# Flash visual evoked potentials at 2-year-old infants with different birth weights

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***Background:*** **Increased prevalence of visual impairments has been reported in preterm populations. However, it remains unclear about the long-term visual electrophysiological outcomes and their association with visual cognitive functions in premature infants. We investigated visual electrophysiological outcome of 2-year-old infants of different birth weights by flash visual evoked potentials (FVEPs) in order to explore the correlation between visual cognitive functions and FVEPs and to assess the application of FVEPs in evaluating the visual capability of an infant.**

***Methods:*** **The FVEPs of 77 infants, including 25 very low birth weight (VLBW) premature infants, 16 low birth weight (LBW) premature infants and 36 full-term infants, were tested with a visual electrophysiological testing device. Neuromotor development was assessed with the Bayley Scales of Infant Development, Second Edition (BSID-II). The visual cognitive functions were evaluated by scoring the proportion passed of 12 items chosen from the BSID-II for infants at 23 to 25 months of age.**

***Results:*** **The second prominent positive wave (P2) was the major component presented in all three groups. The mean latency of P2 in the VLBW, LBW and full-term groups was 149.65±23.79 ms, 129.39±8.70 ms, and 126.14±7.73 ms respectively. There was no significant difference in mean latency of P2 wave between the LBW and full-term groups; the mean latency of the P2 wave in the VLBW group was delayed more significantly than those of the other two groups. The difference in amplitude of the P2 peak to the preceding N2 peak (N2P2) between the three groups was not statistically significant. The latency of the P2 main wave was negatively correlated with mental developmental index (MDI) ($r'_{MDI}$ = -0.35) and visual cognitive capability ($r'_{visual\ capability}$ = -0.21).**

***Conclusions:*** **The latency of the P2 main wave on FVEPs was delayed more significantly in premature infants than in full-term infants at 2 years of corrected age. The visual functional development was delayed in premature infants, especially in VLBW infants (gestational age <32 weeks). The FVEPs were reported low but there were statistically significant correlations between measures of visual cognition and P2 peak latency. As a noninvasive and convenient method, FVEPs are useful in assessing certain aspects of an infant's visual development and visual function.**

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***Key words:*** **flash visual evoked potentials; preterm infants; visual development**





## Introduction

Advances in perinatal care during the last several decades have increased survival rates of extremely premature infants.[1] Premature infants are more likely to have retinopathy of prematurity (ROP), which remains a significant contributing factor in ophthalmologic impairment and even blindness; however, even for premature babies without ROP, their long-term visual outcomes are not satisfactory. In a study of 99 infants with a gestational age (GA) of <37 weeks, 46% had one or more of the following 3 conditions until they were 5 years old: strabismus, amblyopia, and refractive errors.[2] It was reported that both monocular and binocular visual acuities measured by the Teller Acuity Cards were poorer in premature infants than in full-term infants of the same chronological age (6 months).[3] Hebbandi et al[4] followed 69 infants with a GA of <28 weeks or birthweight of <1000 g; at 5 years of age, 43% of them had various ocular disorders. Cooke and colleagues[5] concluded that children born very premature (GA of <32 weeks) and without major neurodevelopmental disabilities still had an increased prevalence of

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ophthalmologic impairment such as visual perceptual deficits, motor defects, and cognitive defects when they attended primary schools. Therefore, the premature infants, especially those with GA of ≤32 weeks, had a significantly higher risk of developing visual functional disability.

The first 2 years of life are known to be marked by rapid anatomic development of the eyes and central visual pathways. Because of the limited cognitive ability of young children, many of the visual function tests cannot be used. It has been suggested that visual evoked potential (VEP) is an objective and noninvasive measurement that can be used in pediatric settings to evaluate maturity and integrity of the visual system, especially in infants. Although there are a number of previously published studies on the predictive value of VEPs in high-risk newborns,[6-13] it remains unclear about the long-term developmental status of VEPs in premature infants and whether the results of VEP tests are correlated with the performance of the visual cognitive functions. The purpose of this study was to investigate visual electrophysiological outcomes in infants of different birth weights at the corrected age of 2 years using flash visual evoked potentials (FVEPs) and to explore the correlation between visual cognitive functions and FVEPs. It is known that FVEP outcomes are associated with age of infants.[14] Therefore, normal infants of the same corrected age as the premature babies were chosen as the control group.



## Methods

### Subjects

Forty-one premature infants with a corrected age of 23 to 25 months were recruited as a study group from the Neonatal Department of the Children's Hospital of Fudan University. Infants with a gestational age between 32 and 36 weeks and birth weight between 1500 g and 2500 g were classified into a low birth weight (LBW) group; those with a gestational age between 28 and 32 weeks and birth weight between 1000 g and 1500 g were classified into a very low birth weight (VLBW) group. All premature infants eligible for the study had no birth asphyxia, ROP, brain damage or other serious complications according to their medical records.

Healthy infants of 23 to 25 months of age with a gestational age of 38 to 42 weeks and birth weight of 2500 g to 4000 g recruited from the Maternal & Children's Health Care Hospital of Luwan District in Shanghai served as a control group. They were born at term with normal perinatal development according to their medical records and Apgar score.

The parents of all the eligible subjects were invited to the Child Health Care Department of the Children's Hospital of Fudan University for an examination of their infants.

Ethical approval was obtained from the Research Ethics Committee of the Children's Hospital of Fudan University. Informed consent was obtained from all the parents.

### Recording techniques

All infants were tested during sound sleep. During the examination, the infants were lying on their parent's lap in a semi-dark and quiet room. Recordings were made from the occipital scalp 1-2 cm above the inion (OZ). The reference electrode was placed on the frontal scalp (FZ) and the ground at the mastoid. Standard silver-silver chloride disc surface electrodes were used, attached with water-soluble paste and tape to the testing sites. Impedance for each electrode was usually below 5 kΩ but sometimes below 10 kΩ. Stimuli were produced from light-emitting diode (LED) goggles and presented to the infants' closed eyes at a frequency of 2 Hz and a distance of 5 cm. Recordings were carried out with the APS2000 visual electrophysiological device (Chongqing Kanghua Technological Company, Chongqing) at 250 ms total sweep time. Band pass filters were set at 0.1-75 Hz. Each trial consisted of 100 responses. The infants' FVEPs were obtained by stimulating each eye. The trials were repeated two or more times to ensure reproducibility of the response. Responses with excessive artifacts were automatically rejected. All recordings were performed by the investigator (FJJ).

We used specific nomenclature for different FVEP components according to visual evoked potential standards (2004).[15] The second prominent positive wave was called P2 and the preceding prominent negative wave was labeled N2. Measurements of P2 amplitude were made from the P2 peak to the preceding N2 peak. We analyzed the latency, amplitude and number of waves present in the FVEPs.

### Assessment of neuromotor and visual cognitive ability

On the same day of the FVEP testing, neuromotor development was measured with the Bayley Scales of Infant Development, Second Edition (BSID-II) by the same examiner who performed the FVEP testing. Mental and motor scores were calculated by the Bayley II Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI). In the items set for 23-25 months of development, 12 items from the 36-item mental scale record of the BSID-II are associated with visual cognitive ability. Visual cognitive functions were evaluated by scoring the proportion of those 12 items

passed. The 12 items associated with visual cognitive ability are 115 (completes pink board), 118 (identifies objects in photograph), 120 (completes the reversed pink board), 123 (builds up a tower with six cubes), 128 (matches three colors), 130 (completes the blue board), 135 (builds a tower with eight cubes), 137 (matches four colors), 138 (builds up a train with cubes), 139 (imitates vertical and horizontal strokes), 143 (recalls geometric forms), and 144 (discriminates pictures).

### Social status of the mothers

As social status is known to affect cognitive outcome,[16] data on maternal education were collected. Mothers who completed secondary school or high school and technical or vocational training up to 18 years of age were classified as having a middle level of education, whereas those who completed some form of post-secondary education were classified as having a high level of education. The educational level of the remaining mothers was classified to be low.

### Data analysis

For normally distributed data, the mean and standard deviation (SD) were calculated. For non-normally distributed data, the median and quartile were calculated. ANOVA (analysis of variance), the Nemenyi test, or the Kruskal-Wallis test were used if appropriate (e.g., when comparing the difference in birth weight, gestational age, postconceptional age, latency or amplitude among the three groups). The Spearman's rank-order correlation coefficient was used to assess the association between the latency of P2 and MDI and the proportion of visual items passed. All of the analyses were conducted with SPSS 13.0 for Windows (SPSS, Chicago. IL). $P<0.05$ was considered statistically significant.

## Results

### Study groups

Examinations were completed for all of the 77 infants eligible for the study, including 25 VLBW, 16 LBW, and 36 full-term healthy infants. General characteristics of the infants are shown in Table 1. There were significant differences in the mean gestational age and mean birth weight among the groups, but no differences in the mean corrected age at the time of the study among the groups. All the premature infants in the present study were recruited from the Neonatal Department of the Children's Hospital of Fudan University. The hospital is a tertiary pediatric medical center in Shanghai that accepts seriously injured patients transferred from other hospitals. Consequently the number of LBW infants was relatively small.

### FVEP wave pattern

Visually evoked responses were elicited in all of the infants. A triphasic waveform with clear negative-positive-negative (N2-P2-N3) components was recorded in all the full-term and LBW infants. Wave N3 of 7 VLBW infants (28%) was not elicited, and the morphological differentiation of the waveform was poorer than those of the other two groups. With increasing birth weight, the morphology of the waves in FVEP became more distinct, and the latency of various components was shorter (Fig. 1). Although the FVEP showed a variety of waveforms, P2 remained the most consistently presented component in FVEP. It was also the most prominent wave.

**Table 1.** General characteristics of the study infants (ANOVA)

| Group | *N* | Mean corrected age | Mean BW (g) | Mean GA (wk) |
|---|---|---|---|---|
| Full-term | 36 | 24 mon 10 d | 3390±382 | 39±1 |
| LBW | 16 | 24 mon 6 d | 2007±404 | 34±1 |
| VLBW | 25 | 23 mon 28 d | 1259±335 | 29±1 |
| *P* value | | 0.418 | <0.01 | <0.01 |

LBW: low birth weight; VLBW: very low birth weight; BW: birth weight; GA: gestational age.

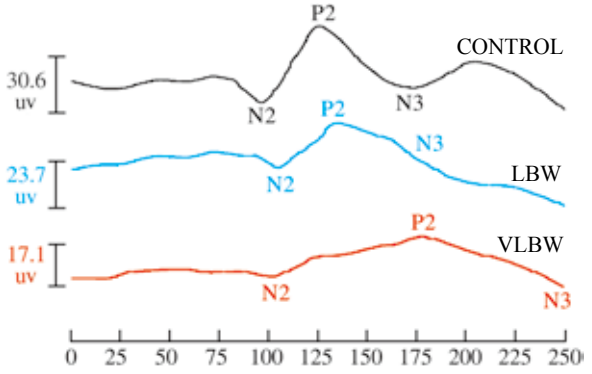


**Fig. 1.** The typical waveform of FVEP from individuals who are representative of each group. LBW: low birth weight; VLBW: very low birth weight.

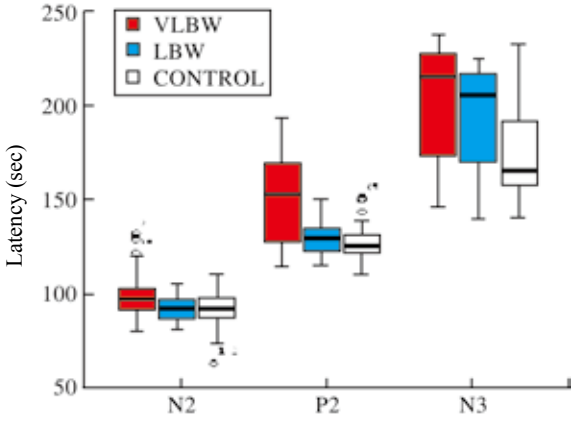


**Fig. 2.** The latency of N2, P2, and N3 in the three groups. LBW: low birth weight; VLBW: very low birth weight.

### FVEP latency

No significant differences were found in the latencies and amplitudes of the major waves between the right and left eyes ($P$>0.05). The average difference between the right and left eyes for latency of P2 was 1.15±5.59 ms. The mean latencies of P2, N2 and N3 are shown in Fig. 2, which demonstrates that the mean latencies of N2, P2 and N3 decreased with an increase of birth weight. We compared the latency of N2, P2 and N3 between any of the two groups with the Nemenyi test. There were no differences in the latency of N2 and P2 between the full-term and LBW groups ($P$>0.05), though there was difference in the latency of N3. There were significant differences in all of the FVEP components between full-term and VLBW infants ($P$<0.05). Between the VLBW and LBW groups, there were still differences in the latency of N2 and P2, but no difference in the latency of N3 ($P$<0.05).

### Amplitude of P2

The mean amplitude of N2-P2 in VLBW, LBW and full-term infants was 21.30±11.76 uv, 27.22±21.33 uv, and 24.86±12.26 uv, respectively. The difference in amplitude of N2-P2 between the three groups was not statistically significant ($P$>0.05, the Kruskal-Wallis test).

### Neuromotor and visual cognitive outcome

The mean and SD of the MDI, PDI, median and quartile of percentage of visual items passed in the three groups are shown in Table 2. We compared the MDI, PDI and the proportion of visual items passed between any of the two groups with the Nemenyi test. The neuromotor and visual cognitive abilities in the full-term group were significantly better than those of the other two groups ($P$<0.01). Interestingly, no significant difference in neuromotor development was found between the LBW and VLBW groups ($P$>0.05), except for the portion of visual items passed ($P$<0.05), suggesting that the visual cognitive function in premature infants is poor, especially in the VLBW group.

### Relationship between FVEP, neuromotor and visual cognitive development outcome

The most robust component of FVEP is P2 deflection. Because P2 latency value showed lower variability, it was used to make Spearmen's rank-order correlation coefficient analysis between the MDI and the percentage of visual items passed. The latency of the main wave P2 was negatively correlated with the MDI and visual cognitive capability ($r_{MDI}$ = -0.37; $r_{visual\ capability}$ = -0.23; $P$<0.01). After adjusting for mother's education, the latency of P2 was still negatively correlated with the MDI and visual capability ($r'_{MDI}$ = -0.35; $r'_{visual\ capability}$ = -0.21; $P$<0.01). It is hypothesized that infants with normal FVEP latency had better neuromotor and visual cognitive development outcomes.

**Table 2.** Mean and standard deviation of MDI, PDI, median and quartile of percentage of visual items passed in the three groups

| Group | MDI | PDI | Visual items passed [% ($P_{25}$-$P_{75}$)] |
|---|---|---|---|
| VLBW | 86±15 | 81±15 | 41.67 (22.92-68.75) |
| LBW | 91±12 | 82±10 | 66.66 (41.67-75.00) |
| Control | 108±8 | 102±13 | 83.33 (75.00-91.67) |

LBW: low birth weight; VLBW: very low birth weight; MDI: mental developmental index; PDI: psychomotor developmental index.

## Discussion

The visual evoked potential is an electrophysiologic signal that can be extracted from the electroencephalographic activity recorded from the human scalp and is generated by neurons in the brain in response to visual stimulation. Analyzing the waveform, latency, and amplitude of VEP may help evaluate the integrity of the retinocortical pathway and detect visual disorders in clinical settings. Usually, VEPs are elicited by patterned stimulus delivered by a black and white checkerboard, or by LED goggles. In this study, we opted for LED goggles rather than pattern reversal-evoked potentials because we were interested primarily in the conduction velocity and not in the spatial processing. As pattern-evoked potentials require highly accurate fixation and ocular movement stability, which is difficult to obtain for children at the age of 2 years, we also preferred flash-evoked potentials.

It is known that VEP amplitude yields important neurological information because the response varies with the stimulus intensity and shows the excitation of neural populations. Although the mean amplitude of waves in FVEP in full-term and LBW infants was higher than that in VLBW infants, there was no significant difference between the three groups. It is possible that the amplitude is variable within the population, especially in infants. The amplitude was easily disturbed by eye movements and effects from the environment. Compared with the amplitude, the latency was more valuable in visual assessment.

The first N2 and the following P2 wave were the most prominent and demonstrated the least intra-subject variability in latency. The consistency of the N2, P2 latency and its appearance in infants may play a role in assessing certain aspects of visual function. The present study showed that there was no difference in the latency of N2 and P2 between LBW infants at the corrected age of 2 years and full-term healthy children. These findings suggest that the visual outcome of

LBW infants is not poorer than that of full-term infants when they are examined at 2 years of corrected age. Researchers[2,3] also concluded that no difference was found in strabismus, amblyopia, refractive errors or visual acuity between the LBW and full-term infants of the same corrected age. However, we cannot yet conclude that LBW infants will eventually achieve normal visual functions. With time, more subtle, but important, impairments including abnormalities of stereopsis, visual movement, integration and contrast sensitivity may become apparent by school age that are not always identified in younger children. We therefore recommend that in addition to being examined in the first year of life, premature infants, especially the extremely premature infants, should have a long-term ophthalmological follow-up, regardless of ROP in the neonatal period. Otherwise, many infants with visual perceptual disorders may be considered to have normal vision, and their poor learning ability will be incorrectly attributed to poor intelligence.

This research also found that the N2, P2 and N3 latency of FVEP in VLBW infants was delayed than that of full-term infants, and their N2 and P2 latency significantly lagged behind that of the LBW infants. It suggests that the visual electrophysiological outcomes at 2 years of age in VLBW infants are poorer than those in full-term infants and even lag behind those of LBW infants. However, poor VEP response in these infants may not herald poor vision, but may indicate delayed maturation of the visual system. Previous studies[17-19] concluded that the incidence and degree of ophthalmologic impairment in preterm infants were negatively correlated with gestational age and birth weight, especially in VLBW infants with higher risk for ocular disorders. It was particularly interesting to find no difference in neuromotor development outcome between the LBW and VLBW groups, with the exception of the proportion passed in the visual cognition test. Geographical studies[5] have compared the intelligence in very preterm infants with or without visual defects. It was concluded that the overall intelligence was poorer in children with poorer contrast sensitivity, stereopsis, or acuity, but this was due to poorer performance on a performance intelligence quotient (IQ). There were no significant differences in verbal IQ. This finding supports the hypothesis that the immature visual system in preterm infants has an impact on functional visual capabilities. Both in monkeys and humans, the primary visual (striate) cortex has a critical period of neuronal and dendritic differentiation during the middle of gestation, thereafter a progressive appearance of synapses is seen.[20] Magoon and Robb[21] found that myelin was first seen in the optic tract and intracranial optic nerve at 32 weeks of gestation. They demonstrated the presence of myelin in the optic nerve near the globe at term. The reduced myelogenesis that is especially found in the optic nerve[22] will, in combination with the reduced synaptogenesis in the visual cortex,[23] restrict the integration of cerebral cortex inputs and might well account for the disturbances of visual cognitive function in VLBW infants. It is possible that premature exposure of the eye to the extrauterine environment during the critical period of visual system development affects the development of extremely preterm infants' eyes. According to electron microscopy observations, the ultrastructure of retinal ganglion cells was not fully developed until 32 weeks of gestation. The inactivity and reduced function of ganglion cells will affect the functioning of the retina. Furthermore, in addition to physical weakness and perinatal complications, the immature nervous system in extremely preterm newborns may adversely affect the visual central system, which results in visual dysfunction and reduced response to stimuli by the visual cortex. Whether the delayed development of visual function in preterm infants is permanent or temporary, long-term follow-up is still needed. Early intervention is necessary for preterm infants, especially for VLBW infants, since it can improve outcome.

Moreover, the current study demonstrated that the latency of the major component P2 of FVEP was negatively correlated with the MDI and the percentage of visual items passed. Although the correlation was weak, it may result from intelligence performance related to genetics, nutritional or environmental factors. Furthermore, the N2, P2 latency was delayed in VLBW infants than in full-term or even LBW infants, and the MDI and percentage of visual items passed were lower in the VLBW group than in the other two groups. This might suggest that the latencies of VEP components are valuable estimators of the visual pathway and cortical function. Some studies[24] also suggest that brain electrical activity is related to intellectual capacity, showing that shorter evoked potential latencies are correlated with better cognitive performance. Any delay or absence in VEP responses[25] is correlated to delayed cortical development and thus is a possible predictor of neurological outcome. In addition, some studies[26] state that VEPs correlate well with neurodevelopmental outcome in full-term infants with birth asphyxia.

We believe that no single clinical or laboratory assessment accurately determines outcome, particularly when more subtle deficits exist. Brain imaging techniques are helpful in the early identification of clinically significant brain damage; however, functional abnormalities in children may be clinically evident without documentation of any structural abnormality

on neuroimaging studies. In that situation, evoked potentials are able to assess the functional integrity of neuronal transmission.

The present study involved only a cross section of the infant population and was a comparison of the visual outcome between infants with different birth weights at the corrected age of 2 years. VEP was proposed as an estimator of visual cognitive function. We are planning to enlarge the sample and are designing a longitudinal study of the visual functions between preterm and full-term infants. It is important to obtain data during the key period of visual development in preterm and full-term infants and to identify the best time to apply FVEP for predicting and evaluating neuromotor outcome in children.

In conclusion, the latency of the main P2 wave measured by FVEP was significantly longer in premature infants than in full-term infants at 2 years of corrected age. The visual functional development was delayed in premature infants, particularly in VLBW infants. Those infants should be screened yearly, and earlier effective intervention is necessary. As a noninvasive and convenient measurement, FVEPs are helpful in assessing certain aspects of the visual development and visual function in infants.

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**Ethical approval:** This study was approved by the data inspectorate of China and by the regional committee for medical research ethics.

**Competing interest:** None declared.

**Contributors:** Feng JJ wrote the first draft of this paper. All authors contributed to the intellectual content and approved the final version. Xu X is the guarantor.

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