Visual Cortical Function in Very Low Birth Weight Infants without Retinal or Cerebral Pathology

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PURPOSE. Preterm infants are at high risk of visual and neural developmental deficits. However, the development of visual cortical function in preterm infants with no retinal or neurologic morbidity has not been well defined. To determine whether premature birth itself alters visual cortical function, swept parameter visual evoked potential (sVEP) responses of healthy preterm infants were compared with those of term infants.

METHODS. Fifty-two term infants and 58 very low birth weight (VLBW) infants without significant retinopathy of prematurity or neurologic morbidities were enrolled. Recruited VLBW infants were between 26 and 33 weeks of gestational age, with birth weights of less than 1500 g. Spatial frequency, contrast, and vernier offset sweep VEP tuning functions were measured at 5 to 7 months’ corrected age. Acuity and contrast thresholds were derived by extrapolating the tuning functions to 0 amplitude. These thresholds and suprathreshold response amplitudes were compared between groups.

RESULTS. Preterm infants showed increased thresholds (indicating decreased sensitivity to visual stimuli) and reductions in amplitudes for all three measures. These changes in cortical responsiveness were larger in the <30 weeks’ gestational age subgroup than in the ≥30 weeks’ gestational age subgroup.

CONCLUSIONS. Preterm infants with VLBW had measurable and significant changes in cortical responsiveness that were correlated with gestational age. These results suggest that premature birth in the absence of identifiable retinal or neurologic abnormalities has a significant effect on visual cortical sensitivity at 5 to 7 months’ of corrected age and that gestational age is an important factor in visual development.
IVH or PVL and ROP. Only by testing such a group can the effects of premature visual exposure alone be investigated during this period of rapid visual development.

Most studies have relied on a single measure (i.e., visual acuity), to assess functioning of the entire visual system, or as an indicator of premature infants' neurologic status. If the effects of prematurity on visual pathway development are selective, as has been suggested, then a measure of a single visual function may fail to identify some deficits or may not identify the maximum differences. A more useful strategy would be to evaluate a number of different visual functions.

In the present study, we focused on specifically visual cortical functions by using the swept parameter visual evoked potential (sVEP). This method can be used to estimate sensory thresholds (e.g., the limits of neuronal performance), as well as responsiveness at suprathreshold levels. Thresholds in the sVEP method are estimated by extrapolating amplitude versus stimulus-intensity functions to 0 amplitude. We measured sVEP response functions for grating spatial frequency as one estimate of visual acuity (two-point resolution, also referred to as vernier acuity). For spatial contrast sensitivity, we used contrast thresholds or contrast sensitivity, and as a function of vernier offset size, for a second estimate of visual acuity based on relative position sensitivity (vernier acuity). These three thresholds develop at different rates, with low spatial frequency contrast sensitivity maturing first, grating acuity second, and vernier acuity last. Grating acuity, a test of spatial resolution that measures the finest grating producing a visual response, reaches half of adult values by 8 months of age.

Contrast sensitivity, a measure of the ability to detect slight changes in luminance across space, is approximately half that of adult sensitivity by 3 months of age. Vernier acuity measures the minimum offset that can be detected between two line segments and is relatively poor during the first year of life when measured with the sVEP. Behavioral and sVEP methods have shown that vernier acuity reaches approximately half of adult values by 5 years of age. Vernier acuity requires recognition of spatial relationships and is believed to require a greater degree of cortical processing. Therefore, it may be a more meaningful indicator of higher-order visual cognitive function than other visual functions.

The goal of this study was to determine whether premature birth itself at different gestational ages in the absence of retinal or cerebral pathology contributes significantly to alterations in visual development.

METHODS

Participants

A total of 58 VLBW preterm infants (preterms; mean birth weight ± SD, 1230 ± 205 g) with gestational age (GA) between 26 and 33 weeks and with corrected ages of between 5 and 7 months and 52 age-matched term infants (terms) were enrolled in the study. Among the 58 preterms, 27 were born at <30 weeks of GA, and 31 were born at ≥30 weeks of GA. sVEP assessment at 5 to 7 months of age allows the comparison of terms and preterms in a period when development is either constant or slow. Table 1 shows the characteristics of the enrolled infants. GA was assessed by the best obstetrical estimate using the last menstrual period and ultrasound examination. Corrected age at examination was calculated as chronologic age minus the difference of full-term assumed GA (40 weeks) and GA at birth. As seen in Table 1, terms were corrected-age–matched (*P = 0.070) to preterms at examination. However, their chronologic age at examination was younger than that of the preterms (*P < 0.001). The corrected age was the same as the chronologic age in the terms because we assumed 40-weeks' GA for the calculation.

VLBW preterms were recruited from the Department of Pediatrics, at Stanford University, from 2002 to 2008. The infants were consecutively enrolled if they were born at less than 34 weeks of GA, were singletons, and weighed less than 1500 g. We excluded any that had IVH, PVL, and ROP. We also excluded infants with major congenital malformations, genetic chromosomal abnormality, metabolic disorders, or congenital infection at the time of the assessment. Infants of 26 weeks' GA were the most premature infants that met our inclusion criterion that we could include in this cohort. All 58 preterms underwent serial head ultrasound (US) scans between 2 days of age and discharge, and 33 underwent magnetic resonance imaging (MRI) scans near discharge. IVH or PVL was determined by US/MRI. ROP was determined by an ophthalmologist on the basis of a fundus examination. The terms were recruited by letter from the local geographic area, based on the basis of information from the birth records maintained by the Department of Vital Statistics of California. They were singletons of at least 38 weeks’ gestation, weighing at least 2500 g, born to a parent who was at least 18 years of age.

The research protocol was approved by the Institutional Review Board of Stanford University and the California Pacific Medical Center and conformed to the tenets of the Declaration of Helsinki.
informed consent was obtained from the parents of the infants after the sVEP recording procedure was explained.

Stimuli

Stimuli were presented on a high-bandwidth monochrome monitor (MR2000HB-MED; Richardson Electronics, LaFox, IL) at a screen resolution of 1600 × 1200 pixels and a 60-Hz vertical refresh rate, as described in detail previously. The stimulus field was 18° × 25°. Viewing distance was 100 cm for all subjects. The mean luminance of the display was 102 cd/m². Three stimulus conditions were presented: sweeps of spatial frequency at high contrast, sweeps of contrast at low spatial frequency, and sweeps of vernier offsets placed in a high-contrast pattern (details in Fig. 1).

sVEP Recording and Procedure

The electroencephalogram (EEG) was amplified (Model 12 amplifier; Grass, Warwick, RI) (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, at locations O₁, O₂, and O₃, of the international 10–20 system. A reference electrode was placed at Cz and a ground electrode at Pz. Electrode impedance was equal to or less than 10 kΩ.

During sVEP recording, infants were seated in their parent’s lap in front of the monitor. The experimenter attracted the infant’s attention to the stimulus with small toys (~1–2 cm in size) dangled over the center of the display. Recordings were interrupted when the infant was judged not to be attending. If the experimenter interrupted the display with a mouse input, both display and data acquisition program

Figure 2. Mean response functions for each of the three visual measures. Vector averaged sVEP response functions in terms and preterms for spatial frequency (a, b), contrast (c, d), and vernier sweep (e–g) stimuli at Oz derivation. Error bars plot the SEM based on the T² circ statistic. Arrows: the mean thresholds derived from the group response functions. The t-test P values for the group threshold differences between preterms and terms are *<0.05, **<0.01, and ***<0.001. Horizontal bars: the significance of amplitude differences between preterm and term infants for P < 0.05 at corresponding sweep values of the stimuli. The response amplitudes were significantly lower, and group thresholds were significantly worse in preterm than those of term infants for all three measures.
Contrast, % was quantified using trast sVEP, and the first, second and fourth harmonics \[1F1, 2F1, \text{and } 4F1\] for the grating and con-
statistic, which tests whether a given response amplitude is signifi-
regressing the group response function obtained by removing the
subjects) estimates of threshold and slope, \(T\) and \(S\), each obtained by
sweep measures and the first (1F1), the second (2F1), and the
fourth (4F1) harmonics for spatial frequency and contrast
response functions at the second (2F1) and
amplitude differences between the groups using the data from
threshold values of the stimuli and the other to estimate differ-
stimulus values go from the invisible to the visible range.
Two approaches were taken to quantify the differences
between groups: one to test amplitude differences at suprath-
threshold values of the stimuli and the other to estimate differ-
ences in sensory threshold for the three stimuli. We compared
amplitude differences between the groups using the data from
each epoch of the stimuli. The horizontal black bars in Figure 2
indicate the significance of amplitude differences between the
preterms and terms for \(P < 0.05\) at corresponding sweep
values of the stimuli. Most individual participant responses
were largest in the stimulus furthest from threshold and there-
fore we will refer these amplitudes as peak amplitudes for
simplicity. The peak amplitudes were lower in the preterms for
both the second and fourth harmonics of the spatial frequency
sweep, for the second harmonic of the contrast sweep, and for
the first harmonics of the vernier offset sweeps. The scalar
means of peak amplitudes, along with standard errors and \(P\)
values, are shown in Table 2, and these correspond to the
epoch data at the most visible sweep value of the stimuli in
Figure 2.

We used regressions of the response functions to 0 amplitu-
de to estimate sensory thresholds for the group functions.
Group thresholds along with standard errors and \(P\) values are
shown in Table 3 and Figure 2. The group thresholds (grating
acuity, vernier acuity, and contrast sensitivity) were signifi-
ificant different from 0, taking into account both response amplitude and
phase consistency across trials. Then, the group VEP amplitudes
were also averaged coherently across observers.

### Results

#### sVEP Response Functions in Term and Preterm Infants

We analyzed sVEP response functions at the second (2F1) and
the fourth (4F1) harmonics for spatial frequency and contrast
sweep measures and the first (1F1), the second (2F1), and the
fourth (4F1) harmonics for vernier sweep measure, because
these harmonic components showed the strongest responses as
described in previous publications. Vector-averaged
response functions for the spatial frequency, contrast, and vernier
sVEP measures are shown in Figure 2. Each of these
functions shows a monotonic increase in amplitude as the
stimulus values go from the invisible to the visible range.

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### Statistical Analysis

To estimate thresholds from the term and preterm response functions, we
constructed vector mean swept parameter response functions for
each stimulus for each group of infants. To estimate the standard errors
of thresholds and slopes of the group average response functions, we
used a jackknife procedure. First, for each group of subjects, we
determined the range of epochs for regression using the algorithm
cited above, and calculated the threshold, \(T\), and slope, \(S\). Then, using
the same regression range, we recalculated a set of \(n\) (the number of
subjects) estimates of threshold and slope, \(T_i\) and \(S_i\), each obtained by
regressing the group response function obtained by removing the \(i\)th
subject from the sample. The SE of the threshold, \(T_i\), was

\[T_i = \sqrt{(n-1)/n^2(T_n - T_i)/n}\]

where \(T_n\) was the mean of the \(T_i\). The
SE of the slope was obtained by the same formula, substituting \(S_i\) for \(T_i\).

Insignificant differences between the group thresholds defined by jack-
knife procedure were identified by two-tailed, heteroscedastic \(t\)tests.

#### Group Thresholds for the Three Measures Shown in Figure 2

<table>
<thead>
<tr>
<th>Group Response</th>
<th>1F1</th>
<th>2F1</th>
<th>4F1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial frequency, cyc/deg</td>
<td>12.66 ± 0.49</td>
<td>13.20 ± 0.53</td>
<td>13.47 ± 0.35</td>
</tr>
<tr>
<td>Contrast, %</td>
<td>0.19 ± 0.09</td>
<td>1.44 ± 0.07</td>
<td>2.12 ± 0.04</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SEM.
significantly higher in the preterm than in the terms for all three measures. The threshold elevations reflect the fact that the response functions were either laterally shifted toward the range that the stimuli became more visible in preterms compared with the terms. For the grating and vernier measures, the response functions in the preterms were shifted toward the lower spatial frequency range for the grating and the larger vernier offset range for the vernier. These leftward shifts of the response function led to a decrease in the estimated grating acuity and vernier acuity in the preterms. For the contrast measure, the response function was shifted toward (rightward) the higher contrast range and that led to a decrease in the estimated contrast sensitivity in the preterms.

Effect of GA on sVEP Response Functions in Preterm Infants

We also compared sVEP response functions in the preterm infants <30 weeks and ≥30 weeks of GA for the three measures, using the approaches just described, except that we compared amplitude differences between these two subgroups using the epoch data at the most visible sweep value of the stimuli (peak amplitude). A GA of 30 weeks was chosen as the threshold for dividing the group to produce equal sample sizes. Vector averaged response functions for each stimulus type and harmonic along with group thresholds are shown in Figure 3. The peak amplitudes were lower in the <30-week GA

![Figure 3](https://via.placeholder.com/150)

**Figure 3.** GA differences in the sVEP mean response functions for each of the three visual measures. Vector-averaged sVEP response functions in the ≥30-week GA subgroup and <30-week GA subgroup for spatial frequency (a, b), contrast (c, d), and vernier (e-g) stimuli at Oz derivation. Error bars represent the SEM. Arrows: the mean thresholds derived from the group response function for each group. The t-test P values for the group threshold differences are *<0.05, **<0.01, and ***<0.001. Horizontal bars: the significance of peak amplitude differences between the < and ≥30-week GA subgroups for P < 0.05. The mean peak amplitudes were significantly lower and group thresholds were significantly worse in the <30-week GA subgroup than those in the ≥30-week GA subgroup for all visual measures.
subgroup than that in the ≥30-week GA subgroup for all measures except for the vernier offset first and second harmonics. In this case, however, midrange values were depressed in the <30-week GA subgroup (Figs. 5e, 5f). In some cases the amplitude differences were present only at the suprathereshold part of the range (Figs. 5b, 5c), but in others, amplitude reduction was present over the full range (Fig. 5g). The scalar means of peak amplitudes along with standard errors and P values are shown in Table 4 and these correspond to the epoch data at the most visible sweep value of the stimuli in Figure 3. Group thresholds were worse in the <30-week GA subgroup than that in the ≥30-week GA subgroup for all visual measures at one or more of the measured response harmonics. Group thresholds along with standard errors and P values are shown in Table 5 and Figure 3.

**DISCUSSION**

Most studies have relied on a single measure (i.e., visual acuity), to assess functioning of the entire visual system, or as an indicator of premature infants’ neurologic status. Most important, these studies did not exclude retinal pathology (e.g., ROP) or cerebral pathology (e.g., IVH or PVL) during the prenatal and neonatal period. Thus, it is not clear whether premature birth itself (premature exposure to the visual world) affects visual development or whether previously reported differences between the term and preterm infants were due to subtle neurologic abnormalities. In the present study, three different assays of spatial vision were obtained by using the sVEP in a cohort of VLBW preterms in the absence of identifiable ROP, IVH, or PVL at 5 to 7 months’ corrected age. Sensory thresholds for all three measures were elevated in the preterms compared with the terms and differed between <30-week GA subgroup and the ≥30-week GA subgroup infants in the preterm group. The VLBW preterms also had significant decreases in cortical responsiveness to suprathreshold stimuli that were more severe within the preterm group when the infants were stratified according to GA. The extrapolation method for estimating thresholds is robust against changes in response amplitude, and thus the threshold elevations we report are not likely to be a simple consequence of reduced amplitude, especially in cases in which the response function is shifted laterally without a change in slope, as is the case with several of the response functions.

The effects of prematurity and GA were present for each of the three sweep types, suggesting that the effect is robust and is not specific to a single visual task. Developmentally, visual maturity is reached at quite different ages for low spatial frequency contrast sensitivity, grating, and vernier acuity, suggesting that our three tasks were tapping at least partially separate cortical mechanisms. At present, we do not know whether the effects observed in this study in infancy persist or are predictive of visual and other developmental outcomes, either in infancy or in later childhood. A recent behavioral study found that performance on the Griffith Mental Developmental Scales was normal at both 3 and 12 months in infants with normal head ultrasound in the neonatal period, but that abnormal head ultrasound results were at least partially predictive of behavioral abnormalities. The Griffith scales measure different aspects of visual function that are being measured by the sweep VEP, and this difference in what is assessed may explain the apparent discrepancy between our results and the results on the Griffith scales.

GA at delivery is a critical factor for visual and neural development, especially for long-term outcomes. The <30-week GA subgroup showed more severe reductions in cortical responsiveness than did the ≥30-week GA subgroup, especially for the fourth harmonic response of vernier sVEP (see Fig. 3g). The substantially decreased vernier threshold and strong reduction in amplitude at fourth harmonic response of sVEP clearly shows the presence of a neural deficit in the infants born at <30 weeks of GA. This result is consistent with previous behavioral findings that GA at birth of ≤28 weeks is associated with a higher risk of long-term visual abnormalities. The effects of GA were larger on the vernier sVEP than on the spatial frequency and contrast threshold measures. Effects seen in our study with preterm infants and results in ambylophia and cortical visual impairment suggest that vernier offset responses are more sensitive to disruption by abnormal visual experience or perinatal experience than are grating-based measures. The first-harmonic response to vernier offsets requires the encoding of the spatial relationships between stimulus elements, not just detection of the presence or absence of spatial pattern, and is believed to require a greater degree of cortical processing.

Reductions in the amplitude of the sVEP at suprathreshold levels could be caused by several factors. A decrease in neuronal mass, as occurs in profound brain damage, has been shown to adversely affect the response amplitude. However, this group of VLBW infants had normal head ultrasounds. It is possible that some of the infants had subtle neurologic injuries that were undetected by the imaging modalities that were used. If so, sVEP measures would provide a sensitive tool for detecting neurologic changes. It is plausible, given what is known about the effects of premature birth, especially birth a <28 or 30 weeks of GA or extremely low birth weight (<1000 g), to consider that this occurs even in preterm infants without ROP and detectable neurologic morbidity (e.g., IVH or PVL). Another theoretical explanation is the

### Table 4. Scalar Means of Peak Amplitudes for the Three Measures Shown in Figure 3

<table>
<thead>
<tr>
<th>Group Response</th>
<th>1F1</th>
<th>2F1</th>
<th>4F1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial frequency, cyc/deg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 wk (n = 24)</td>
<td>4.90 ± 0.78</td>
<td>1.45 ± 0.20</td>
<td></td>
</tr>
<tr>
<td>≥30 wk (n = 28)</td>
<td>7.47 ± 0.98</td>
<td>2.78 ± 0.40</td>
<td></td>
</tr>
<tr>
<td>Difference (P)</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

| Contrast, %             |     |     |     |
| (<30 wk (n = 27)        | 3.77 ± 0.49 | 1.15 ± 0.13 |
| ≥30 wk (n = 31)         | 5.44 ± 0.65 | 1.83 ± 0.23 |
| Difference (P)          | <0.05 | <0.05 |

| Vernier, arcmin         |     |     |     |
| (<30 wk (n = 22)        | 6.43 ± 0.75 | 2.36 ± 0.26 | 1.09 ± 0.15 |
| ≥30 wk (n = 29)         | 9.00 ± 1.07 | 3.19 ± 0.46 | 2.14 ± 0.28 |
| Difference (P)          | 0.055 | 0.12 | <0.01 |

Data are expressed as the mean ± SEM.

### Table 5. Group Thresholds for the Three Measures Shown in Figure 3

<table>
<thead>
<tr>
<th>Group Response</th>
<th>1F1</th>
<th>2F1</th>
<th>4F1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial frequency, cyc/deg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 wk (n = 24)</td>
<td>11.34 ± 0.70</td>
<td>12.35 ± 1.17</td>
<td></td>
</tr>
<tr>
<td>≥30 wk (n = 28)</td>
<td>11.67 ± 0.58</td>
<td>12.13 ± 0.61</td>
<td></td>
</tr>
<tr>
<td>Difference (P)</td>
<td>&lt;0.05</td>
<td>0.86</td>
<td></td>
</tr>
</tbody>
</table>

| Contrast, %             |     |     |     |
| (<30 wk (n = 27)        | 1.14 ± 0.06 | 2.83 ± 0.06 |
| ≥30 wk (n = 31)         | 0.94 ± 0.06 | 1.02 ± 0.08 |
| Difference (P)          | <0.05 | <0.001 |

| Vernier, arcmin         |     |     |     |
| (<30 wk (n = 22)        | 1.11 ± 0.07 | 1.07 ± 0.12 | 1.28 ± 0.06 |
| ≥30 wk (n = 29)         | 0.57 ± 0.06 | 0.71 ± 0.07 | 0.80 ± 0.03 |
| Difference (P)          | <0.0001 | <0.05 | <0.0001 |

Data are expressed as the mean ± SEM.
possibility that the normal balance of neuronal excitation and inhibition is altered in preterm balance of infants with neurologic injury. Indeed, it has been reported that the GABA pathway is vulnerable to perinatal brain injury, with a loss of GABAergic neuron expression found in premature infants. As a shift of this balance toward inhibition would have the effect of reducing signal amplitude. It is also possible that decreases in the temporal precision (synchronization) of synaptic activity could occur and result in reduced response amplitudes. Recent studies of MRI and diffusion tensor imaging suggest that white matter changes are responsible for alterations in vision in premature infants. Such changes can be subtle and perhaps not even visible on conventional MR scanning. Deficits in processing local and global motion can also occur in the apparent absence of cerebral pathology. It is possible that the infants in our study had such MRI changes and that these changes account in part for our findings.

Findings in this study indicate significant threshold and suprathreshold neurophysiological changes in infants with VLBW. Changes were detected several months (5–7 months) after the birth and were present in all three visual sensitivity measures, suggesting a more generalized effect of premature birth, especially birth at <30 weeks of GA on visual development. These three measures (grating acuity, contrast sensitivity, and vernier acuity) are most likely subserved by different cortical mechanisms. Whether these changes portend subclinical or clinical alterations in visuocortical functioning is an open question requiring longer follow-up and additional investigation.

Acknowledgments

The authors thank Patricia Hartsell, Sharon Cassinelli, and Judith Y. Hall for their assistance in recruiting and co-coordinating preterm participants’ visits and Margaret Q. McGovern for the assistance in recruiting and conducting term infants’ experiments.

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