Visuocortical Function in Infants With a History of Neonatal Jaundice

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Purpose. High concentrations of unconjugated bilirubin are neurotoxic and cause brain damage in newborn infants. However, the exact level of bilirubin that may be neurotoxic in a given infant is unknown. The aim of this study was to use a quantitative measure of neural activity, the swept parameter visual evoked potential (sVEP) to determine the relationship between neonatal bilirubin levels and visual responsivity several months later.

Methods. We compared sVEP response functions over a wide range of contrast, spatial frequency, and Vernier offset sizes in 16 full-term infants with high bilirubin levels (>10 mg/dL) and 18 age-matched infants with no visible neonatal jaundice, all enrolled at 14 to 22 weeks of age. The group means of sVEP thresholds and suprathreshold response amplitudes were compared. The correlation between individual sVEP thresholds and bilirubin levels in jaundiced infants was studied.

Results. Infants who had a history of neonatal jaundice showed lower response amplitudes ($P < 0.05$) and worse or immeasurable sVEP thresholds compared with control infants for all three measures ($P < 0.05$). Swept parameter visual evoked potential thresholds for Vernier offset were correlated with bilirubin level ($P < 0.05$), but spatial acuity and contrast sensitivity measures in the infants with neonatal jaundice were not ($P > 0.05$).

Conclusions. These results indicate that elevated neonatal bilirubin levels affect measures of visual function in infancy up to at least 14 to 22 weeks of postnatal age.

Keywords: jaundice, hyperbilirubinemia, contrast sensitivity, spatial frequency, Vernier acuity, swept parameter visual evoked potentials

More than 40% of Caucasian newborn infants have serum bilirubin levels greater than 7 mg/dL during the newborn period, and the incidence may be higher in Asian populations.[1] Unconjugated bilirubin is a known neurotoxin and, at high concentrations, causes brain damage in newborn infants. Studies from the 1950s[2] performed in infants who had hyperbilirubinemia (total serum bilirubin level above 5 mg/dL) due to hemolysis from Rhesus blood group (Rh) demonstrated severe and permanent brain damage. With Rh incompatibility, kernicterus (bilirubin-induced brain dysfunction, i.e., encephalopathy) occurred in more than 50% of infants with total serum bilirubin levels greater than 30 mg/dL, but rarely occurred at levels less than 20 mg/dl. However, the exact level of bilirubin that may be neurotoxic in a given infant is unknown.

Recognizing that kernicterus had become a rare event, in part because Rh incompatibility had declined significantly, in 1994, the American Academy of Pediatrics published guidelines for the management of neonatal jaundice.[3] These recommendations advise that bilirubin levels in excess of 15 to 17 mg/dL can be watched without treatment if the elevation occurs after 72 hours of life. The guidelines are supported by research that shows no identifiable neurologic abnormality in infants with higher bilirubin levels, even when peak levels reach 25 to 29 mg/dL.[3,4] Subsequent guidelines (2004)[5] acknowledge that serum bilirubin levels should be considered in conjunction with age of the infant, rapidity of development of elevated bilirubin, and other factors.

It is, however, possible that a spectrum of injury can occur in response to central nervous system bilirubin exposure, and that injury can include loss of function short of full-blown kernicterus. Studies suggest that lower levels of bilirubin may result in subtle neurotoxicity.[6] Abnormalities of the brainstem auditory-evoked response have been shown in newborns with high total serum bilirubin levels, with return to normal as the bilirubin level was lowered.[7] An auditory nerve/auditory processing syndrome has been described in some children, in which hearing and understanding speech and language are affected by elevated bilirubin.[8–11] Moderate hyperbilirubinemia can cause other, persistent neurologic changes, including motor alterations,[6] brain damage,[12–14] and, rarely, persistent kernicterus.[3] Lastly, animal models show that hyperbilirubinemia can cause an increase in apoptosis and other undesirable cellular alterations in the developing brain.[15–17]

Given the large number of infants who develop jaundice, any finding that indicates persistent neurologic change, or even shows that changes are transient, could have significant ramifications for healthcare of children. Because it is known that bilirubin has neurotoxic effects in the auditory system[7–11] and causes other forms of brain damage,[12–14,18,19] our hypothesis is that elevated neonatal bilirubin would also have a deleterious or neurotoxic effect on visual cortex and visual

Table 1. Characteristics of Enrolled Infants

Demographics	Jaundice, $n = 16$	Control, $n = 18$	*P* Value
Sex	M = 8, F = 8	M = 10, F = 8	
Race			
White	7	8	
Hispanic	7	6	
Asian	2	3	
Other		1	
Birth weight, g, mean ± SEM	3180 ± 420	3293 ± 450	<0.05
Gestational age, wk, mean ± SEM	39.6 ± 1.3	39.4 ± 1.2	<0.05
Age at exam, wk, mean ± SD	18.4 ± 3.8	19.7 ± 3.1	<0.05

function. However, there have been few studies evaluating the effects of jaundice on the visual pathway in infancy. Chen and Kang[20] examined flash visual evoked potentials (VEP) in 72 infants with neonatal jaundice and 22 controls and found that within 8 weeks after birth, the wave latencies were significantly more prolonged in infants in the severe and moderate groups than in the controls. The amplitudes of VEP were lower in severe and moderate groups than in the control group, but only in the first week after birth. In a small sample study, Chen and Wong[21] reported that only 4 of 24 infants (16%) had abnormal flash VEP before 1 year, and the abnormalities returned to normal thereafter. Studies that have examined visual function at an older age have not found alterations in VEP.[21,22]

To test our hypothesis, in the present study, we used steady-state swept parameter visual evoked potential (sVEP) to measure visual thresholds and suprathreshold response amplitudes in a cohort of infants who had moderate levels of total bilirubin within the first 3 days of life. The sVEP has previously been shown to be very sensitive to the effects of neurotoxins present during the perinatal period. Examples include maternal lead exposure,[18] maternal thyroid hormone insufficiency,[23] and vigabatrin exposure.[24] Here, we measured three types of pattern-evoked responses: contrast response functions for a 2 c/deg reversing grating, spatial frequency response functions for a high-contrast, reversing-grating, and Vernier-offset response functions.

Multiple-response measures were obtained in order to probe different aspects of visual responsivity (e.g., threshold versus suprathreshold performance) and to test the generality of any effects observed. Contrast sensitivity develops rapidly, and by the age of 24 weeks it has stabilized to near adult levels.[25] On the other hand, grating acuity shows a slower developmental rate, reaching within a factor of 2 of the adult by 8 months.[26] Vernier acuity does not reach maturity until early adolescence.[25,27] We targeted slightly older infants (14–22 weeks), as this age is sufficiently long after birth to not reflect acute effects. By 14 to 22 weeks of age in infants, contrast sensitivity has stabilized to near adult levels, but the other two functions are still in a period of rapid growth, allowing us to sample over a range of developmental states and processes. Both sVEP Vernier and grating acuity are sensitive measures of cortical development in disorders, such as amblyopia[28] and cortical visual impairment.[29] Together, these three measures were used to provide a survey of the fundamental limits on visual capacity in the early parts of the visual pathway and how these processes are affected by bilirubin level.

Methods

Participants

This study uses the term "jaundice" to indicate bilirubin levels high enough to cause visible changes to the skin. The study infants all had neonatal jaundice. Sixteen infants with a history of neonatal jaundice from the Department of Pediatrics at Lucile Packard Children's Hospital (Palo Alto, CA, USA), El Camino Hospital (Mountain View, CA, USA), and Mountain View Hospital (Mountain View, CA, USA) were recruited prospectively and enrolled in the study, all of whom had a total serum bilirubin level measured before day 3 of life. The inclusion criterion was a total bilirubin level within the first 3 days of life of greater than 10 mg/dL. The highest measure recorded (peak total bilirubin within the first 3 days after birth) was used for the analysis. Other inclusion criteria included birth at full term, no known organ system abnormality, including no known brain injury, no known hemolytic jaundice, no ocular structural defect, and no other illness that could cause an increase in bilirubin levels. Three infants with bilirubin higher than 20 mg/dL had phototherapy. The length of treatment was between 12 and 24 hours. Eighteen healthy, full-term, age-matched infants served as controls and were recruited by letter from the local geographic area using information from the birth records maintained by California Department of Public Health, Office of Health Information and Research. Infants with any complications of pregnancy or labor and with parents younger than 18 years old, as indicated by their birth records were excluded. Measurements of serum bilirubin were not available for the control group but all controls had no visible neonatal jaundice. Table 1 shows characteristics of the participants.

The institutional review board for human subjects research at Stanford University (Palo Alto, CA, USA), El Camino Hospital, and the Smith-Kettlewell Eye Research Institute (San Francisco, CA, USA) approved the study. The research adhered to the tenets of the Declaration of Helsinki. Signed informed consent was obtained from the parents of the enrolled infants after explanation of the study procedures. The infants were consented and tested on the same day. They had been recruited from the nursery several weeks preceding this.

Stimulus Presentation

Stimuli were presented on a monochrome video monitor (1600 × 1200 pixels; 60 Hz vertical refresh, video bandwith, 150 MHz, model MR2000-HB; Richardson Electronics, LaFox, IL, USA). For all stimuli, the stimulus field-size was 18° × 25°. The display was viewed binocularly from 100 cm.

Three sVEP response functions were measured over wide ranges of spatial frequency, contrast and Vernier offset size. The sVEP technique has been described in detail previously.[23,30] In brief, VEP response amplitude was measured as each stimulus parameter (spatial frequency, contrast, or Vernier displacement) was varied continuously over a range covering both below- and above-threshold values. The spatial frequency tuning function was measured with a sinusoidal horizontal grating that phase-reversed at a rate of 3.76 Hz at 80% contrast.

The swept range of spatial frequency was 2 to 16 c/deg in 10 equal, linear steps. The contrast response function was measured with a 2 c/deg sinusoidal horizontal grating phase-reversed at a rate of 3.76 Hz. The contrast was swept from 0.5% to 20% in 10, equal, logarithmic steps. The Vernier-displacement stimulus comprised a 2 c/deg, 80% contrast square wave grating into which Vernier offsets were periodically introduced and removed at a rate of 3.76 Hz. The size of the Vernier offsets was swept from 8 to 0.5 min arc in 10, equal, logarithmic steps. The sweep duration for each of the three measures was 10 seconds. This 10-second presentation was preceded by a 1-second presentation of the first value of the sweep in order to allow the visual system to achieve a steady-state. The three different sweep types were presented in random order.

VEP Recording

The electroencephalogram (EEG) was amplified using a Grass Model 12 amplifier (filter settings: 1–100 Hz at –6 dB; F-E5GH; Grass Telefactor, West Warwick, RI, USA) at a gain of 20,000. Active gold-cup surface electrodes (F-E5GH; Grass Telefactor) were placed over the infant's scalp at O_1, O_z, and O_2 of the International 10-20 system. A reference electrode was placed at C_z and a ground electrode was placed at P_z. Data acquisition and stimulus presentation were controlled using an in-house software system.[31] 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 dangled in front of the monitor's display. Recordings were interrupted when the participant was judged not to be attending to the stimulus and were resumed when the participant looked back at the screen; see details in our previous studies.[23,30,32]

Statistical Analysis

The sVEP data analysis has been described in detail previously.[23,30,32] In order to quantify statistical differences in swept parameter response functions between infants with neonatal jaundice and control infants, we constructed vector mean of swept parameter responses for each epoch for each stimulus in each group of infants (Fig. 1). The noise level (uncorrelated background EEG activity) was calculated as the average amplitude at frequencies 0.5-Hz lower and higher than the stimulus driven harmonics. To estimate the standard errors of thresholds in the group average response functions, we used a jackknife procedure.[33] Significant differences between the group thresholds were identified by two-tailed, heteroscedastic *t*-tests (Tables 2, 3).

Group differences in suprathreshold response amplitudes were computed on the basis of individual participant response amplitudes and phases (vector means) and tested with multivariate analysis of variance (MANOVA) (Table 2). The vector means focused the analysis on a combination of amplitude and phase differences that comprise differences between vector means.

Results

sVEP Response Functions in Jaundiced and Control Infants

We analyzed sVEP response functions at the second and the fourth harmonics for the spatial frequency and contrast sweep measures and at the first, second, and fourth harmonics for Vernier sweep measure. These harmonic components showed the strongest responses for the stimuli. Vector-averaged response functions for the spatial frequency, contrast, and Vernier sVEP measures are shown in Figure 1. In Figure 1, the response functions for the spatial frequency (Fig. 1A), contrast (Fig. 1B), and Vernier offset (Fig. 1C) each show a monotonic decrease in amplitude as the stimulus values go from the visible to the invisible range. Visibility decreases from left to right in Figures 1A and 1C and from right to left in Figure 1B.

Two approaches were taken to quantify the differences between the groups (infants with a history of neonatal jaundice versus control infants): one was to test amplitude differences at suprathreshold values of the stimuli and the other was to estimate differences in visual threshold for each of the three stimuli. We compared suprathreshold amplitudes between the groups using the data from three most visible stimulus values at different harmonics for each stimulus condition, as indicated by the black bars in Figure 1. We submitted these data to a $2 \times 2 \times 3$ MANOVA analysis for the spatial frequency and contrast measures, and to a $2 \times 3 \times 3$ analysis for the Vernier offset measure. The between subjects factor was Group (jaundice versus control) and the within subjects factors were Harmonics (second and fourth harmonics for the spatial frequency and contrast measures, and first, second, and fourth for the Vernier offset measure), and Sweep values (three most visible stimulus values). There was a main effect of group and a significant interaction between the factors of harmonics and sweep values for the spatial frequency and contrast measures (Table 2). There was no main effect of group ($F_{(2,30)} = 1.70$; $P = 0.20$), but significant interaction between the factors of group and harmonics and significant interaction between the factors of group and sweep values for the Vernier offset measure (Table 2).

Secondly, we used regressions of the response functions to zero amplitude to estimate sensory thresholds for the group functions. The solid lines in each panel of Figure 1 indicate the regression lines calculated by a jackknife procedure.[33] Thresholds estimated from the group response functions for the two groups on all three measurements are shown in Table 3. A significant worsening of grating acuity at both second and fourth harmonic responses was present in the infants with a history of jaundice. Contrast thresholds at the second harmonic response were worse in the jaundice group. The contrast response function at the fourth harmonic (Fig. 1B, right panel) was at the noise level at all contrasts in jaundice group, as such, it was not possible to estimate a group threshold using jackknife procedure (referred to as "immeasurable sVEP thresholds"). Vernier acuity at the first and the second harmonic responses did not differ between jaundice and control groups. However, as was the case for the fourth harmonic of the contrast response, there was a large difference in responsiveness at the fourth harmonic: the response amplitudes were too low to estimate a threshold in infants with jaundice, but a threshold (1.47 min arc) was readily measured in control infants. The threshold elevations reflect the fact that the response functions were laterally shifted toward the range that the stimuli became more visible in infants with a history of neonatal jaundice compared with the control infants.

Correlation Between sVEP Thresholds and Bilirubin Level in Jaundiced Infants

We also measured sVEP thresholds from the spatial frequency, contrast, and Vernier offset response functions for each infant using the regression to zero amplitude approach. These individual sVEP thresholds were taken from the second harmonic responses in spatial frequency and contrast measures and the first harmonic response in Vernier measure. These harmonics were chosen due to their higher signal-to-noise ratio.[34]

We evaluated the correlation between sVEP thresholds and bilirubin level for all three measures (spatial frequency, contrast, and Vernier offset) in the infants with a history of

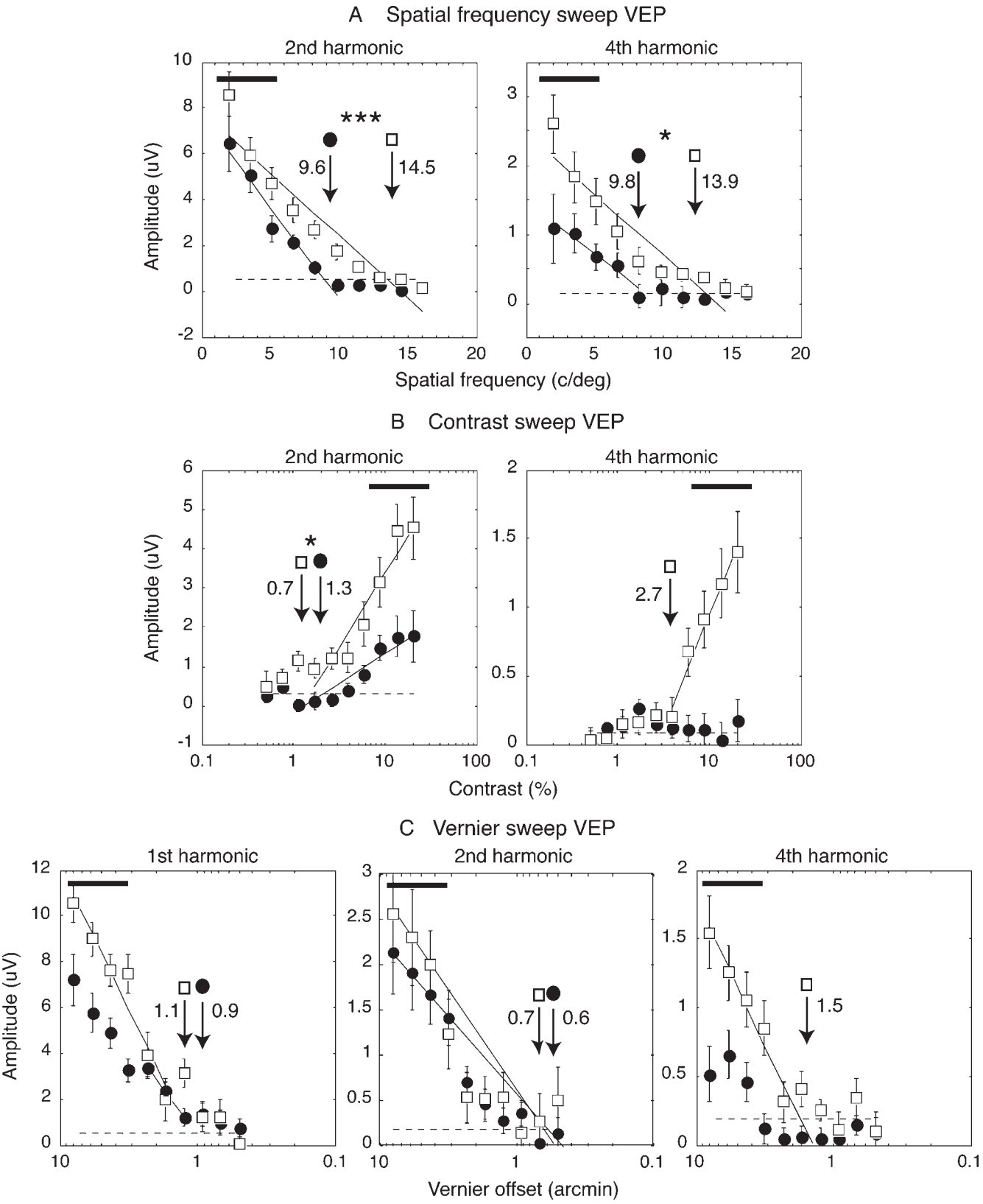

FIGURE 1. Vector-averaged group response functions in infants with a history of neonatal jaundice (*filled circles*) and age-matched control infants (*open squares*). *Error bars* indicate SEM. The *dashed line* indicates EEG noise level. The *solid lines* indicate the regression lines calculated by a jackknife procedure. The *black bars* at the *top* of each panel indicate the epochs of the three most visible stimulus values. Infants with a history of neonatal jaundice show smaller suprathreshold response amplitudes at the three most visible stimulus values compared with control infants (see MANOVA results in Table 2). Group differences in thresholds are present over spatial frequency, contrast and Vernier-offset measurements ($^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ with corrected P values; Table 3).

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Table 2. Three Most Visible Stimulus Sweep Response Amplitude MANOVA Analyses in Figure 1

Measures	Group	MANOVA		
Spatial frequency, c/deg	Jaundice, $n = 12$	Group	F (2, 26)	3.39
			P	0.049
	Control, $n = 18$	Harmonic × sweep value	F (4, 24)	13.74
			P	<0.001
Contrast, %	Jaundice, $n = 16$	Group	F (2, 31)	3.33
			P	0.049
	Control, $n = 18$	Harmonics × sweep value	F (4, 29)	5.88
			P	0.001
Vernier, min arc	Jaundice, $n = 15$	Group × harmonic	F (4, 28)	5.35
			P	0.003
	Control, $n = 18$	Group × sweep value	F (4, 28)	3.63
			P	0.0135

neonatal jaundice. We found that the Vernier thresholds were correlated with bilirubin level (Fig. 2, $r^2 = 0.428$, $P = 0.008$), but for the other measures did not correlate with bilirubin levels. Bilirubin levels for controls were unavailable, but none of the controls was visibly jaundiced at birth.

Discussion

Our measurements indicate that at 14 to 22 weeks of age, long after bilirubin levels return to normal, alterations in neural responses to visual targets can be measured in infants with a history of neonatal jaundice. The infants were evaluated nearly 5 months after their neonatal jaundice had subsided. All the infants were full term, and none had any other known condition or disease that would potentially influence central nervous system (CNS) functioning. We excluded infants with known hemolytic disease of any type.

We found that suprathreshold response amplitudes were diminished in infants with a history of elevated bilirubin levels before day 3 of life. Amplitudes were remarkably reduced at the fourth harmonic of the contrast response (Fig. 1B, right panel) and of the Vernier response (Fig. 1C, right panel) presented in the jaundiced infants, and these amplitude reductions were so large as to preclude the estimation of a response threshold (right panels of Figs. 1B, 1C; Table 3). In the remaining cases where the group response thresholds were measurable, they were also significantly elevated in the jaundiced infants in spatial frequency and contrast measures. In addition, the individual Vernier thresholds vary according to the level of hyperbilirubinemia. While this finding is mitigated by the absence of bilirubin values in the control group, it suggests a correlation and reason for further research in this area.

A diminution in response amplitude is seen in other conditions where the brain is adversely affected, for example, in generalized hypoxia and ischemia,[35] and in amblyopia,[28] although whether VEP changes in hyperbilirubunemia are permanent is debated.[20–22] The reduction in response amplitude could be indicative of either a decrease in the number of active neurons, or their degree of synchronous activation. Postmortem analysis of cortex from survivors of severe jaundice made with cresyl violate staining indicated a general sparseness of cells throughout cortex, but especially in the frontal and occipital lobes.[36]

A number of studies have reported that exposure to hyperbilirubinemia also affects the retina.[37,38] Contrast sensitivity depends on the photon efficiency of the retina and the levels of neural noise in the early visual pathway as well as the integrity of the retinogeniculate projections and visual cortex.[39] Thus, elevated contrast thresholds may result from decreased photon efficiency or increased neural noise in the retina due to neurotoxicity of hyperbilirubinemia. These same factors may also have contributed to the elevations in grating and Vernier acuity thresholds. However, these losses cannot be the whole story because these processes would affect the different response harmonics equally. We find larger response losses at the fourth harmonic for contrast and Vernier functions and this suggests that jaundice produces effects downstream from the retina, either in the geniculostriate projection or in visual cortex.

Vernier acuity is the most complex task of the three we measured and is widely believed to involve considerable cortical processing. The dose-response finding for Vernier thresholds suggests that cortical functioning is affected by hyperbilirubinemia, with infants exposed to higher levels before day 3 of life being affected the most. On the other hand, enthusiasm for this finding is mitigated somewhat by the unavailability of bilirubin values for the control infants, and therefore our inability to graph infants with low levels of bilirubin.

Table 3. Group Thresholds for the Three Measures Shown in Figure 1

Group Response			First Harmonic	Second Harmonic	Fourth Harmonic
Spatial frequency, c/deg	Jaundice, $n = 12$	Threshold ± SEM		9.62 ± 0.47	9.75 ± 1.26
	Control, $n = 18$	Threshold ± SEM		14.52 ± 0.35	13.86 ± 0.57
	Difference	P		<0.001	<0.05
Contrast, %	Jaundice, $n = 16$	Threshold ± SEM		1.30 ± 0.13	Immeasurable
	Control, $n = 18$	Threshold ± SEM		0.69 ± 0.44	2.67 ± 0.12
	Difference	P		<0.05	
Vernier, min arc	Jaundice, $n = 15$	Threshold ± SEM	0.89 ± 0.11	0.64 ± 0.13	Immeasurable
	Control, $n = 18$	Threshold ± SEM	1.05 ± 0.12	0.71 ± 0.09	1.47 ± 0.22
	Difference	P	>0.05	>0.05	

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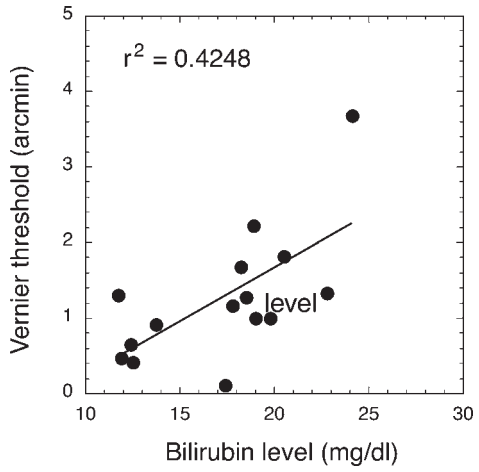

FIGURE 2. Correlation between sVEP thresholds for Vernier offset and bilirubin level among infants with a history of neonatal jaundice. The correlation was significant at the level $P = 0.008$. Without the outlier (Vernier threshold = 3.68 min arc), $r^2 = 0.26004$ and $P = 0.0521$.

The effort to define a "safe" level of bilirubin (i.e., a level that is not associated with lasting CNS dysfunction) is complicated by many factors. Only unconjugated or free bilirubin crosses the blood–brain barrier. Most studies only measure total serum bilirubin and the "free fraction" may vary, depending on the serum albumin or other physiologic factors affecting binding to bilirubin. Neurotoxicity may also be a function of both the level and the duration of exposure to elevated bilirubin levels, factors usually not accounted for in most studies. Comorbidities such as prematurity, perinatal hypoxia, infection, acidosis, and hemolysis may also increase the risk of neurotoxicity.

Limitations of the Present Study

Although findings in this study suggest a measurable and probably adverse effect on neural functioning nearly 5 months after exposure to bilirubin, our results are tempered by several issues. We did not measure "free" bilirubin and therefore cannot say with certainty that infants' brains were exposed to the type of bilirubin that crosses the blood–brain barrier. Measurements of serum bilirubin were not available for the control group, and thus we cannot definitively assign the entire difference to bilirubin, as we did not measure magnitude of the difference in bilirubin levels. Mild to moderately elevated bilirubin levels (clinical or subclinical jaundice) in the control group may be missed by visual inspection, but excluding these infants would only have increased the difference in bilirubin levels between control and jaundiced infants. The number of subjects in this study is relatively small and the two groups may not be entirely representative of the larger population. A larger study that correlates neural measures, such as those obtained here, with sensitive behavioral measures of sensory functions over a larger range of ages is needed in order to fully understand the ultimate implications of the present results obtained during infancy for functioning in the mature visual system.

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