Visual Development in Very Low Birth Weight Infants

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ABSTRACT: Extremely preterm infants are at risk for neurodevelopmental problems and the visual system is particularly vulnerable. However, development of visual function in preterm infants with little or no retinal or neurologic injury has not been well defined. This study compared development of visual function in preterm infants without severe retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) to that of term infants at 5–7 mo corrected age. Twenty-one very low birth weight (VLBW) preterm infants (24–32 wk gestational age, weighing < 1500 g), and 22 healthy term infants were tested at 5–7 mo corrected age. Infants with any IVH/PVL and > Stage II ROP or Plus disease were excluded. Contrast sensitivity, grating acuity, and vernier acuity were measured using swept-parameter visual evoked potentials. Thresholds and maximum amplitudes were compared between groups. VLBW and term infants showed no differences in sensitivity for contrast (67.5 versus 63.8), grating resolution (12.4 versus 12.5 cpd) or vernier acuity (1.2 versus 1.0 arcmin). However, the amplitudes for swept contrast ($p < 0.03$) and swept vernier offset ($p < 0.04$) stimuli were higher in VLBW infants. Visual thresholds in VLBW infants without serious retinal or neurologic abnormalities were not significantly different from those of term infants, suggesting that increased visual experience does not influence visual sensitivity. The higher amplitudes in VLBW infants, suggests that visual experience may affect responses to suprathreshold stimuli. (*Pediatr Res* 60: 435–439, 2006)

Preterm infants are at higher risk for visual and other neurodevelopmental problems compared with infants born full-term (1–7). Those who are very low birth weight (VLBW ≤ 1500) are at particularly high risk due to an increased prevalence of retinopathy of prematurity (ROP) (2,5,6,8,9), intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL), among other complications (6,7,10–14). One area of the brain that is particularly vulnerable during the prenatal and neonatal period is the primary visual pathway (from the retina to the visual cortex) because it undergoes

significant development during this time (15–19) and therefore may be vulnerable to disruption by perinatal events. Several studies have shown an increased incidence of visual impairment with ROP (1,3,20,21) and with periventricular leukomalacia or hemorrhagic lesions (10–13). A number of studies have also demonstrated the co-existence of visual impairment in preterm infants with other neurologic deficits (4,6,14).

One issue that has not been adequately addressed has been whether visual problems in premature infants result solely from the effects of morbidity (e.g. ROP, IVH or PVL), or whether premature exposure to the visual world in itself may influence visual functioning. Studies using behavioral techniques have shown either no trend (22), a trend toward rapid development (23), or reduced acuity with preterm birth (24–26), while those employing electrophysiological techniques have shown either no trend (27) or a trend toward a more rapid maturation in preterm infants (28–31). However, research on this question is inconclusive because these studies have not excluded infants with ROP or cerebral lesions and have typically included a wide range of gestational ages from 26–36 wk. No study, to our knowledge, has examined visual functioning in a group of VLBW infants excluding for detectable cerebral abnormalities and significant ROP. Only by testing such a group can the effects of premature visual exposure alone be investigated.

Most previous studies have relied on a single measure to assess functioning of the entire visual system. If the effects of prematurity on visual pathway development are selective, as has been suggested (31,32), then a measure of a single visual function may fail to identify problems, or may not identify maximal differences. A more useful strategy would be to evaluate a number of different visual functions.

In the present study we assessed visual functioning in VLBW infants using the sweep visual evoked potential (sVEP) technique. This technique offers a quantitative electrophysiological method to assess the response to different types of visual stimuli by determining a sensory threshold (i.e., the smallest stimulus that produces a cortical visual response) as well as response amplitudes (i.e., the strength of the response) to suprathreshold stimuli (33). Visual thresholds are sensitive measures of visual function and may provide

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Abbreviations: IVH, Intraventricular Hemorrhage; PVL, Periventricular Leukomalacia; ROP, Retinopathy of Prematurity; sVEP, Sweep Visual Evoked Potentials; VLBW, Very low birthweight

independent information relative to suprathreshold measures such as the response amplitude to a clearly visual stimulus. The three different visual thresholds that were measured by this technique were contrast sensitivity, grating acuity and vernier acuity, each of which has different rates of development and has been studied extensively (34,35). Contrast sensitivity measures the ability to detect slight changes in luminance across space. It is the first of the three functions to mature, with sensitivity being half that of adult sensitivity by three months of age (34,36). Grating acuity is a test of spatial resolution, and measures the finest grating that can be resolved. Grating acuity thresholds reach half of adult values by eight months of age (37). Vernier acuity measures the minimum offset that can be detected between two line segments. Vernier acuity as measured by the sVEP is relatively poor during the first year of life (35). Behavioral and sVEP methods have shown that vernier thresholds reach approximately half of adult values by five years of age (38,39). Vernier acuity, since it requires recognition of spatial relationships, is believed to require a greater degree of cortical processing, and be a more meaningful indicator of higher-order visual cognitive function than other visual functions (35).

The goal of this study was to determine whether premature birth itself, in the absence of significant retinal or cerebral pathology, contributes significantly to alterations in visual development either by accelerating or delaying development.

METHODS

Participants. Twenty-one VLBW and 22 term control infants were each tested between five and seven months corrected age. Information regarding birth weight and gestation for the VLBW group was obtained from the medical record. Infants included in the VLBW group were 24–32 wk gestation, and weighed less than 1500 g (mean $\pm$ SD, 1102 $\pm$ 218.5g). The mean post-conceptual age of VLBW infants was 63.5 $\pm$ 4.3 wk (mean $\pm$ SD) and mean chronologic age was 34.9 $\pm$ 4.8 wk. Gestational age was assessed by the best obstetrical estimate using the last menstrual period and ultrasound examination. Mean chronologic age of the term infants was 26.9 $\pm$ 5.6 wk (67 wk post-conceptual age). Term infants were either self-referred by parents interested in participating or referred by pediatricians aware of the study. Data regarding the highest degree of ROP was recorded by the ophthalmologist, and IVH or PVL was determined by a head ultrasound examination, as recorded in the medical record. Inclusion criteria for VLBW infants included $\leq$ than Stage II ROP, no Plus disease and no IVH or PVL. Of the four study infants who had ROP, three had Stage I and one had Stage II. Term infants were assumed to be appropriate for gestational age based on information regarding date of birth and neonatal course obtained from parents.

The Institutional Review Board for human subject research at Stanford University approved the study. Signed informed consent was obtained from the parents of the enrolled infants after explanation of the study procedures.

EEG recording. The EEG (EEG) signal was amplified using a Grass® Model 12 amplifier (filter settings: 1–100 Hz at –6 dB) at a gain of 20,000. Active electrodes were placed over the infant's scalp at the occipital pole (location O_z of the International 10–20 system) and at locations 3 cm to the left and right of O_z (O₁ and O₂) to record evoked potentials (40). A reference electrode was placed at Cz and a ground electrode was placed at Pz (50 and 30% of theinion-nasion distance at midline, respectively). Electrode impedance was equal to or less than 5 k Ω . Data acquisition and stimulus presentation were controlled using an in-house software system (37,41).

Stimulus presentation. Stimuli were presented on a high-bandwidth monochrome monitor (MR2000HB-MED, Richardson Electronics) at a screen resolution of 1600 $\times$ 1200 pixels and a 60-Hz vertical refresh rate. The display was calibrated using a linear PIN-diode photometer with a photopic filter. The photo-diode was used to measure the luminance of a 5 $\times$ 5-cm² region of the display monitor. The luminance of this region was incremented in 128 steps over the 256 available voltage levels of the video card. These values were used to correct the nonlinear voltage to luminance function in software. The contrast of each spatial frequency was not measured.

The effect of the monitor on high spatial frequencies is small with the display used. The monitor has a very high video bandwidth and patterns were displayed at 1600 $\times$ 1200 screen resolution. The slight reduction in contrast that occurs at the highest spatial frequencies would have affected both groups of infants and should not have affected the results reported, especially given the relative steepness of the high spatial frequency portion of the contrast sensitivity function. There is no attenuation at the low spatial frequencies used to measure contrast sensitivity or vernier acuity.

The nonlinear relationship between voltage and luminance was corrected in software. Mean luminance of the display was 102 cd/m². A small toy, dangled 0–2 cm from the screen, directed the infant's attention to the monitor for the duration of the trials, each of which lasted 10 s. Viewing was binocular and the infants viewed the screen from 100 cm while seated in their parent's lap.

Contrast sensitivity was measured by presenting a phase-reversing, 2 cycles per degree (cpd) sine wave grating that was swept from 0.5–20% contrast over the 10-s trial. Grating acuity was measured with an 80% contrast that was swept from 2–16 cpd. Vernier acuity was measured using a 2 cpd, 80% contrast grating into which vernier displacements were periodically introduced and removed. The size of the vernier displacements was swept from 8 to 0.5 arc minutes. All stimuli were modulated at 3.76 Hz. A schematic illustration of the three sweep types is shown in Fig. 1.

Sweep VEP analysis. The sweep VEP technique has been described in detail previously (37,42). Briefly, VEP response amplitude is measured as a stimulus parameter such as contrast, spatial frequency or vernier displacement is varied continuously over a range covering both below- and above-threshold values. The stimulus is presented at a given temporal frequency (3.76 Hz in this study), that drives visual cortical neurons at that frequency, and exact integer multiples of that frequency, as long as the stimulus is in the visible range. The visual response synchronized to the display is sampled with appropriately positioned leads, and the VEP amplitude *versus* stimulus intensity function is measured as the stimulus-driven response drops into the background EEG noise. In this study, sweeps were repeated several times (4–8) to increase the signal to noise ratio through averaging out the uncorrelated background EEG activity. Thresholds were estimated by extrapolating the suprathreshold portion of the response function to zero amplitude using linear regression as described below.

To measure the response functions, EEG recordings from the scalp for each 10-s trial were digitized and divided into 10 sequential epochs or "bins" of one-second duration. For each bin, a recursive, least-squares algorithm (41) was used to generate a series of complex-valued spectral coefficients representing the amplitude and phase of response components tuned to various multiples (harmonics) of the stimulus frequency. These spectral coefficients for each bin were averaged together across trials for each subject, channel, harmonic, and stimulus condition. Statistical significance for each bin was quantified using *p*-values derived from the circular T (T² circ) statistic (43), which tests whether a given response amplitude is significantly different from zero taking into account both response amplitude and phase consistency across trials.

Figure 1. Schematic diagrams of visual stimuli. The sweep VEP measures thresholds by varying or "sweeping" the stimulus parameter. To determine contrast sensitivity, grating acuity and vernier acuity, the contrast, spatial frequency and the line offset, respectively, were varied over 10-s intervals. Contrast was swept from 0.5–20%, spatial frequency was swept from 2–16 cpd and vernier offset was swept from 8–0.5 arc minutes.

Threshold estimation. The range of bins used for regression depended on the statistical significance and phase-consistency of the response across bins according to an algorithm adapted from Norcia *et al.* (37). Once the regression range was established, the threshold stimulus value was determined by extrapolating the regression line to zero response amplitude. Figure 2 shows the extrapolation of the second harmonic amplitude function to estimate a grating acuity threshold for an individual participant. The first harmonic (3.76 Hz) was used to estimate vernier thresholds because that harmonic has been shown to be specific for relative position (35,44) and the second harmonic (7.52 Hz) was used to estimate contrast sensitivity and grating acuity thresholds as the second harmonic is the dominant component of the reversal response.

Amplitude and phase analysis. The amplitude for each one-second bin in the trial was averaged across subjects to calculate response functions for each group (Fig. 3). Finally, we also measured the response timing for each of the three measures by comparing the phases between the groups. We used the phase from the bin with the highest amplitude since this is the most statistically reliable datum. Phase differences were tested using the complex amplitudes (43).

Statistical analysis. All threshold scores were converted to log values before conducting analyses. The mean threshold and amplitude values for each function measured were compared using the independent sample *t*-tests.

RESULTS

As shown in Table 1, thresholds for the three measures were remarkably similar between the two groups. There were no significant differences on any of the threshold measures. A power analysis indicated that, given our sample sizes and the SD of the measures, we should have been able to detect 10% or smaller differences in each of the thresholds, if these differences were present. To detect a threshold difference of

10% between premature and control infants for $p = 0.05$ and power 0.80 would require approximately 20 subjects for contrast sensitivity, 15 for grating, and 18 for vernier acuity. To detect a 25% difference would require 10 infants for contrast sensitivity, 6 for grating, and 9 for vernier acuities (also 80% power). This small sample size assumes that standard deviations were intermediate between those observed in controls and those observed in prematures.

A comparison of response phase (Table 2) showed no differences between the two groups.

We also compared the amplitude of the averaged response functions for the two groups (Fig. 3). Only those bins that were used to extrapolate thresholds (based on the average threshold for each group) were included in the analysis. Since thresholds were identical between the groups, the identical bins were compared. There was a significant difference in response amplitude between the groups for contrast sensitivity ($p < 0.04$) and vernier acuity ($p < 0.02$). In both cases the preterm group displayed higher amplitudes. Although the preterm group had higher amplitude in the grating acuity condition, this difference was not statistically significant.

DISCUSSION

The contrast sensitivity, grating acuity, and vernier acuity in this cohort of 5–7 mo adjusted age VLBW infants were comparable to that of term infants of similar age. These results suggest that premature birth in the absence of identifiable retinal or neurologic abnormalities does not have a detrimental effect on visual sensitivity at age 5–7 mo as indexed by threshold measures. Our results also demonstrate that earlier exposure to visual stimuli as occurs in preterm infants does not accelerate these abilities either, as has been suggested by pattern VEP studies with older preterm infants (30). Infants in the VLBW group had up to 16 wk of additional visual experience compared with the term group, and yet we found no evidence of improved thresholds.

Visual development as measured by thresholds appears to be regulated by a biologic clock, *i.e.*, maturation of various visual functions is predetermined per a temporal schedule. Early exposure to visual stimuli experienced by these infants did not affect the threshold performance of the visual system. There remains the possibility that since the mean post-conceptual age of the term infants was 4 wk higher than that of the preterm infants, that the VLBW group would have performed better on all measures if the ages had been more similar. Another possible explanation for the results is that the cohort of preterm infants in the study may not have been as homogenous as assumed at the time of enrollment by virtue of having a normal head ultrasound and less than stage II ROP. Some of the infants may have had subtle neurologic damage that was undetected by the imaging modalities that were used.

Although thresholds were unaffected, preterm birth did affect the strength of the neuronal signal in the contrast and vernier displacement sweeps, with premature infants showing significantly higher amplitudes. There is a nonsignificant trend in the spatial frequency tuning function for higher amplitudes in the preterm group at the lowest spatial frequencies. The

Figure 2. Measurement of visual threshold. Sweep VEP thresholds are determined by extrapolating the response function to zero amplitude *via* linear regression. The point where the (gray) line touches the abscissa is taken as the threshold. Here, a spatial frequency response function is used to estimate grating acuity for an individual infant. The dots indicate the background EEG levels measured simultaneously at frequencies that were 1 Hz above and 1 Hz below the response frequency of 7.6 Hz. The lower panel plots response phase. Thrsh, Threshold; Spat Freq, Spatial frequency; Pk SNR, the maximum signal-to-noise ratio in the record; Pk Sc SNR, the maximum signal-to-noise ratio in the range of values used to determine threshold. In this case, Peak Sc SNR and Peak SNR are the same.

Figure 3. Mean response functions for each of the three visual measures. Voltage vs. contrast functions (A) were measured by presenting a phase-reversing, 2 cycles per degree (cpd) sine wave grating that was swept from 0.5% (bin 1) to 20% contrast (bin 10) over the 10-s trial. Grating acuity (B) was measured with an 80% contrast grating that was swept from 2 to 16 cpd (bins 1 to 10, respectively). Vernier acuity (C) was measured using a 2-cpd, 80% contrast grating, with its lateral offset swept from 8–0.5 arc minutes (bins 1 to 10, respectively). Amplitudes were higher for the contrast and vernier offset sweeps in the preterm VLBW (●) group compared with term infants (■).

Table 1. Mean log thresholds ($\pm$ SEM) for visual measures in VLBW and Term groups

	Contrast sensitivity	Grating acuity	Vernier acuity
VLBW	1.77 $\pm$ 0.06 (67.5) n = 18	1.09 $\pm$ 0.02 (12.38 cpd) n = 15	0.04 $\pm$ 0.06 (1.25 arcmin) n = 17
Term	1.75 $\pm$ 0.06 (63.8) n = 20	1.09 $\pm$ 0.02 (12.45 cpd) n = 21	–0.08 $\pm$ 0.08 (1.08 arcmin) n = 19

Numbers in parentheses show raw (anti-logarithmic) values of mean values. Number of infants (n) in the calculation of each mean is shown. There were no significant differences between the VLBW and Term groups on any of the three measures.

lowest spatial frequency in the spatial frequency sweep was also used for the contrast sensitivity and vernier acuity measurements. It is possible that the higher amplitudes of the preterm infants reflect accelerated visual cortical development of suprathreshold (low spatial frequency) mechanisms not responsible for the infants’ thresholds. It may also be that the increased amplitudes reflect a hyperexcitability in the premature infants, possibly from an alteration of inhibitory neuron function in the visual cortex. Perhaps both accelerated cortical development and hyperexcitability are spatial frequency dependent. The visual pathway contains gamma aminobutyric acid (GABA) as its main inhibitory neurotransmitter and GABA plays a critical role in many neurodevelopmental processes (in addition to transmission) including the regulation of neuronal survival, dendrite and axonal maturation, and neuronal plasticity (44–46). Thus, disruptions in cortical development in visual cortex may be selectively affecting GABAergic neurons, resulting in a higher than normal neuronal signal. But again, if this is the case, it does not appear to directly affect infant thresholds.

Table 2. Mean phase (and SEM) in degrees for each group for each of the three visual measures

	Contrast Sensitivity	Grating Acuity (cpd)	Vernier Acuity (arcmin)
VLBW	151.7 (50.2)	–122.9 (31.1)	–53.3 (79.0)
Term	68.6 (22.3)	–148.3 (34.9)	101.6 (39.8)

There were no significant differences between the VLBW and Term groups on any of the three measures.

In conclusion, we found that VLBW infants with no IVH or PVL on a head ultrasound and only mild or no ROP are largely spared from major disruptions in visual system function. We found no differences from age-matched term infants on three different measures of visual function. Since we observed no visual deficits these current data support that visual system disruption often seen during prematurity is predominantly affected by severe retinopathy or significant cerebral abnormalities. However, a single-point measurement may not necessarily be representative of the entire spectrum of visual development. Therefore it is important to follow these infants longitudinally through the first few years of childhood. Data from serial examinations, vision screening at older ages and, developmental follow up will be important to understand the effect of premature birth on visual development. In addition, further research with this cohort during early childhood will determine whether the higher than normal amplitudes in the premature group are clinically significant or related to any lasting effects on visual function.

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