Principles and Practice of Clinical Electrophysiology of Vision

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Visual Acuity Estimation in Infants by Visual Evoked Cortical Potentials

Christopher W. Tyler

PHILOSOPHY OF VISUAL TESTING IN INFANTS AND CHILDREN

Accurate visual testing has an immense clinical significance in the first few years of life because the developing nervous system is most vulnerable to disruption during this time. A complementary motivation is that a developing system has the plasticity to recover from disruption during the same period, but such recovery becomes progressively less effective as the years go by. Thus visual testing is needed both to identify the degree of disruption and to monitor and guide the clinical treatment.

Nevertheless, visual tests of all types are likely to underestimate the visual skill they test in children, particularly in infants, for three reasons. First, any test of visual function, such as visual acuity, requires some level of visual performance from the infant. This is obviously true of behavioral tasks, but it is also the case for electrophysiological indices such as the visual evoked potential (VEP) because the optimum acuity is obtained when the infant's eyes are properly focused on the target. (An exception to this requirement is the electrical response to uniform field stimulation through the eyelids, but this is essentially a measure of light perception rather than a measure of any practical visual function.)

A related factor is the infant's cooperation in allowing placement of the requisite electrodes for VEP and eye movement studies. Infants may be expected to be less motivated than adults to pay full attention to the target for the duration of the test.

Finally, there are additional sources of noise in infant VEP testing relative to adults, and this makes it harder to determine the limiting signal levels corresponding to optimal performance. This is particularly a problem in electrophysiological assessment, where electrical noise from high levels of muscle activity may be superimposed in the signal from the eye or the brain.

In summary, there is no magic technique that is immune from the difficulties of infant testing. Each type of test—eye tracking, electrophysiological, and behavioral—should best be viewed as measuring visual performance at their respective levels of visual processing. The electroretinogram (ERG) measures retinal function, the VEP measures early cortical function, and behavioral tests assess the overall performance of the complete visual system. Each has a place in the full evaluation of visual loss since it may show losses at one level to which the other techniques are insensitive.

VISUAL PERFORMANCE TASKS AND THEIR USES

All the following visual tasks are of interest from the standpoint of the processes of visual development. Their clinical relevance varies, both in relation to common visual disorders and in relation to the age of the patients.

Grating Acuity

Grating acuity is a pure measure of visual resolving power in terms of the narrowest bar pattern to which a visual response can be obtained. Grating

acuity is pure in the sense that it is not influenced by interactions between cortical mechanisms responding to different pattern elements, in the way that Snellen letter acuity is, for example. The detectability of different Snellen letters differs, even though they are all composed of lines of the same thickness. Such differences, which can be attributed to interactions between the pattern elements in the letters, are absent in the uniform bars of a grating stimulus (see Chapter 58).

Grating acuity is also a purer measure than is checkerboard acuity, which is often measured electrophysiologically. This is partly because of the nature of the fundamental Fourier component, which is all that remains of the checkerboard at the acuity limit when filtered by the optics of the eye.[36] Consequently, the spatial frequency of the fundamental component differs from the spacing of the checks because it is oriented at ±45 degrees to the orientation of the edges of the checks. However, checkerboard acuity is a valid acuity measure if its properties are clearly understood. In particular, the checkerboard would need to be placed at a 45-degree angle to provide an unbiased measure of the acuity for vertical and horizontal bars. The analysis of grating and checkerboard stimuli is depicted in Figure 52–1 for check sizes of 1 minute of visual angle (corresponding to 20/20 letters on a Snellen chart). The sinusoidal grating is shown at the fundamental spatial frequency of 21 cycles per degree for this checkerboard (a period of 1.4 minutes or a width of 0.7 minutes for each bright or dark bar). In the standard configuration, checkerboard acuity is subject to the oblique effect of reduced acuity for oblique gratings[7] and thus underestimates acuity by about one third in addition to the misestimation that would occur if the fundamental frequency were not taken into account. Electrophysiological studies on the development of grating acuity are reviewed below.

Contrast Sensitivity

Contrast sensitivity is a measure of visual response to low levels of contrast (gray on gray) for patterns that are easily detectable at high contrast. This task provides a measure of the signal-to-noise ratio (SNR) required for the most sensitive visual detectors. It is affected by visual disorders, such as cataract, that reduce the contrast of the visual signal or those, such as optic neuritis, that increase its noise level. It was first measured electrophysiologically in infants by Atkinson and associates.[2]

Vernier Acuity

Vernier acuity measures the visual response to small displacements of a visible target. In adults, the

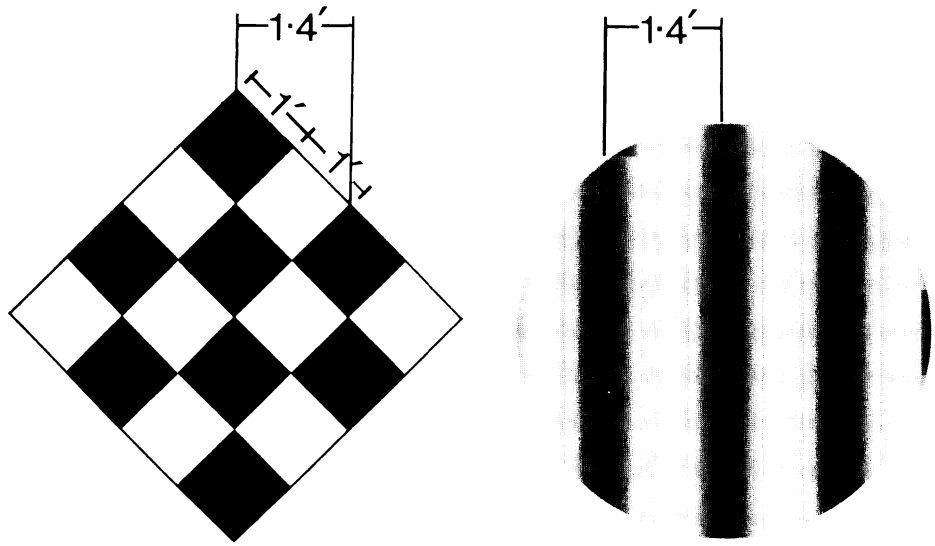

FIG 52–1.
Comparison of grating and checkerboard stimuli. The *right* panel shows that checks of 1 minute on a side (near the acuity limit) generate light and dark strips with a period of 1.4 minutes (not 2 minutes). When the checkerboard is oblique, the fundamental Fourier component of the pattern is a vertical sinusoid, as shown in the *left* panel (plus a horizontal component, not shown).

threshold displacement for vernier acuity is usually much less than the size of the bars and much less than the narrowest visible bars; hence it has been called a hyperacuity measure.[41] The main configuration that has been studied is to record the response to shifts in a grating by a small amount relative to the width of its bars. Vernier acuity has been measured in infants both behaviorally[30] and electrophysiologically.[16]

Stereopsis

Tests of the pure three-dimensional sensation of stereoscopic depth provide the most sensitive measure of the precision of binocular function in integrating the separate images from the two eyes. They also provide an initial assay of monocular acuity and equality in the binocular viewing situation. If either eye is not operating at a full performance level, stereopsis will also suffer.

VEP studies of the development of binocularity and stereopsis have been conducted by Braddick et al.[6] and Petrig and colleagues.[25] Developmental progression on each of these tasks has been explored by several methods that have provided valuable information about the mechanisms of human development. Many other interesting tasks have also been studied electrophysiologically, including the development of intracortical inhibition,[18] binocular rivalry,[5] etc.

MEASUREMENT METHODS

The most commonly used method for visual assessment is the determination of visual resolution or acuity—the smallest example of some pattern that can be resolved. Although the other tasks mentioned above are all used to some degree in adult testing, there have been essentially no efforts to apply them to routine testing in infants. Visual acuity will therefore be taken as the exemplar for describing the array of electrophysiological methods that are available for testing in infancy and childhood.

Electroretinogram

For ophthalmological diagnosis the ERG has the advantage of being a signal derived from a fairly well-established level of retinal processing. It should therefore be of value in assessing the integrity of optical and early retinal dysfunction. From the point of view of visual acuity measurement in infants, however, the ERG has two major disadvantages. One is that the pattern ERG has only been studied relatively recently and is technically difficult to generate up to the acuity limit because of interference with the optical quality of the eye. The other is that the optimal method for ERG measurement is the corneal contact lens electrode, which is a relatively invasive procedure for young infants. For these reasons the ERG has yet to be used as a method of acuity measurement in infants.

Transient Visual Evoked Potential

The first study of infant acuity by the use of transient VEPs seems to have been by Marg et al.,[17] although Harter and Suitt[14] had earlier measured transient VEPs in infants 1 to 6 months old. Marg et al.[17] took the step of varying check size up to and beyond the acuity limit and determining the smallest stripe pattern that could elicit a reliable response. This is then a true acuity measurement, and the data showed the remarkable result of infant acuities reaching adult levels of 30 cycles per degree by 6 months of age. The amplitude properties for transient VEPs' to larger check sizes were also shown to be similar to the adult form by the same age in a study by Sokol and Dobson.[32] Such data were extended over the full range of childhood by Spekreijse.[35]

Any doubt that was cast by the small number of infants involved in the original finding of adult acuity levels as early as 6 months has been removed by the recent replication performed by Orel-Bixler and Norcia,[24] who obtained almost identical data on the same apparatus as used by Marg et al.[17] They also evaluated the effect of the scoring criterion, the results of which will be discussed in a following section.

Visual Evoked Potential Latency

A clear correlation between VEP latency and visual acuity during development has been established by Sokol and Jones,[31, 33] who claim that latency is therefore a valid measure of acuity. They also show that the latency measure is relatively reliable and can be established in a short time since it requires the presentation of only one size of stimulus.

The problem with this approach is that a correlation established in normal observers may not hold under conditions of visual dysfunction. There are many examples of diseases, such as demyelination of the optic tract, that may cause a slowing of the

cortical VEP without affecting visual acuity. If an unknown condition is found that produces slowing of the VEP, it may therefore be incorrect to suppose that the increased latency implies a lower acuity. The same logical flaw applies to developmental studies. Even though latency decreases as age increases, there is no necessarily causal relation among individuals of the same age, and acuity and latency need not be related. However, if latency is pathologically increased, some visual defect—nor necessarily a loss of visual acuity—can be expected.

Steady-State Visual Evoked Potential

If the stimulus presentation is increased to a sufficiently high rate (about 8 Hz), the brain response becomes sinusoidal and is said to have reached a "steady state."[8, 12, 34] This approach has the advantage of simplifying the amplitude specification to a straightforward peak-to-trough measurement without requiring decisions as to which components to measure, of increasing the stimulus rate for improved noise averaging, and of allowing the use of frequency analysis to eliminate noise contributions from distant frequency regions.

It should be mentioned that the steady-state response is still subject to additive and subtractive interactions between different components of the VEP because they vary in amplitude with stimulus variables such as spatial frequency of the bar stimuli. Tyler et al.[38] showed that the spatial and temporal amplitude spectra contained numerous peaks and troughs rather than the smooth profile typical of psychophysical sensitivity profiles.[29] The steady-state amplitude at a particular frequency is therefore unsuitable for use as a direct indicator of visual acuity.[27] Instead, it is important to extrapolate to zero amplitude to obtain the best estimate of the point at which no response should first have been obtained. The extrapolation should be done in such a way as to maximize the resolution of acuity differences in the spatial frequency region of the acuity limit.[37]

The Sweep Visual Evoked Potential Technique

The idea of recording the steady-state response continuously while sweeping rapidly through a large range of stimuli was introduced by Regan.[28] This technique was first applied to the measurement of grating acuity by Tyler et al.,[37] who used a 12-Hz counterphase grating swept through a set of spatial frequencies up to and beyond the acuity limit (Fig 52–2). When they analyzed the brain response at the reversal rate of 24 Hz, they showed good correlations between the acuity extrapolated from the linear sweep of spatial frequencies and psychophysical acuity when acuity was degraded by blurring, reducing contrast, reducing luminance, or moving the stimulus out to the peripheral retina. The technique was found to be relatively robust to differences in the temporal recording frequency[38, 39] despite wide variations in reponse amplitude with spatiotemporal stimulus conditions.[20, 31, 38]

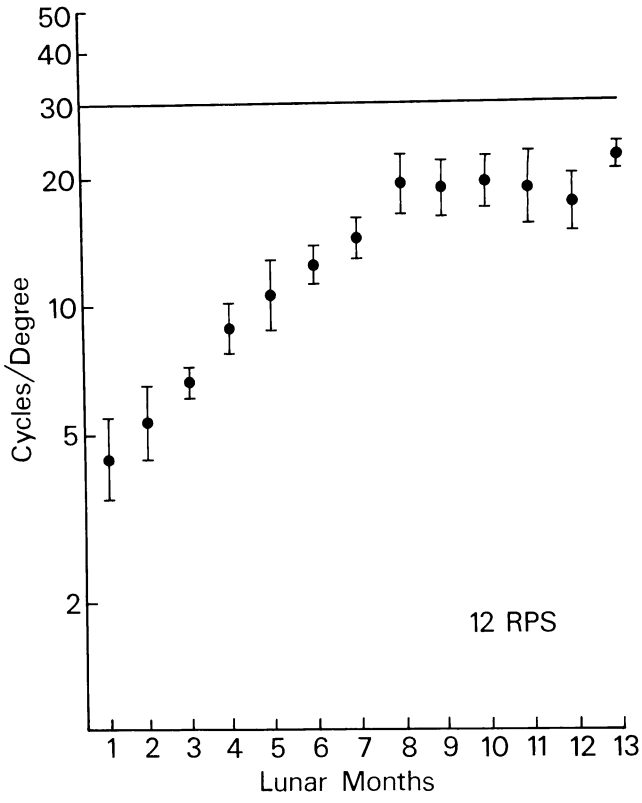

FIG 52–2.
Development of visual acuity according to the sweep VEP. Mean acuities in cycles per degree are shown for 4-week increments of age. The mean luminance was 80 cd/m^2. Note the high values in the first month that increase to an asymptotic level near adult acuity by 8 months.

The development of the sweep VEP was studied at a 6-Hz alternation rate (12 Hz recording for the second harmonic) by Norcia and Tyler.[21] The data for more than 200 infants over the first year after birth (Fig 52–2) showed that acuity rises from a surprisingly high neonatal level of about 5 cycles per degree to a plateau of about 20 cycles per degree by 8 months. Under their conditions this plateau was close to but not quite at adult acuity levels. The sweep VEP thus showed higher acuity at birth but slower development within the first year than did the transient VEP method.[17]

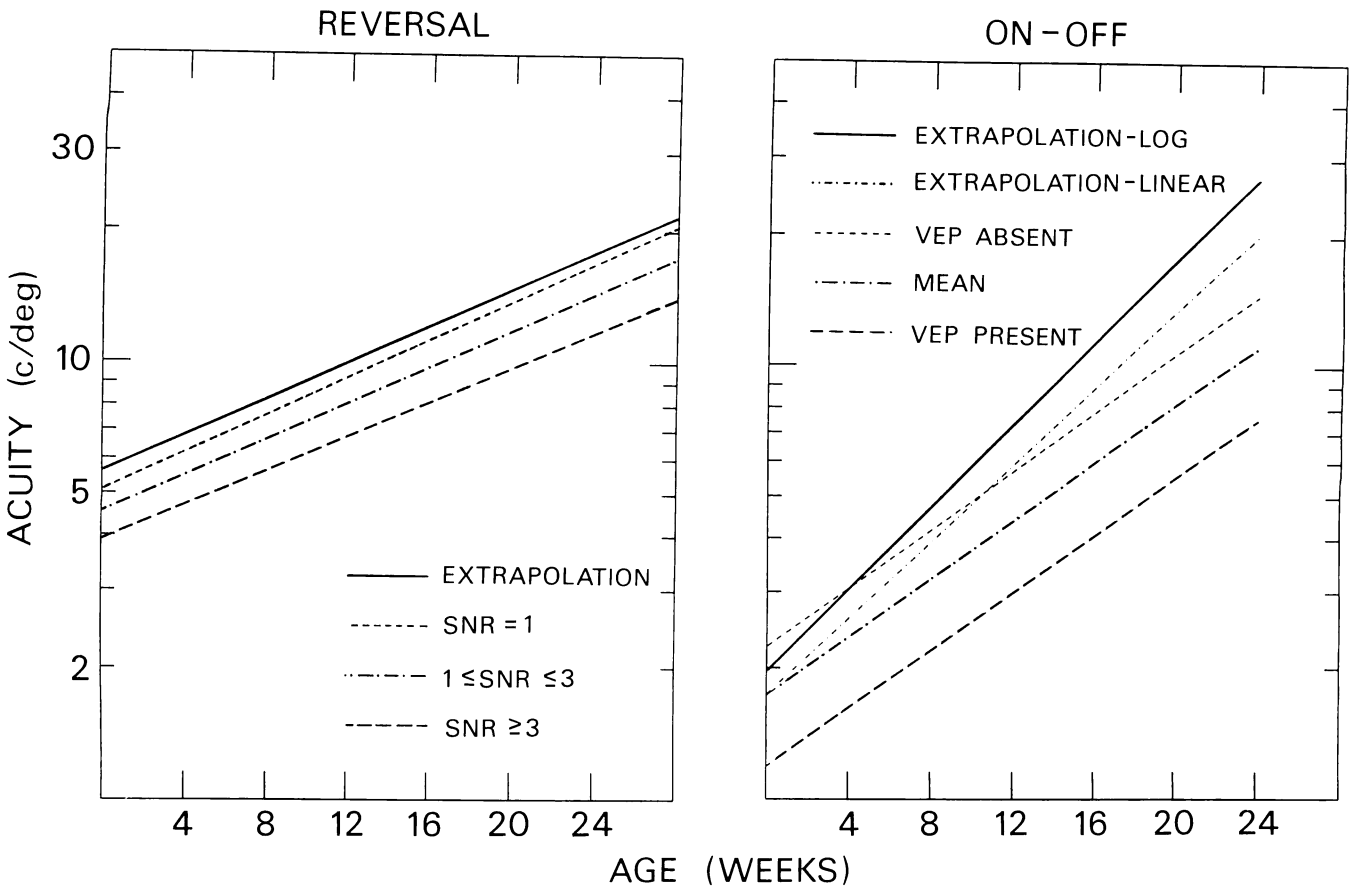

FIG 52–3.
Effect of scoring criterion on VEP acuity estimates for the sweep VEP (*left* panel) and the transient VEP (*right* panel). The regression lines are shown for several scoring criteria applied to the complete set of responses on each method. Higher acuities and more robust results are found with the sweep VEP method.

Was this transient/steady-state difference real? Orel-Bixler and Norcia[24] tested a set of 14 infants on both the Freeman-Marg and the Norcia-Tyler apparatus. They were able to compare not only the basic results but also the effect of different criteria on the two methods. Their results, shown as the regression lines in Figure 52–3, provide a full replication of the slope and acuity differences found originally with the two methods. This result indicates that acuity measured by transient (on-off) stimulation matures more rapidly but from a lower initial value than does acuity measured in the same infants with rapid steady-state (reversal) stimulation.

However, the effect of different scoring criteria on the estimated acuity is much greater for the transient than for the steady-state method. Various criteria for scoring the VEP data are indicated on the graphs, where "extrapolation" implies the zero-voltage intercept of a best-fitting line to the high spatial frequency shoulder of the data (on a logarithmic or linear frequency axis) and SNR refers to the signal-to-noise ratio of the response relative to the noise level at an adjacent, independent temporal frequency. It is evident from Figure 52–3 that the effect of the criterion is always less than about half an octave for the VEP sweep (reversal) technique, whereas it increases from about 1 octave at young ages to about 2 octaves at the older ages for the transient (on-off) method. These data indicate that the sweep VEP technique is quite robust with respect to wide variations in scoring criterion; this can be attributed to the fact that so many separate frequencies are measurable near the acuity limit.

RECENT RESULTS IN VISUAL DEVELOPMENT

Is Human Visual Development Controlled By Visual Experience?

An important question in visual development is to what extent the presence of visual stimulation of

the retina affects the sequence of development. For example, in cats it has been shown that delaying the onset of visual experience by patching both eyes for up to 1 year delays the whole progression of visual development by about the same amount. To what extent is this true of human infants? This question could be answered for infants within the normal length of gestation by comparing the acuity development for those born within 1 week of term to its development for infants up to 1 month preterm and for those up to 1 month post-term. Tyler and Norcia[40] adopted this approach for sweep VEP acuity measurements and found a significant delay in acuity development in post-term babies relative to preterm babies, as though visual development was controlled by the duration of visual experience rather than the maturational time from conception.

The same conclusion was reached from a study of healthy premature infants.[23] The acuities all fell within the normal range expected on the basis of time from birth (i.e., duration of visual experience), even though the infants were born from 1 to 4 months preterm. Their lack of maturational time in the womb had no detectable effect on their acuity development. Of course, many other factors such as nutrition also covaried with visual experience in these conditions. However, given the experimental results of purely visual manipulation in animals, it seems plausible to assume that visual experience is the major controlling factor in human visual development. It may be concluded that wide-range visual experience is a major controlling factor in human visual development over a range of at least 5 months.

Monocular Acuity Measurement

One important aspect of acuity that has not been addressed until recently is the accuracy of monocular acuity assessment. From a clinical standpoint, it is monocular acuity that is the key diagnostic parameter because an eye disorder affecting one eye only would have little effect on binocular acuity. However, monocular testing poses significant problems in infants because of the difficulty of patching one eye to test the other and the bias effects of sequential testing of one eye before the other.

The reliability of monocular acuity assessment has been determined for the sweep VEP technique by Hamer et al.[13] They found that, in a normal population of infants between 2 months and 1 year old, 96% gave a measurable acuity value for each eye in one test session. The acuities fell very close to each other (within about ± 0.2 octaves except in the youngest age group), in contradistinction to comparable behavioral data that were often so different for the two eyes as to suggest independent development of acuity in the two eyes.[4] Sweep VEP results indicate that there is essentially no difference in the development of monocular visual pathways up to the level of the cortex. Thus the sweep VEP provides a highly consistent measure of the normal acuity development under monocular conditions. This measure can act as a benchmark against which one can compare the effects of eye diseases and disorders on infant vision.

The first clinical application of sweep VEP measures of monocular acuity was in infantile esotropia. Day and associates[9] measured both monocular and binocular acuities in 15 infants with a strabismus angle and alternating fixation. As expected, the VEP demonstrated approximately equal acuity between the two eyes, thus indicating the absence of amblyopia in this group of alternators. However, across the whole age group all infants showed lower acuity than did their normal peers by an average of 1.04, 1.06, and 0.75 octaves for right, left, and binocular testing conditions. Thus the equality of acuity in the two eyes did not imply (as commonly supposed) that the acuities were normal. Some aspect of the esotropic condition had resulted in a significantly reduced acuity by both monocular and binocular measurement. This result requires a reevaluation of management protocols for alternating esotropia within the first year of life.

Contrast Sensitivity

Contrast sensitivity is another aspect of visual performance that is amenable to testing by VEP methods. Once again, the sweep methodology allows contrast thresholds to be measured within a test period of only 10 seconds. In this case, spatial frequency is held constant, and the contrast is swept up from below threshold to high levels in a logarithmic fashion. (It is important to avoid downward contrast sweeps where the brain is likely to manifest adaptation since at every level it is viewing a lower contrast than the one it has just seen.) The contrast sweep is then repeated at a series of spatial frequencies to generate a contrast sensitivity function. Extrapolated contrast threshold estimates show an excellent match to psychophysical thresholds for adults under the same display conditions.[1]

Typical normal infants will give sufficient attention for contrast thresholds at 3 to 6 spatial frequencies, together with an acuity sweep. Norcia et al.[22] reported strikingly high contrast sensitivities by

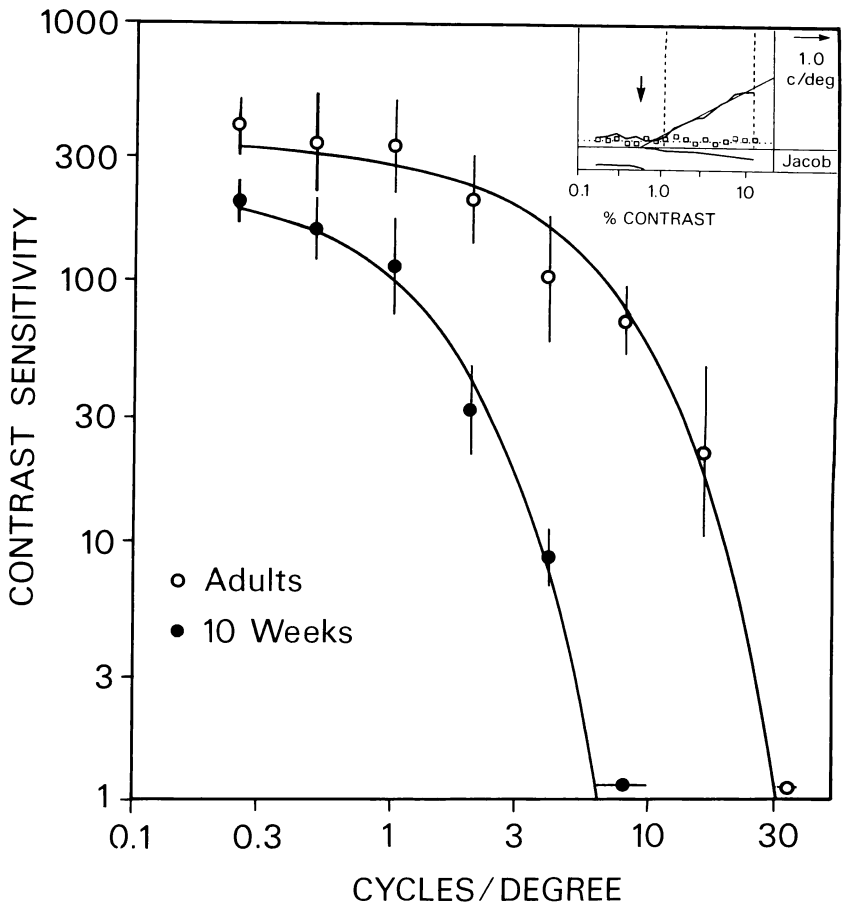

FIG 52–4.
Sweep VEP contrast sensitivity at 10 weeks of age. Contrast sensitivities were measured, as shown in the *inset*, by recording the steady-state response amplitude as the contrast was swept up from below threshold. (*Squares* show the EEG noise estimated simultaneously at an adjacent frequency.) Contrast sensitivities, obtained by the reciprocal of threshold extrapolation to zero amplitude (*arrow* in the *inset*), are plotted as a function of spatial frequency for adults and a group of 10-week-old infants. Note the high infant contrast sensitivity for low spatial frequencies, which is fitted by the same exponential template with a leftward shift relative to adult values.

these methods for sinusoidal grating stimuli in a group of 10-week-old infants. (Note that the high alternation rate of 6 Hz means that there should be no inhibitory falloff in sensitivity at low spatial frequencies.) The contrast sensitivity function measured for a 10 × 20-degree field at at a luminance of 220 cd/m^2 is compared in Figure 52–4 with that for adults obtained from the same apparatus. At the lowest spatial frequency (0.25 cycles per degree), the average sensitivity corresponded to a threshold level of 1% to 2% contrast between the darker and brighter bars of the grating. Acuity at 10 weeks was degraded by about a factor of 4 relative to adults, which implies that the main insufficiency at this age is in resolution of detail rather than a reduction in effective contrast in the visual process. In fact, if the infant curve in Figure 52–4 is slid rightward to adjust for the difference in acuities, there is no significant difference in contrast sensitivities between infants and adults.

These contrast sensitivity data allow three conclusions to be drawn. First, in normal infants, visual development after 10 weeks of age is principally a matter of acuity development. Second, the shape of the contrast sensitivity function is encapsulated by the same function and differs only by a scaling factor corresponding to the acuity level. This means that the normal contrast sensitivity at any spatial frequency can be computed solely from the normal acuity at that age (assuming the same experimental conditions). Finally, the high contrast sensitivities imply that the efficiency of phototransduction and neural processing in a 10-week-old eye is comparable with that of adults, at least for the large-field conditions used in that study.[22]

CLINICAL IMPLICATIONS OF HIGH VEP SENSITIVITY IN INFANTS

The VEP demonstration of adult levels of both acuity and contrast sensitivity by 6 to 8 months of age has powerful clinical implications. In contrast, behavioral results[3, 10] imply that infant visual capability is quite poor in the first year or two of life and may not reach maturity before 3 to 5 years of age. The VEP data indicate that the optical, photoreceptoral, and retinal processing of the infant eye is of sufficient precision to deliver signals of adult quality

to the visual cortex. Whether or not the infant cortex is sufficiently mature to use this information is a question that must be left to the methodology of behavioral studies. But from a clinical perspective, a large proportion of problems of pediatric ophthalmology are located in the eye and the early visual pathway prior to VEP generation. The high quality of the VEP data therefore indicate that by 6 to 8 months of age the infant visual system requires the same degree of image quality as does the adult's for optimal stimulation.

The main clinical relevance of optical image quality is in the relationship between the two eyes. A significant difference between the image quality in the two eyes is thought to be likely to lead to the amblyopic suppression of one eye's input during visual development.[15] The visual acuity and contrast sensitivity at a particular age is the limiting factor on what degree of difference will be significant in this context. Clearly, there is no need to correct the refraction with the same accuracy if acuity is at a 20/100 level at 6 months as there is if acuity is at the 20/20 level. The high acuities shown by the VEP data emphasize the importance of accurate screening and treatment of infants within the first year of life for refractive error and other visual defects that might impair image quality.

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