be successfully detected by the T^2_{circ} statistic mostly in the second harmonic component of the DRDC-VEP responses (Fig. S2). 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). Table S3 presents the curve fitting parameters of the cumulative distribution of DRDC onset ages.

PR-VEP measurements. After around 4 mo of adjusted age, VEP latencies evoked with 120 arc/deg check size are resembling to that of adults (92–100 ms). The maturation of the PR-VEP in this study (Table S4) confirms earlier results (3).

When data are arranged as a function of PNA, the model showed a 1.78 mo difference between groups, which is significant. This difference corresponds to the mean GA difference (1.79 mo) between preterm and full-term groups. In terms of adjusted age, the analysis did not show significant difference between groups (see Table S4).

1. Engle WA; American Academy of Pediatrics Committee on Fetus and Newborn. (2004) Age terminology during the perinatal period. *Pediatrics* 114:1362–1364.
2. Markó K, et al. (2009) Contrast independence of dynamic random dot correlogram evoked VEP amplitude. *J Vis* 9:8, 1–10.
3. McCulloch DL, Orbach H, Skarf B (1999) Maturation of the pattern-reversal VEP in human infants: a theoretical framework. *Vision Res* 39:3673–3680.

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

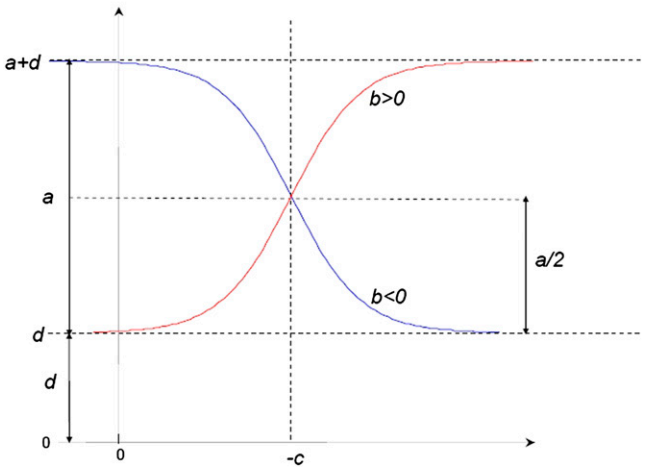

Fig. S1. The four-parameter logistic function. (*Upper*) General formula of the four-parameter logistic function. The *e* is the natural logarithm; the variables *a*, *b*, *c*, and *d* are constants determining the range steepness and *x* and *y* offset. (*Lower*) Logistic function curve when *b* is positive (red) and when *b* is negative (blue). Note that *b* is always multiplied by –1 according to the formula. Parameter *a* represents the range of the function, and *d* determines the vertical minimum value. The midpoint, where the function takes 50% of its full range, is an inflection point, where the second derivative becomes zero. Parameter *b* determines the steepness of the slope, whereas the midpoint location is determined by *c*.

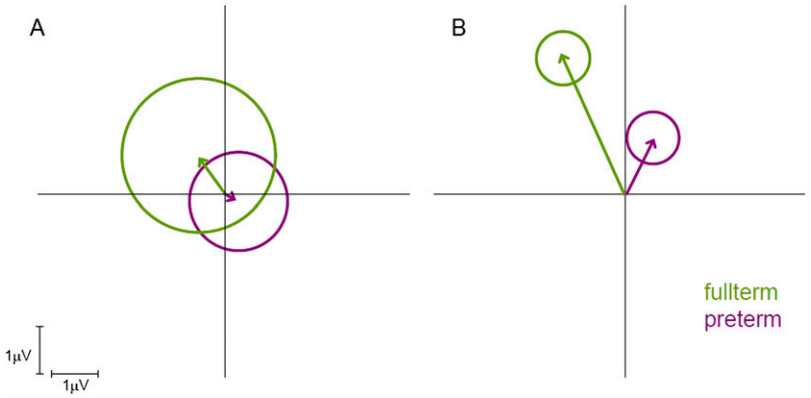

Fig. S2. Vectographic representation of DRDC-VEPs. Vectors representing the Fourier components of the DRDC-VEPs belong to the stimulus second harmonic frequency. The circles represent the confidence intervals of the average vectors at $P = 0.99$, derived from the T^2_{circ} statistic. (*A*) Before the onset of cortical binocularity. The average vectors are null vectors; the stimulus has no significant effect on brain electrical activity. (*B*) When the radius of the circle is smaller than the averaged vector length, the DRDC-VEP second harmonic frequency is phase locked to the stimulus, and it is significantly present in the electrical brain response. The phases for full terms and preterms are significantly different from each other [$F(2,3098) = 34.36$; $P < 0.001$], suggesting an age-dependent processing time of DRDC-VEPs.

Table S1. Age terminology

Age and scale	Days	Weeks*	Months*
PNA			
Symbol	PNA_{DAY}	PNA_{WEEK}	PNA_{MONTH}
Calculation	PNA_{DAY}	$PNA_{DAY}/7$	$PNA_{DAY}/(365/12)$
GA			
Symbol	GA_{DAY}	GA_{WEEK}	GA_{MONTH}
Calculation	$GA_{WEEK}x7$	GA_{WEEK}	$GA_{DAY}/(365/12)$
ADJ			
Symbol	ADJ_{DAY}	ADJ_{WEEK}	ADJ_{MONTH}
Calculation	$GA_{DAY} + PNA_{DAY} - 280$	$ADJ_{DAY}/7$	$ADJ_{DAY}/(365/12)$

The table presents different age calculations used in our study. PNA_{DAY} and GA_{WEEK} were used to calculate all other ages. ADJ, adjusted age.
*In general, we used age in months or weeks with a two-digit decimal precision in the figures and the text.

Table S2. Calculation of mature and immature asymptotes of the PR-VEP response

	a	−*b*	−*c* (onset age, ADJ_{MONTH})	d (mature asymptote ms)	R^2/df	Immature asymptote (ms)
Average	190.3	1.772	1.653	95.45	0.91/248	285.12
95% confidence limits	(174, 207)	(1.50, 2.04)	(1.53, 1.77)	(92, 99)		(266, 306)

Determination of mature and immature asymptotes based on a large data set, established previously. Because these asymptotes are not entirely independent of the equipment of a particular laboratory, the most reliable way of estimating them is to use the standards of the laboratory (1). In this study, we are relying on earlier measurements carried out at the University of Pécs Medical School and involving 250 subjects (age range: ADJ, 0–8 mo). The table provides the asymptotes based on these measurements.

1. Odom JV, et al. (2010) DL ISCEV standard for clinical visual evoked potentials (2009 update). *Doc Ophthalmol* 120:111–119.

Table S3. Cumulative distribution of DRDC onset ages (curve-fitting parameters)

	Model parameters		
Group	*b*	−*c*	Residual analysis (R^2/*df*)
ADJ PRE	2.09 (1.80–2.38)	1.99 (1.93–2.05)	0.98/13
ADJ FULL	1.73 (1.30–2.17)	3.50 (3.38–3.62)	0.95/13
PNA PRE	1.22 (1.02–1.42)	4.07 (3.93–4.20)	0.97/13
PNA FULL	1.32 (1.08–1.56)	3.78 (3.64–3.91)	0.97/13

When onset ages are plotted as a function of PNA, preterm (PRE) onset ages are delayed by 0.29 mo (~10 d), which is not a significant difference (see main text for the results of the *t* tests). When age is calculated as adjusted age (ADJ), cortical binocularity appears 1.51 mo earlier in preterm (PRE) than in full-term (FULL) infants, which is a significant difference. Values in parentheses are 95% confidence intervals.

Table S4. PR-VEP P_1 wave latency as a function of age (curve-fitting parameters)

	Model parameters		Residual analysis				
Group	−*b*	−*c*	R^2/*df*	*F*/*df**	*P*	KS	*P*
ADJ PRE	1.97 (1.62–2.31)	1.52 (1.44–1.61)	0.93/52				
ADJ FULL	1.97 (1.49–2.45)	1.50 (1.39–1.62)	0.90/39				
ADJ COMM	1.97 (1.70–2.24)	1.52 (1.45–1.58)	0.93/93	0.0159/80	0.9001	0.188	0.34
PNA PRE	0.95 (0.62–1.29)	3.40 (3.08–3.73)	0.65/52				
PNA FULL	2.04 (1.58–2.50)	1.62 (1.52–1.71)	0.92/39				
PNA COMM	0.89 (0.60–1.18)	2.47 (2.19–2.81)	0.47/93	56.1/80	7.9×10^{-11}	0.7543	1.2×10^{-12}

Values in parentheses are 95% confidence intervals. ADJ, adjusted age; COMM, common function; FULL, full term; PRE, preterm.
*ANOVA test.