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.

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Prematurity, defined as a gestational age (GA) <37 weeks at birth, and low birth weight, defined by a birth weight <2500 g at birth, are the leading causes of neonatal mortality and morbidity in the United States.[1] This group of infants is at higher risk for visual, cognitive, and motor impairment, as well as for behavioral deficits and disorders of attention compared with infants born full term.[2–10] Very low birth weight infants (VLBW, defined as weighing ≤1500 g at birth) are at particularly high risk because of an increased prevalence of retinopathy of prematurity (ROP),[3,5,7–9,11–15] intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL),[16–19] among other complications.[4,5,16–20] Several studies have demonstrated the co-occurrence of visual impairment in preterm infants with other neurologic deficits.[4,5,10,16–21] These preterm infants were mostly of extremely low weight (defined as <1000 g) at birth,[5,10,20,22,23] with short gestational age.[23,24] Analyses of prognostic factors for mid- and long-term outcome of extremely low birth weight infants have indicated that the most significant variable correlated with long-term neurologic outcome is gestational age.[23] For example, among short-gestational-age infants, over one third develop neurocognitive (learning disability), motor or behavioral deficits and disorders of attention,[2,6] and gestational age at birth of ≤28[1] or ≤32[25,26] has been associated with a higher risk of long-term visual abnormalities.[25]

The visual pathway from the retina to the primary visual and association cortex is particularly vulnerable during the prenatal and neonatal period, because it undergoes significant development during this time.[21,27–30] Visual impairments in infants and children born prematurely have been reported for decades.[3–5,7–10] However, one question that has not been adequately resolved is whether visual deficits 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. Behavioral studies have shown either no trend,[13,31] a trend toward rapid development,[32] or reduced acuity with preterm birth,[33–35] whereas those in which electrophysiological techniques were used have shown no trend,[36] a trend toward a more rapid maturation,[37–40] or delayed latency in preterm infants.[25] 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 to 36 weeks. A single study in 8- to 12-year-old children born preterm but without major brain and neuromotor impairment showed no significant differences between the groups on the ophthalmic, visual cognitive, neurologic, neuromotor, or MRI measures.[41] However, no previous study, to our knowledge, that has examined visual functioning in VLBW infants has excluded detectable cerebral abnormalities (e.g.,

TABLE 1. Characteristics of Enrolled Infants

Demographics	Terms (n = 52)	Preterms (n = 58)	t-Test P
Sex	M = 26 F = 26	M = 20 F = 38	
Gestational age, wk <30 wk (n = 27), ≥30 wk (n = 31)	40	30.2 ± 3.4	
Corrected age at examination, wk	28 ± 4*	27 ± 4	0.070
Chronologic age at examination, wk	28 ± 4	36 ± 5	**<0.001**

* Same as chronologic age.

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,[13,32,34,35] or as an indicator of premature infants' neurologic status.[42–44] If the effects of prematurity on visual pathway development are selective, as has been suggested,[39,45] 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.[37,46,47] Thresholds in the sVEP method are estimated by extrapolating amplitude versus stimulus–intensity functions to 0 amplitude.[48] We measured sVEP response functions for grating spatial frequency as one estimate of visual acuity (two-point resolution, also referred grating threshold as grating acuity), for spatial contrast to estimate visual sensitivity at a low spatial frequency (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.[47,49] 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.[50,51] 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.[49,52] 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.[51,53] 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.[47]

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.[48,49] 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 the 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, 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. Written

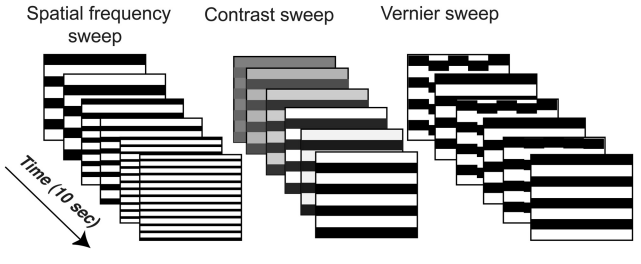

FIGURE 1. sVEP stimuli. Spatial frequency sVEP (*left*): an 80% contrast, 3.76-Hz, phase-reversing cosine grating (shown as a square-wave grating) was swept from 2 to 16 cyc/deg in 10 linear steps. Contrast sVEP (*middle*): a 3.76-Hz, phase-reversing, 2-cyc/deg, cosine grating was swept from 0.5% to 20% contrast in 10-logarithm steps. Vernier sVEP (*right*): a 2-cyc/deg, 80% contrast, square-wave grating contained vernier displacements that were periodically introduced and removed at 3.76 Hz. The size of the vernier displacements was swept from 8 to 0.5 arcmin in 10-logarithm steps. The sweep duration for all three measures was 10 seconds.

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.[46] The stimulus field was 18° × 25°. Viewing distance was 100 cm for all subjects. The mean luminance of the display was 102 cd/m^2. 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 O_1, O_z, and O_2, of the international 10-20 system.[54] A reference electrode was placed at C_z and a ground electrode at P_z. 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

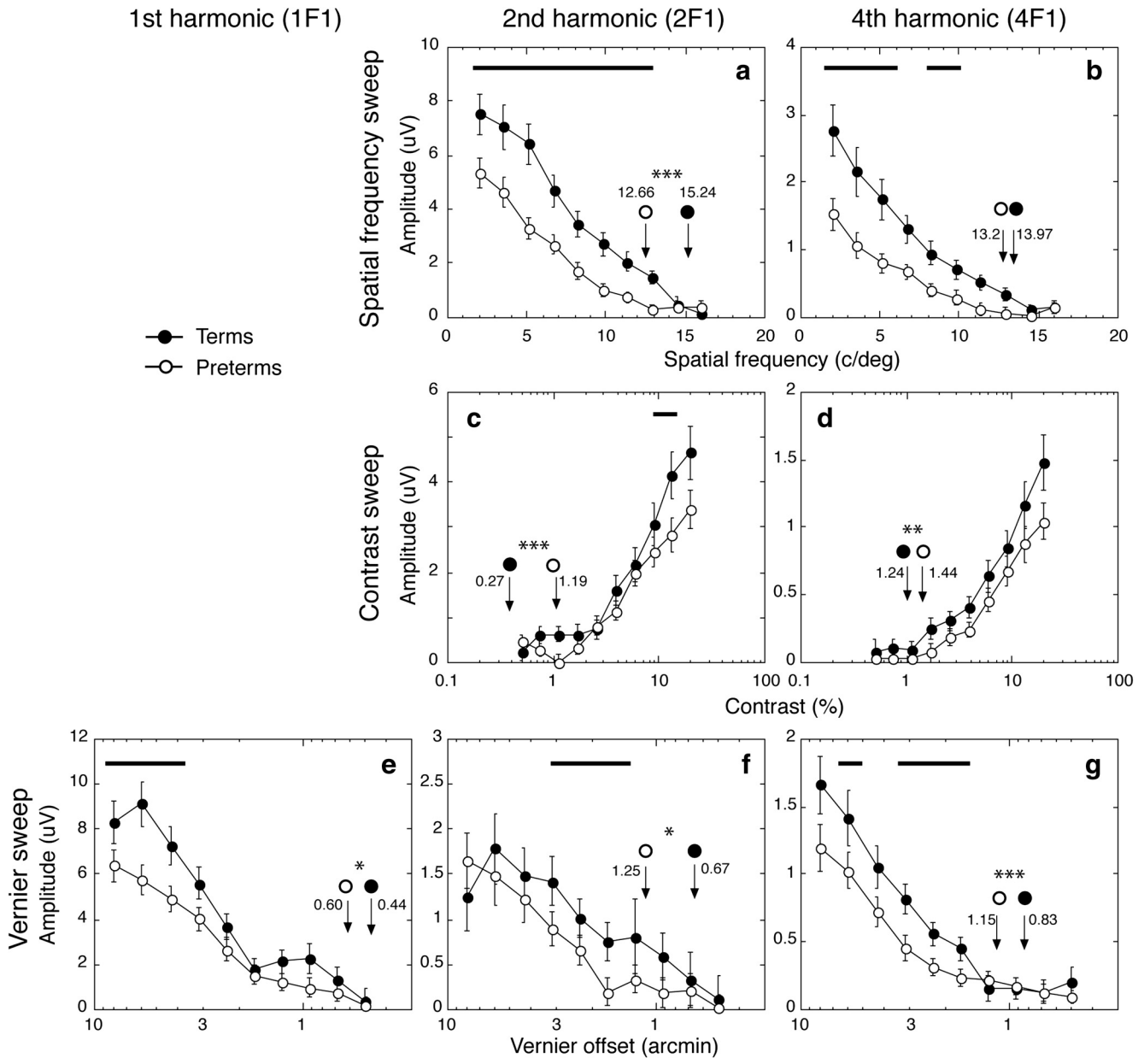

FIGURE 2. Mean response functions for each of the three visual measures. Vector averaged sVEP response functions in terms and preterms for spatial frequency (**a**, **b**), contrast (**c**, **d**), and vernier sweep (**e**–**g**) stimuli at O_z derivation. Error bars plot the SEM based on the T^2 circ statistic.[57] *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.

TABLE 2. Scalar Means of Peak Amplitudes for the Three Measures Shown in Figure 2

Group Response	1F1	2F1	4F1
Spatial frequency, cyc/deg			
Preterms (n = 52)		6.29 ± 0.66	2.17 ± 0.25
Terms (n = 46)		8.73 ± 0.83	3.47 ± 0.42
Difference (P)		**<0.05**	**<0.01**
Contrast, %			
Preterms (n = 58)		4.49 ± 0.42	1.47 ± 0.14
Terms (n = 50)		5.93 ± 0.66	1.86 ± 0.25
Difference (P)		0.065	0.157
Vernier, arcmin			
Preterms (n = 47)	7.89 ± 0.71	2.83 ± 0.28	1.63 ± 0.18
Terms (n = 51)	10.47 ± 0.94	3.30 ± 0.30	2.15 ± 0.24
Difference (P)	**<0.05**	0.252	0.084

Data are expressed as the mean ± SEM.

loops were reset to a previous point in the display that was 1 second before the mouse click.

sVEP Analysis

The sVEP technique has been described in detail previously.[46,50,55] Briefly, the VEP response amplitude was measured as a spatial frequency, contrast, or vernier displacement was 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 at 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, swept parameter presentations were repeated several times (four to eight) to increase the signal to noise ratio through averaging out the uncorrelated background EEG activity.

To measure the response functions, sVEP recordings for each 10-second trial were divided into 10 sequential epochs that corresponded to the swept stimulus values. For each epoch, a recursive least square (RLS) adaptive filter[56] was used to generate a series of complex-valued spectral coefficients representing the amplitude and phase of response components tuned to various multiples (harmonics, e.g., the second and fourth harmonics [2F1 and 4F1] for the grating and contrast sVEP, and the first, second and fourth harmonics [1F1, 2F1, and 4F1] for the vernier sVEP) of the stimulus frequency (e.g., 3.76 Hz in the present study). These spectral coefficients for each epoch were averaged across trials for each subject, recording the derivation, harmonic, and stimulus conditions. Statistical significance for each epoch was quantified using P values derived from the circular T (T^2 circ) statistic,[57] which tests whether a given response amplitude is significantly 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.

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.[58] 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 ith subject from the sample. The SE of the threshold, T_{se}, was $T_{se} = \sqrt{(n-1)[\sum_n (T_i - T_\mu)]/n}$, where T_m was the mean of the T_i. The SE of the slope was obtained by the same formula, substituting S_i for T_i. Significant differences between the group thresholds defined by jackknife procedure were identified by two-tailed, heteroscedastic t-tests.

Group differences in suprathreshold response amplitude were computed on the basis of individual participant response amplitudes (scalar means) and tested with two-tailed, heteroscedastic t-tests. The scalar means focused the analysis on amplitude differences, rather than a combination of amplitude and phase differences that comprise differences between vector means.

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.[46,50,59] 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.

Two approaches were taken to quantify the differences between groups: one to test amplitude differences at suprathreshold values of the stimuli and the other to estimate differences 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 therefore 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 amplitude 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-

TABLE 3. Group Thresholds for the Three Measures Shown in Figure 2

Group Response	1F1	2F1	4F1
Spatial frequency, cyc/deg			
Preterms (n = 52)		12.66 ± 0.49	13.20 ± 0.53
Terms (n = 46)		15.24 ± 0.43	13.97 ± 0.35
Difference (P)		**<0.001**	0.224
Contrast, %			
Preterms (n = 58)		1.19 ± 0.09	1.44 ± 0.07
Terms (n = 52)		0.27 ± 0.19	1.24 ± 0.04
Difference (P)		**<0.0001**	**<0.01**
Vernier, arcmin			
Preterms (n = 51)	0.60 ± 0.05	1.25 ± 0.07	1.15 ± 0.03
Terms (n = 47)	0.44 ± 0.07	0.67 ± 0.22	0.83 ± 0.03
Difference (P)	**<0.05**	**<0.05**	**<0.0001**

Data are expressed as the mean ± SEM.

cantly 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

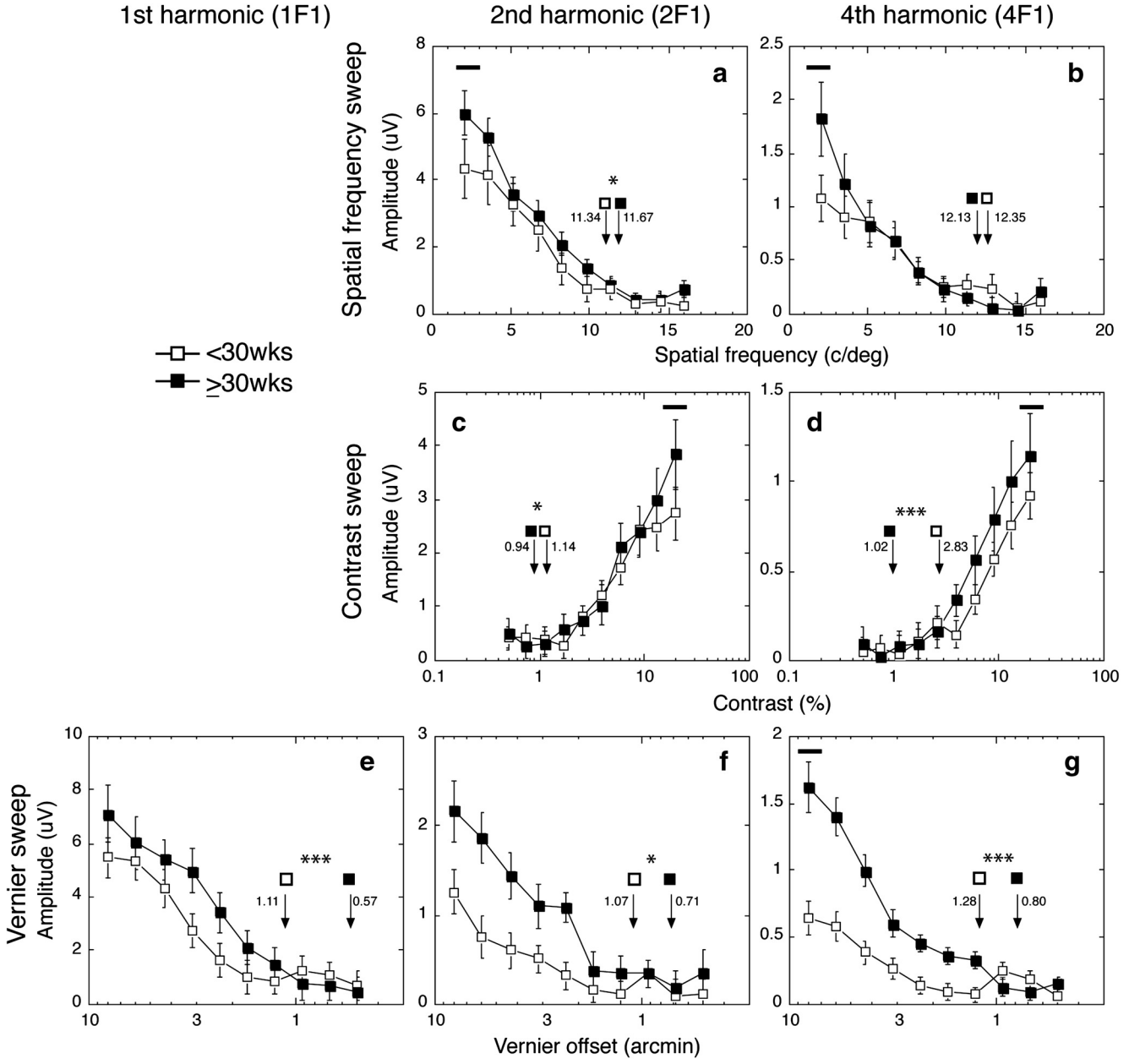

FIGURE 3. GA differences in the sVEP mean response functions for each of the three visual measures. Vector-averaged sVEP response functions in the ≥30-week GA subgroup and <30-week GA subgroup for spatial frequency (**a**, **b**), contrast (**c**, **d**), and vernier (**e**–**g**) stimuli at O_z derivation. 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.

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

Group Response	1F1	2F1	4F1
Spatial frequency, cyc/deg			
<30 wk (n = 24)		4.90 ± 0.78	1.45 ± 0.20
≥30 wk (n = 28)		7.47 ± 0.98	2.78 ± 0.40
Difference (P)		**<0.05**	**<0.01**
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.

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. 3e, 3f). In some cases the amplitude differences were present only at the most suprathreshold part of the range (Figs. 3b, 3c), but in others, amplitude reduction was present over the full range (Fig. 3g). 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,[13,32,34,35] or as an indicator of premature infants' neurologic status.[42–44] Most important, these studies did not exclude retinal pathology (e.g., ROP) or cerebral pathology (e.g., IVH an/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,[60] 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.[47,61] 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[62] 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 neuronal development, especially for long-term outcomes.[23] 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[1] or ≤32[25,26] 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 amblyopia[63,64] and cortical visual impairment[61] suggest that vernier offset responses are more sensitive to disruption by abnormal visual experience or perinatal experience than are grating-based measure. 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.[61,63,64]

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.[65] 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),[1,25,26] to consider that this occurs even in preterm infants without ROP and detectable neurologic morbidity (e.g., IVH or PVL). Another theoretical explanation includes the

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

Group Response	1F1	2F1	4F1
Spatial frequency, cyc/deg			
<30 wk (n = 24)		11.34 ± 0.70	12.35 ± 1.17
≥30 wk (n = 28)		11.67 ± 0.58	12.13 ± 0.61
Difference (P)		**<0.05**	0.86
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 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.[66] 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.[67,68]

Recent studies of MRI and diffusion tensor imaging suggest that white matter changes are responsible for alterations in vision in premature infants.[69,70] 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.[71] 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.[47,61] Whether these changes portend subclinical or clinically important alterations in visuocortical functioning is an open question requiring longer follow-up and additional investigation.

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