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Does a front-end nonlinearity confound VEP acuity measures in human infants?

Catherine M. Suttle [a,*], Martin S. Banks [a,b], T. Rowan Candy [c]

[a] *School of Optometry, University of California, Berkeley, CA, USA*
[b] *Department of Psychology, University of California, Berkeley, CA, USA*
[c] *Smith-Kettlewell Eye Research Institute, San Francisco, CA, USA*

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Abstract

The visual evoked potential is commonly used to estimate visual acuity in infants. The stimulus used is temporally modulated in order to drive the cortical response. Here it is proposed that distortion products generated by a front-end nonlinearity may contaminate the acuity estimate. Specifically, the nonlinearity might convert temporal modulation of a high spatial frequency grating into apparent whole-field flicker. Thus, the VEP may reflect an artifactual response to a high spatial frequency that is not resolved at the cortical level. If this were the case, one could null or attenuate the flicker response by adding whole-field flicker to the grating stimulus. We looked for such nulling effects in 18 infants aged 6–17 weeks. No consistent evidence was found for the nulling effect, so it was concluded that infant VEP acuity estimates are not significantly contaminated by the hypothesized distortion product. © 2000 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Visual-evoked potentials (VEPs) have been used for over 20 years to measure infants' visual acuity (Sokol, 1978; Tyler, Apkarian, Levi & Nakayama, 1979; Norcia & Tyler, 1985a,b; Orel-Bixler & Norcia, 1987; Sokol, Moskowitz, McCormack & Augliere, 1988). The technique involves recording visually-driven electrical activity at the scalp over the occipital cortex. Infant VEP acuities are higher than those measured using behavioral techniques such as preferential-looking by about a factor of 2 in early infancy (Atkinson, Braddick & Moar, 1977; Banks & Salapatek, 1978; Sokol, 1978; Norcia & Tyler, 1985a). The possible causes of this difference have been widely discussed, but not resolved (Dobson & Teller, 1978; Banks, Stephens & Dannemiller, 1982; Teller, Mayer, Makous & Allen, 1982; Banks & Dannemiller, 1987; Allen, Bennett & Banks, 1992).

As the above discussion points out, the measure of acuity, or the infant's performance on the task, depends in part upon the technique used, and is not necessarily a reflection of the infant's true acuity, or competence. The determination of the true acuity as a function of age is important theoretically and clinically. It is important theoretically because theories of the neural underpinnings of functional visual development hinge on empirical measurements, including acuity (Banks, 1980; Brown, Dobson & Maier, 1987; Banks & Bennett, 1988; Wilson, 1988; Banks & Crowell, 1993). It is important clinically because visual and neural disorders are commonly diagnosed by sub-normal acuity; such diagnoses should be based, to the degree possible, on the true acuity.

In this paper, the possibility that a front-end nonlinearity in the infant's visual system gives rise to distortion products that drive the VEP was tested.[1] It was

* Corresponding author. Present address: School of Optometry, University of New South Wales, Sydney, NSW 2052, Australia. Fax: + 61-2-93136243.
E-mail address: cmsuttle@unsw.edu.au (C.M. Suttle).

[1] By a 'front-end nonlinearity', we mean a nonlinear response that occurs very early in visual processing (probably in the photoreceptors or possibly in the bipolar cells) before significant spatial interaction occurs.

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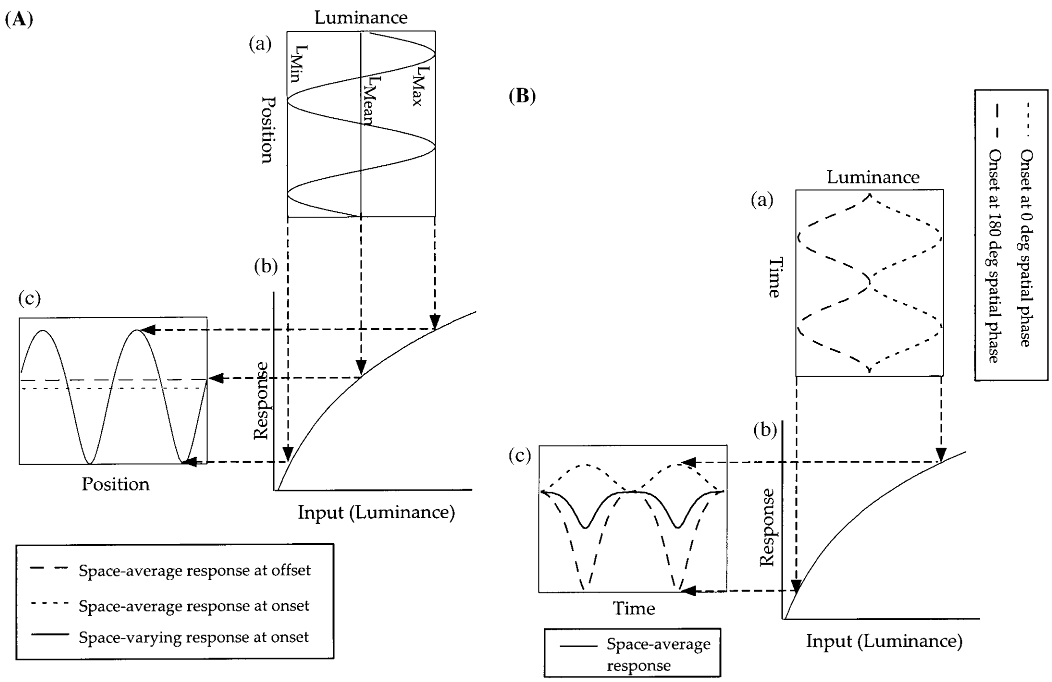

Fig. 1. (A) The spatial luminance profile of an onset–offset sinewave grating stimulus is shown (a). The solid horizontal line indicates mean luminance (occurring at pattern-offset), and peaks and troughs on the sinusoid indicate maximum and minimum luminances of the pattern, occurring at pattern-onset. These waveforms provide the input to a compressive nonlinearity (b), the output of which is shown by the solid response function (c). Space-average response is higher at pattern offset (---) than at pattern onset (· · ·). (B) Stimulus luminance at each of two points in space, with a spatial phase difference of 180 deg, is shown with respect to time (a). Luminance at pattern onset at one point is represented by the dotted curve, and at the second point by the dashed curve. The waveform is input to a compressive nonlinearity (b), the output of which is shown by the response function in panel (c). Output at the two spatial points is shown by the dotted and dashed curves. The space-average response over time is shown by the solid trace in (c). Note that space-average response is higher during the offset phase than during the onset phase of the stimulus.

proposed that the VEP may reflect responses to distortion products rather than to the spatial modulation of the pattern stimulus; if so, the VEP could overestimate acuity of the infant visual system. This idea will be referred to as the *nonlinearity hypothesis*.

1.1. Theory

Processing by the optics, retina, and early visual pathways has been described as a series of filters (Chen, Makous & Williams, 1993). The first is a linear spatiotemporal filter representing the eye's optics and photon absorption. The second filter is a nonlinearity early in visual processing. This model has been useful in explaining a number of spatiotemporal visual phenomena (He & MacLeod, 1996).

In adults, the resolution of the eye's optics and the foveal neural system are nearly matched (Campbell & Gubisch, 1966). However, spatial blurring due to the first filter (the optics and photon absorption) can be almost eliminated by presenting patterns using laser interferometry (Williams, 1985, 1988). In this way, spatial frequencies greater than the resolution of the foveal neural system can be imaged on the fovea. When adults view a laser-generated onset–offset grating, whose spatial frequency is too high to detect, they sometimes perceive a spatially-uniform temporal modulation of luminance (whole-field flicker) (MacLeod & He, 1993; He & MacLeod, 1996). The flicker percept can be nulled by adding luminance flicker to the stimulus. MacLeod and colleagues (MacLeod, Williams & Makous, 1992; MacLeod & He, 1993) have shown that the perceived flicker is generated at a nonlinearity early in retinal processing; this is the aforementioned second filter.

Infants' spatial resolution is poor (e.g. Atkinson et al., 1977), but the optical transfer function is almost adultlike (Williams & Boothe, 1981; Banks & Bennett, 1988; Candy & Banks, 1999); consequently, patterns that are passed by the optics to the infant fovea might not be resolved by later stages of the visual system. Thus, the situation generated in adults with laser interferometry may arise in infants under normal viewing conditions: when viewing a temporally modulated high spatial frequency pattern, an early nonlinearity may give rise to the percept of whole-field flicker. This flicker could then drive the VEP even though the spatial frequency in the stimulus cannot be resolved at the visual cortex.

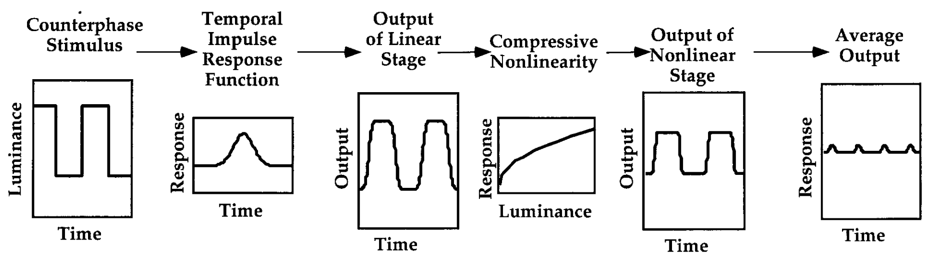

Fig. 2. This figure illustrates how a pattern-reversal grating stimulus squarewave modulated over time may give rise to the hypothesized distortion product. Stimulus luminance at one point in space is shown with respect to time (left). The photoreceptor output is linearly filtered, as indicated by the temporal impulse response function, so that response changes gradually between each temporal phase of the reversing stimulus. In the model, this response is input to a compressive nonlinearity, the space-average output of which varies over time.

He and MacLeod (1996) proposed that the flicker is generated in the following way. In Fig. 1A, a sinewave grating modulating on and off sinusoidally in time (panel a) is passed through a compressive nonlinearity (panel b) to generate an output (panel c). In panel a, the luminance profile during the onset phase is represented by the sinusoid, and in the offset phase, by the straight line. Note that there is no change in space- or time-average luminance in this stimulus. The stimulus is then passed through a compressive, nonlinear function (panel b). The mean output of the nonlinearity is greater for the offset phase of the stimulus than for the onset phase (panel c: the highest input luminance values are compressed to lower response values). The dotted line is the average response across space during stimulus onset, and the dashed line is the average response during stimulus offset.

Fig. 1B shows how the output of the nonlinearity varies over time. Panel a shows the luminance at two spatial points (180 deg out of spatial phase) with respect to time. One spatial point during the onset phase is represented by the dotted curve and the second point by the dashed curve. This luminance variation over time becomes the input for the compressive nonlinearity (panel b), the output of which is shown by the response function (panel c). In panel c, dotted and dashed curves represent response during stimulus onset. The solid line represents space-average response as a function of time. The space-average output varies at the onset–offset rate.

The modulation of the space-average output is a distortion product generated by the nonlinearity and is equivalent to whole-field flicker. One should be able to null the effect by adding whole-field flicker to the stimulus. To null the apparent flicker, the added flicker would have to create a response 180° out of phase and equal in amplitude to the distortion product. If the nonlinearity that creates the distortion product is compressive, nulling should occur when the pattern stimulus and the added luminance flicker are in phase (see Fig. 1B). In their work with adults, MacLeod and He (1993) found that nulling of the distortion product varied with temporal frequency, from a phase lead of 0 deg at high frequencies (above 24 Hz) to a phase lead of around 60 deg at lower frequencies (below 12 Hz). This indicates that the nonlinearity generating the distortion product in adults is compressive, at least at high temporal frequencies.[2]

A pattern-reversal stimulus that is sinewave modulated over time passes through the same 'on' and 'off' states as described above for the onset–offset stimulus, but twice as often per stimulus cycle. The first 'on' phase occurs when the stimulus is at maximum contrast, comparable to pattern onset. The first 'off' phase occurs when the pattern is reversing and the stimulus is spatially uniform at the pattern mean luminance, comparable to pattern offset. The next 'on' phase occurs when the pattern is fully reversed and is again at maximum contrast, but has a 180 deg spatial phase shift from the first phase. Finally, the stimulus is reversed again and passes through the spatially uniform 'off' state at the pattern mean luminance. As described above, the maximum output from a compressive nonlinearity would occur at each spatially-uniform phase, and the minimum output would occur at each maximum contrast phase. Therefore, the distortion product generated at the nonlinearity would occur at twice the temporal frequency of the stimulus (its second harmonic).

A pattern-reversal stimulus that is squarewave modulated over time changes abruptly between two maximum contrast states with an instantaneous transition through mean luminance. One would expect no modulation in space-average output in response to this type of stimulus. This modulation, however, becomes the input for photoreceptors, which act as a low-pass temporal filter, as shown in Fig. 2. A low-pass-filtered squarewave resembles a sinewave, so the input to the nonlinearity could approximate a temporal sinewave.

[2] The shift from 0 deg phase to phase leads was presumably caused by adaptation mechanisms (MacLeod & He, 1993). It is unlikely that such adaptation occurred in our experiment because the retinal intensities were much lower than the ones presented by MacLeod and He.

Consequently, the argument described above for sinewave pattern reversal could apply to squarewave modulated stimuli. Importantly, the distortion product in response to a pattern-reversal stimulus, squarewave modulated over time, is likely to be smaller than that in response to an onset–offset stimulus or a pattern-reversal stimulus sinewave modulated over time. This is because in the squarewave pattern-reversal case the distortion would not occur without temporal filtering, whereas in the onset–offset or sinewave pattern-reversal cases it would still occur without such filtering.

In the work presented here, we considered the effect the nonlinearity hypothesis would have on acuity measurements.[3] Specifically, we attempted to distinguish a response to a spatial pattern from a response to a distortion product. To do so, VEPs to onset–offset gratings were recorded with added whole-field flicker. At least two outcomes can be predicted. First, if the response to spatial frequencies near the acuity limit cannot be nulled, this would suggest that the response is a true response to the spatial variation of the stimulus, inconsistent with the nonlinearity hypothesis. Second, if nulling is observed, the result would be consistent with the nonlinearity hypothesis. Nulling would be indicated by a reduction in the amplitude of the response to the grating stimulus when flicker is added. The latter outcome would imply that onset–offset VEP acuity overestimates the spatial resolution limit in infants.

2. Methods

2.1. Subjects

Twenty-six infants were tested between the post-natal ages of 6 and 17 weeks. The infants were recruited from the City of Berkeley birth records and a signed declaration of informed consent was obtained from a parent before proceeding. Infants with a record of systemic or ocular pathology were not recruited. Results from 18 (ten male, eight female) of the infants were included in the analysis. Exclusion criteria were incomplete sets of test results and unreliable results due to sleepiness or other attention-related problems.

2.2. Stimuli and procedures

Vertical squarewave gratings were displayed on a Dotronix EM 2400 monitor with a frame rate of 66 Hz and mean luminance of 163 cd/m^2. All grating stimuli were presented at 80% contrast. The monitor was gamma-corrected regularly. The screen calibration was checked in two ways to ensure that no unintended luminance variation occurred. (1) A photometer was used to measure average luminance at different temporal phases of the stimulus. (2) Two adults viewed the monitor from a viewing distance at which they could not resolve the grating. We then presented the temporally modulated stimulus used in the experiments and asked if they could detect any flicker. They could not.

Five types of stimuli were used: (1) onset–offset gratings were used to measure each infant's normal VEP acuity for use in the main experiment; (2) pattern-reversal gratings were also used to measure acuity and allowed comparison with onset–offset acuity; (3) fixed spatial frequency onset–offset gratings were used to select a high 'critical' spatial frequency; (4) whole-field flicker was used to see if a flicker VEP response could be obtained; and (5) the 'critical' spatial frequency grating plus flicker constituted the main experimental condition.

2.2.1. Onset–offset grating acuity

The onset–offset gratings were squarewave temporally modulated at 5.5 Hz. Squarewave modulation was used rather than sinewave modulation because it is more commonly used for infant acuity measurements. The VEP was recorded in response to onset–offset gratings decreasing linearly in spatial frequency over a 10-s sweep period. Viewing distance was 1–2 m, depending on the highest spatial frequency presented. The highest frequency was determined by the infant's age. Visual acuity was determined by linear extrapolation to zero response amplitude (Tyler et al., 1979; Norcia & Tyler, 1985b; Norcia, Clarke & Tyler, 1985). As conventionally noted, the largest response to onset–offset gratings and to flicker was at the fundamental frequency, while the response to pattern-reversal stimuli was dominated by the second harmonic component. Consequently, response amplitude at the fundamental frequency was used to estimate onset–offset acuity, and amplitude at the second harmonic was used to estimate pattern-reversal acuity.

2.2.2. Pattern-reversal grating acuity

In 13 of the 18 infants included in the analysis, visual acuity was also determined using pattern-reversal gratings for comparison with onset–offset acuity estimates. Vertical squarewave gratings were squarewave phase-reversed at 5.5 Hz. As with the onset–offset gratings, a range of spatial frequencies was presented over a 10-s period in order to determine acuity.

We did not attempt to null the pattern-reversal responses. Pattern-reversal and onset–offset stimulus trials were interleaved as much as possible to increase the

[3] Teller et al. (1982) proposed that the alleged infant preference to look away from a high spatial frequency grating (Held, Gwiazda, Brill, Mohindra, & Wolfe, 1979) might be the result of distortion caused by a compressive nonlinearity. Their hypothesis is similar to the one proposed and evaluated here.

comparability of acuity estimates. As explained earlier, a distortion product would be easier to create with onset–offset presentation. The nonlinearity hypothesis, therefore, predicts higher acuity estimates with onset–offset than with pattern-reversal stimuli.

2.2.3. Fixed spatial frequency grating

VEPs were recorded in response to onset–offset gratings at a fixed spatial frequency near the previously determined VEP acuity limit. A frequency near acuity was chosen because the responses to high spatial frequencies are most likely to be contaminated by the hypothesized distortion product. The appropriate spatial frequency was chosen by first recording the VEP in response to gratings at a frequency just lower than acuity. If the response was insignificant, the frequency was decreased in steps of 0.5–1 cyc/deg until a significant response was evoked. The highest spatial frequency at which a significant response was recorded will be referred to as the *critical spatial frequency*.

2.2.4. Whole-field flicker

The hypothesized distortion product should, by our reasoning, drive the VEP in the way whole-field flicker would. For this reason, responses to whole-field flicker (no grating) were recorded, to determine whether the response was significant, in each individual infant. If so, the final condition of the experiment (see below) was also carried out. If the response to flicker was not significantly above noise, the final condition was carried out in some cases, but not in most. Whole-field luminance modulation increasing linearly from 0 to 18 cd/m^2 across a 10-s sweep period was added to the uniform field of 163 cd/m^2. Thus, the luminance would vary from a constant 163 cd/m^2 at the start of the sweep to modulation between 163 and 181 cd/m^2 at the end of the sweep. The flicker was squarewave modulated at a temporal frequency of 5.5 Hz.

2.2.5. Grating plus flicker

The swept whole-field flicker stimulus was added to the fixed critical spatial frequency onset–offset grating stimulus. The response to the grating plus increasing flicker was recorded over the 10-s sweep period. For the first set of trials, the relative phase between the added flicker and grating was set to zero, so that flicker amplitude was highest at pattern-onset and lowest at pattern-offset. Responses to as many relative phases as possible were then recorded from each infant. The number of phase conditions varied from one (0 deg only) to five (0, 180, 90, 45, and 135 deg). As mentioned previously, perceptual nulling occurs in adults between 0 and 60 deg relative phase depending on temporal frequency (MacLeod & He, 1993; see Footnote 2).

2.3. VEP recording and analysis

Infants viewed the stimuli while seated either on their parent's lap or in an infant seat. Evoked responses were recorded from O1 and O2 of the International 10–20 system, and both were referred to Oz, with Cz used as ground. Scalp positions were abraded using Omniprep before 1-cm diameter gold cup Grass electrodes were attached using EEG conductive paste. Active and reference electrodes were held in place using an elastic headband. Responses were amplified and bandpass filtered by Grass P511 amplifiers. The response recorded over a 10-s sweep period constituted one trial; at least three, in most cases five, trials were averaged. Response amplitude and phase were extracted from the signal, at the 1st, 2nd, 3rd and 4th harmonics of the stimulus temporal frequency (5.5 Hz) using a recursive least squares filter (Tang & Norcia, 1995). For each harmonic, amplitude and phase at two adjacent frequencies were also extracted, and their mean value was used to estimate EEG noise levels. Responses with a peak signal-to-noise ratio of 3:1 or greater were considered significant (Norcia et al., 1985).

3. Results

The following effects should be observed if the nonlinearity hypothesis is correct. (1) Infants should exhibit a significant VEP to whole-field flicker presented by itself, at the same harmonic used to estimate acuity. This is required because the hypothesis claims that the distortion product has the same characteristics as whole-field flicker. (2) The response to a high-spatial-frequency grating plus whole-field flicker should change in a particular fashion as the flicker amplitude is increased. At low flicker amplitude, the response should be quite similar to the response to a grating alone. At high flicker amplitude, the response should be similar to the response to flicker alone. At an intermediate amplitude, the response should decrease as the whole-field flicker nulls the distortion product. (3) Onset-offset acuity should be higher than pattern-reversal acuity. Here we discuss whether the results are consistent with these expectations.

As expected, the largest response to onset–offset gratings and to flicker was at the fundamental harmonic (5.5 Hz). In all results shown, the signal is the response at 5.5 Hz, and noise is the mean of responses at 4.5 and 6.5 Hz. The results fell into three groups as shown by Table 1.

Figs. 3–6 show sweep VEP results for different infants. In each case, the signal amplitude (filled squares), signal phase (circles), and noise amplitude (open squares) are plotted as a function of time. The upper panels in the figures show the VEP response when the

Table 1
Classification of results

	No flicker response	Flicker response but no nulling	Flicker response and nulling
No. infants	11	5	2
Age range	6–13 weeks (mean 9 weeks)	7–15 weeks (mean 9 weeks)	14 and 13 weeks

stimulus was a grating of fixed spatial frequency (the critical frequency). The middle rows show the response when the stimulus was whole-field flicker that increased in amplitude overtime. The lower rows show the response when the stimulus was the critical spatical frequency grating plus whole-field flicker and the flicker amplitude increased over time. It is useful to divide the results into three groups (Table 1): infants who exhibited no response to whole-field flicker, infants who exhibited a flicker response, but no nulling, and infants who exhibited a flicker response and nulling.

3.1. No flicker response

Of the 18 infants, 11 demonstrated no significant response to whole-field flicker. This finding is exemplified by one infant whose results are displayed in Fig. 3. Panel a shows the response over the 10-s sweep period to the critical spatial frequency, onset–offset grating. The response to the grating is significantly above noise, and signal phase is fairly constant. Panel b shows the sweep VEP to increasing flicker over the 10-s period with no grating present. The evoked response is not significantly above EEG noise levels at any flicker amplitude and signal phase is not constant. Panel c shows the response when the increasing flicker stimulus was added to the critical spatial frequency grating at 0 deg relative phase. The amplitude of the grating response decreases steadily over the first 5 s of the sweep; the decrease could manifest nulling. However, response phase remains fairly constant across the sweep. All 11 infants in this group showed no significant response to flicker. The small response to flicker, in addition to the relatively constant phase when flicker is added to the grating stimulus, is evidence that the decrease in amplitude (Panel c) is not a manifestation of nulling. The data from these infants provide little evidence for the nonlinearity hypothesis.

3.2. Flicker response: no nulling

The remaining seven infants all demonstrated significant responses to flicker alone. In five of them, the response to a critical frequency grating was not diminished (nulled) when flicker was added. This behavior is exemplified by one infant's data in Fig. 4. Similar results were obtained from the other four infants. If the response to the onset–offset grating were due to the distortion product described above, one would expect the addition of real flicker to have a nulling effect at an appropriate amplitude and temporal phase. Nulling was not observed in any of these five infants, which suggests that the VEP was not a response to the distortion product.

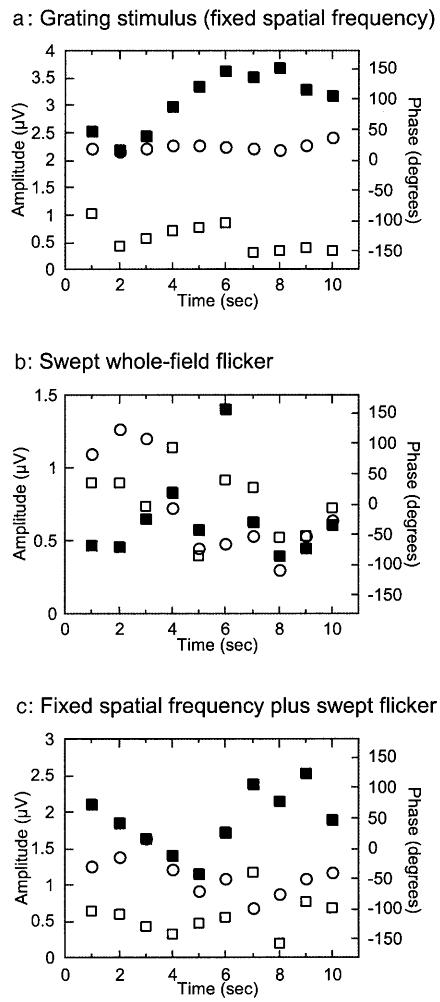

Fig. 3. Results from one infant (AS; 8 weeks post-natal). The ordinates for each panel are amplitude (left side) and phase (right side). ■, represent signal amplitude; □, represent noise amplitude; and ○, represent signal phase. The results for this infant show an evoked response significantly above noise to the critical spatial frequency (7 cyc/deg) onset–offset grating stimulus (a), no significant response to the flicker–only stimulus (b), and no effect on the grating response when flicker is superimposed.

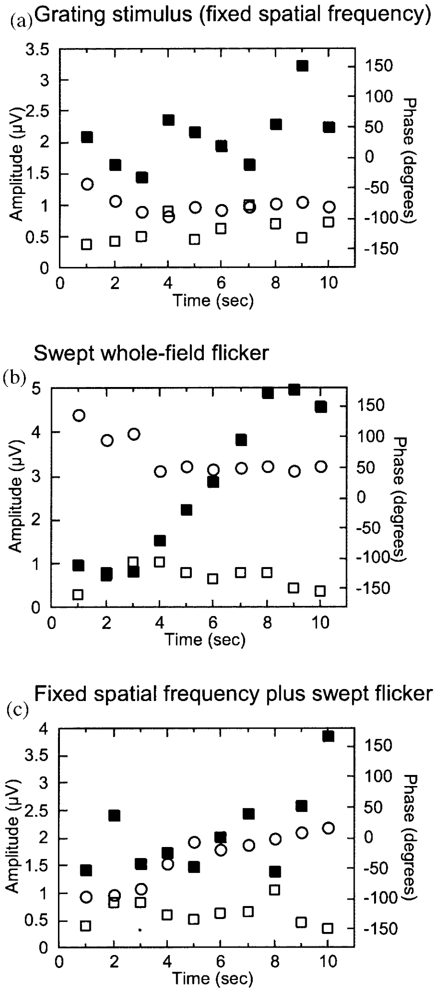

Fig. 4. Results from one infant (CH; 15 weeks post-natal). The axes and symbols are described in the caption to Fig. 3. The results show an evoked response significantly above noise to the critical spatial frequency (5 cyc/deg) onset–offset grating stimulus (a), an evoked response significantly above noise to the flicker–only stimulus (b), and no effect on the grating response when flicker is superimposed (c).

It remains possible that we failed to observe nulling because the flicker was not added at the appropriate amplitude and phase. It is, however, unlikely that we missed the appropriate amplitude because a wide range of flicker amplitudes was presented (0–18 cd/m^2). In addition, in most of these infants the response to the highest modulation whole-field flicker reached amplitudes above that of the response at the critical spatial frequency. The flicker response should, therefore, have been large enough to allow nulling. In regard to the phase, one would expect nulling to occur with added flicker at a relative phase of 0 deg for a compressive nonlinearity (MacLeod & He, 1993) or at 180 deg for an expansive nonlinearity. Flicker was always presented at 0 deg relative phase, and usually also at 180 deg so the appropriate phase was probably presented. Adaptation like MacLeod and He (1993) observed, would affect the appropriate phase, but it is unlikely that such adaptation occurred in our experiment because the retinal intensities were much lower than the ones presented by MacLeod and He.[4] For these reasons, it is

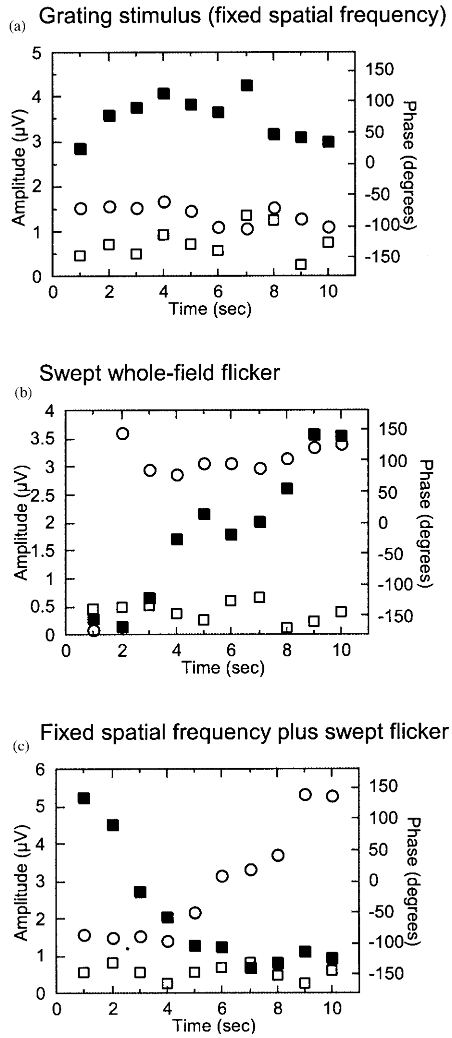

Fig. 5. Results from one infant (GS; 10 weeks post-natal). The axes and symbols are described in the caption to Fig. 3. The results show an evoked response significantly above noise to the critical spatial frequency (12 cyc/deg) onset–offset grating stimulus (a), and an evoked response significantly above noise to the flicker-only stimulus (b). When the grating and flicker stimuli are combined (c) the response amplitude decreases, and signal phase changes from that corresponding to the grating response (a) to that corresponding to the flicker response (b), as flicker amplitude is increased.

[4] If the grating response in these infants was due to the hypothesized distortion product, in what phase should we have presented the nulling flicker stimulus in order to cancel the distortion product response? There are two relevant sources of information on this point. (1) MacLeod and He (1993) found that the most effective nulling flicker stimulus had a phase of 0 deg relative to the grating stimulus. (2) We have data on the grating-alone and flicker-alone responses in infants who showed a significant flicker response (see Figs. 4–6). The phase differences (when the response amplitudes were high) were all within 40 deg of 180 deg. Thus, if the hypothesized distortion product caused the grating response, we would need to add nulling flicker at roughly 0 deg phase to cancel it. The nulling flicker was always presented at 0 deg phase (and sometimes at other phases, too) so we are confident that the nulling stimulus was presented in the appropriate phase or close enough to it.

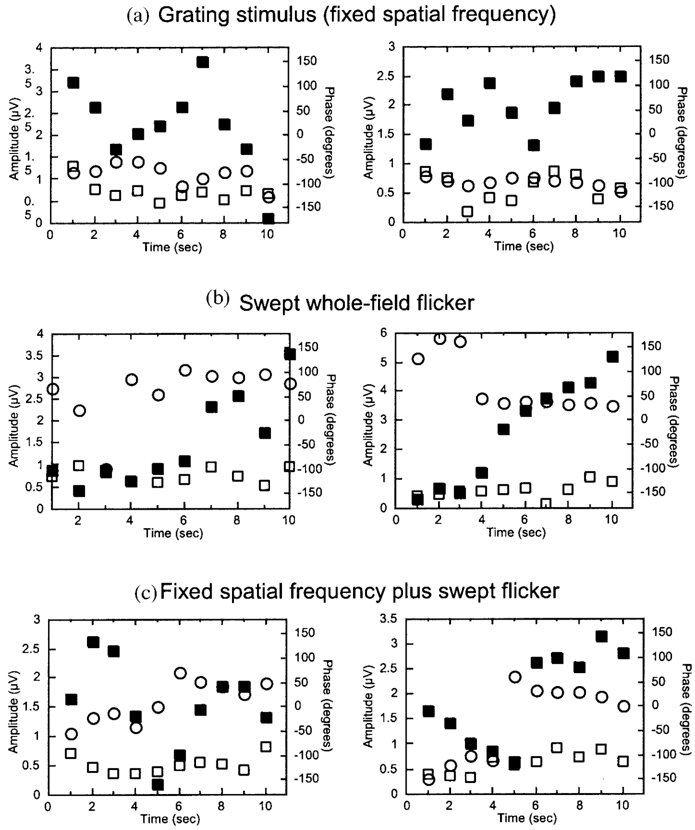

Fig. 6. Results from infant JO. The axes and symbols are described in the caption to Fig. 3. Left column shows results at age 13 weeks post-natal, and right column shows results 4 weeks later, at age 17 weeks. Responses to the critical spatial frequency (8 and 7 cyc/deg, respectively) onset–offset grating stimulus (a), and to flicker (c) are significant. When flicker is added to the grating (b) response amplitude decreases, and in this infant subsequently increases. As flicker increases, signal phase switches from that corresponding to this infant's grating response (a) to a level which corresponds to the flicker response (c), as also seen in results from infant GS (Fig. 5).

unlikely that we failed to observe nulling due to presentation of inappropriate amplitudes and phases. Thus, the nonlinearity hypothesis probably does not explain these infants' acuity data.

3.3. Flicker response: nulling observed

Two infants demonstrated clear responses to flicker alone and then some nulling when flicker was added to the grating stimulus. Their results are shown in Figs. 5 and 6; the two sets of data in Fig. 6 were collected from the same infant at different visits. In both infants, the response to flicker alone was significant (Fig. 5b; Fig. 6b) and response phase was constant when the luminance modulation was greater than ~ 6 cd/m^2. When flicker was added to the critical frequency grating at a relative phase of 0 deg (Fig. 5c; Fig. 6c), the response amplitude and phase changed in ways consistent with the nonlinearity hypothesis. Specifically, when the flicker amplitude was low (0–4 s on the time axis), the response amplitude was significantly greater than noise, and the response phase was the same as that of the grating (or distortion product) response (Fig. 5a; Fig. 6a). In other words, at low flicker amplitudes, the evoked response was driven by the grating or the distortion product. As the flicker amplitude increased, the response amplitude decreased. In one infant (Fig. 6c), amplitude increased with a further increase in flicker amplitude; in the other infant (Fig. 5c), it did not. The decrease in response amplitude with increasing flicker modulation could be evidence for nulling of the distortion product by added whole-field flicker; the decrease is consistent with the nonlinearity hypothesis. However, as will be argued in Section 4, there is another possible explanation for the amplitude decrease that cannot be ruled out. It is interesting to note that the response phase changed as the flicker amplitude was increased; this is evidence that the grating or distortion product drove the evoked response at low flicker amplitudes and that the flicker drove it at high flicker amplitudes. (Note that the distortion product should have the same phase as the flicker response because the post-nonlinearity processing would treat the two equivalently.)

We tested one of of the infants exhibiting nulling (JO) on two occasions, at 13 and 17 weeks of age (Fig.

6, left and right columns, respectively). The retest results showed a similar pattern of amplitude and phase change, so the nulling effect was repeatable.

3.4. Onset–offset versus reversal acuity

Onset–offset and pattern-reversal acuities were compared because the nonlinearity hypothesis predicts higher onset–offset than reversal acuity estimates (see Section 1). It was possible to estimate both acuities in 13 infants.

The average onset–offset acuity (8.8 cyc/deg) was indeed significantly higher ($P = 0.04$) than the average pattern-reversal acuity (6.7 cyc/deg). This outcome is consistent with the hypothesis, but is not strong evidence in favor of it. If the difference between onset–offset and pattern-reversal acuities were a manifestation of the VEP being driven by distortion products, one would expect to find the difference in only those infants who had demonstrated a response to flicker alone. On the contrary, there was no systematic relationship between the acuity difference and the response to flicker alone. Thus, the acuity difference offers little support for the nonlinearity hypothesis.

4. Discussion

The infant visual system as a whole has very poor spatial resolution, but the optical transfer function is similar to the adult function. For this reason, spatial frequencies far beyond the system's acuity cutoff can be imaged on the retina. In this circumstance, temporally modulated, high-spatial-frequency stimuli could generate visible time-varying distortion products even though the stimuli themselves cannot be spatially resolved by the whole visual system (MacLeod & He, 1993; He & MacLeod, 1996). The distortion products would be created at a nonlinearity early in visual processing and would have the same appearance and VEP-driving properties as whole-field flicker. If this occurred, the VEP might overestimate the spatial acuity of the infant visual system.

We tested this hypothesis — the nonlinearity hypothesis — by looking for signs of the time-varying distortion product. In the main experiment, we asked whether adding spatially uniform flicker to a high-spatial-frequency stimulus could lead to a *decrease* in response; that is to say, we asked whether we could null the grating response by adding uniform flicker. Most (11 of 18) infants showed no significant evoked response to flicker alone. If infants do not exhibit a clear response to flicker alone, it is hard to imagine how the hypothesized distortion product could be the primary source of the VEP in conventional acuity measurements. Thus, this finding is clearly inconsistent with the nonlinearity hypothesis.

The remaining seven infants exhibited significant evoked responses to flicker alone, a result that might offer support for the nonlinearity hypothesis. In five of these infants, however, it was not possible to null the response to a near-acuity grating by adding flicker. This latter result is inconsistent with the hypothesis.

Before rejecting the nonlinearity hypothesis as an explanation of the acuity data from these infants, we should consider alternative explanations for the inability to null the grating response with uniform flicker. There are four possible alternatives: (1) the spatial frequency of the grating was either too high or too low; (2) the amplitude and/or phase of the added flicker was inappropriate to null the distortion product; (3) the age range tested was not the most likely to demonstrate distortion; and (4) the whole-field flicker added does not have the characteristics of the flicker distortion product created at the nonlinearity. Each of these possible explanations is considered before turning to the data from the two infants who exhibited nulling.

In regard to the choice of spatial frequency, we had to present gratings of spatial frequencies too high to be resolved by the system as a whole, but low enough to plausibly create the hypothesized distortion product. It is conceivable that the spatial frequencies used were too low to satisfy these conditions. Perhaps it would have been possible to demonstrate response nulling with added flicker at higher spatial frequencies. This seems unlikely, however, because we chose the spatial frequency based on the outcome of a VEP acuity measurement. In each case, acuity was measured in order to determine the critical spatial frequency for the main experiment. In most cases, the critical frequency was within 70% of the measured acuity (50% in one case), so it was high enough to plausibly produce the hypothesized distortion product and low enough to drive a measurable response.

The flicker amplitude and phase also had to be chosen wisely in order to provide a fair test of the nonlinearity hypothesis. As was mentioned earlier, the appropriate amplitudes and phases were probably covered because a wide amplitude range and the most likely phases were presented (0 and 180 deg). It remains possible, however, that nulling would have been observed at a different phase (MacLeod & He, 1993).

Perhaps an inappropriate age range was tested. The difference between VEP and FPL acuity is greater in infants 12–24 weeks of age than in younger infants (Dobson & Teller, 1978). Infants 6–17 weeks of age were tested, which may have been too young to observe the distortion that characterizes the nonlinearity hypothesis. On the other hand, the disparity between the infant's acuity and the resolution of the retinal image decreases with age as the child's acuity improves. Consequently, the range of spatial frequencies that are high enough to be unresolved by the system as a whole, but low enough to form a high-contrast retinal image becomes smaller with age. Thus, it would have been very difficult to test the hypothesis in older infants. We think we chose the most plausible age group.

Perhaps the whole-field flicker which was added to the gratings does not have the same VEP-driving properties as the hypothesized distortion product. This explanation for the failure to find evidence for the nonlinearity hypothesis is reasonable, but essentially impossible to test. The hypothesized distortion would presumably be created at the photoreceptors or bipolar cells, so it would be a local effect (MacLeod et al., 1992; MacLeod & He, 1993). It is known that the receptors and bipolars differ markedly as a function of retinal eccentricity even in human infants (Hendrickson & Drucker, 1992; Candy, Crowell & Banks, 1998), so it seems plausible that the distortion product could differ in amplitude and even phase from one retinal location to another. The whole-field flicker presented was obviously uniform in amplitude and phase across the retina and perhaps it does not drive a VEP in the same way as a flickering stimulus whose amplitude and phase differs with position.

There were some data that were consistent with the nonlinearity hypothesis. In two infants, significant responses to flicker alone and nulling of the response to the grating were observed when whole-field flicker was added. There is, however, another explanation for these data that does not require the nonlinearity hypothesis. It is conceivable that the grating-plus-flicker stimulus generated two cortical responses, one to the grating and another to the flicker. The two stimuli — grating and flicker — were in 0 deg relative phase in most of the measurements, but their responses could become out of phase at the cortex if different neural mechanisms subserve responses to high-frequency gratings and whole-field flicker. The grating and flicker responses would be necessarily summed at the VEP electrodes, so perhaps the nulling observed was the consequence of cancellation of the responses at the electrodes rather than nulling of a flickering distortion product. The only way to decide is to ask the subject what the percept looks like and this obviously cannot be done with infants in the age range of interest.

To ask about the percept, we might consider doing a forced-choice preferential looking experiment. Pilot observations by Hartmann and Banks (1992) suggest that young infants may not preferentially fixate such stimuli (although Teller, Lindsey, Mar, Succop & Mahal, 1992, observed some responses to very high flicker contrasts). For this reason, we did not attempt to record FPL responses in the present study.

In conclusion, the possibility that VEP acuity estimates are contaminated by distortion products created at a nonlinearity early in visual processing was considered. Specifically, we looked for evidence for such distortion products by attempting to null the response with added whole-field flicker. Little evidence was found to support the nonlinearity hypothesis because most infants did not exhibit a clear VEP to whole-field flicker alone. Two of the 18 infants exhibited a response to flicker alone and a decreased grating response when flicker was added; these data are consistent with the hypothesis. Even this result can be explained, however, without the nonlinearity hypothesis. We concluded, therefore, that VEP acuity estimates are generally not contaminated by nonlinear distortion products of the sort considered here.

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