Principles and Practice of Clinical Electrophysiology of Vision

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Methodology of Testing for Albinism With Visual Evoked Cortical Potentials

Patricia Apkarian

All albino mammals share a unique anomaly of the visual pathway. Nerve fibers that originate in the temporal retina erroneously decussate at the optic chiasm, disrupting retinotopic organization throughout the visual system.[9] The presence of abnormal temporal fiber decussation can be determined by recording the visual evoked cortical potential (VECP) from the surface of the scalp.[2, 8] A typical visual evoked potential (VEP) profile of an adult normal compared to an adult albino is presented in Figure 54–1. Binocular (OU), left eye (OS), and right eye (OD) responses are shown. Note that the stimulus is a large appearing/disappearing checkerboard pattern. The upper five traces in each column are derived from one of five electrodes positioned across the occiput as shown in the schematic to the right of the traces and also in Figure 54–2. The electrodes are positioned in a row 1 cm above the inion. The reference is either "linked ears" or a frontal electrode positioned 1 cm above the hairline; the ground is placed at the vertex. The bottommost trace is a bipolar derivation obtained by subtracting a right hemispheric derivation (R) from a left (L). In the normal control, the potential distribution across the scalp remains constant following monocular stimulation. Inspection of the difference potential (which appears relatively flat) reveals that for this particular observer, hemispheric asymmetry is present and is similar for left and right eye stimulation. If these results are compared with the visual evoked responses of an albino, the shift in potential distribution from left to right eye stimulation is immediately apparent. Following full-field left eye stimulation, note the early positive deflection of the pattern-onset response, which is largest on the right hemisphere, whereas following stimulation of the right eye, the response lateralizes to the left hemisphere. The difference potential (lowest trace) following binocular stimulation is flat and reveals hemispheric symmetry, while the monocular stimulation difference potentials are approximately reversed in polarity (see the arrows) from negative to positive with left and right eye stimulation, respectively.

The electrophysiological correlate of albino optic pathway misrouting is apparent from visual inspection of the raw traces; this approach is presented schematically in Figure 54–3. One need attend only to an early time window of the response. In albinos older than about 3 years of age, contralateral asymmetry in the pattern-onset response is typically most pronounced from about 80 to 110 ms. In the mature pattern-onset response, this latency corresponds to the first major positive waveform deflection, which is classically labeled C_{I}.[10]

For experimental purposes, a quantitative estimate of VEP hemispheric lateralization may be obtained by plotting the amplitude of the responses at particular times for each electrode. Again, the maxi-

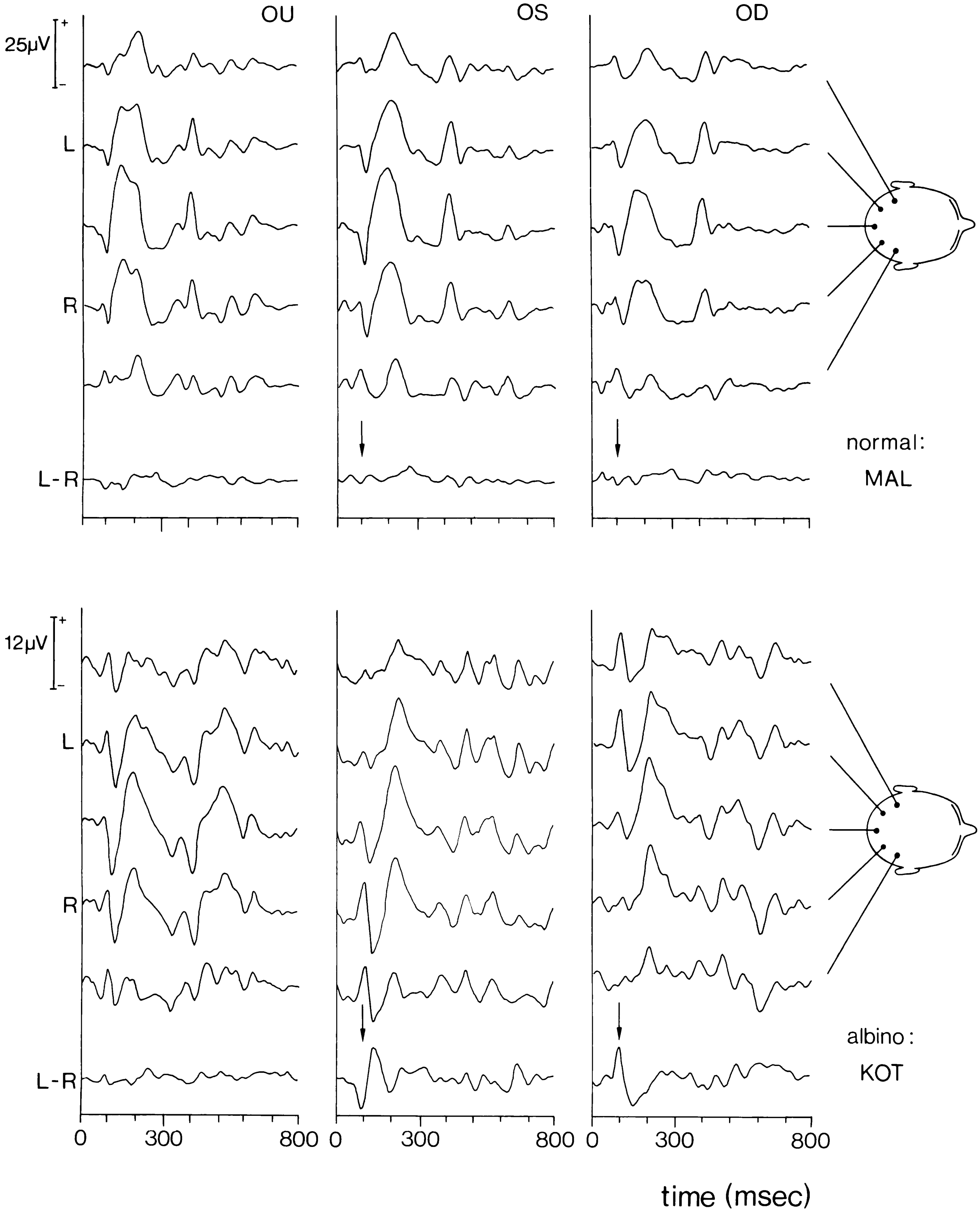

FIG 54–1.
Binocular *(OU),* left eye *(OS),* and right eye *(OD)* pattern onset (300 ms) and offset (500 ms) responses (check size equals 55 minutes) from a normal control and an albino. The reference for traces *1 to 5* was linked ears; the *bottom*most trace is a bipolar derivation obtained by subtracting trace *R* (right hemispheric derivation) from trace *L* (left hemispheric derivation). (From Apkarian P, Reits D, Spekreijse H, Van Dorp D: *Electroencephalogr Clin Neurophysiol* 1983; 55:513–531. Used by permission.)

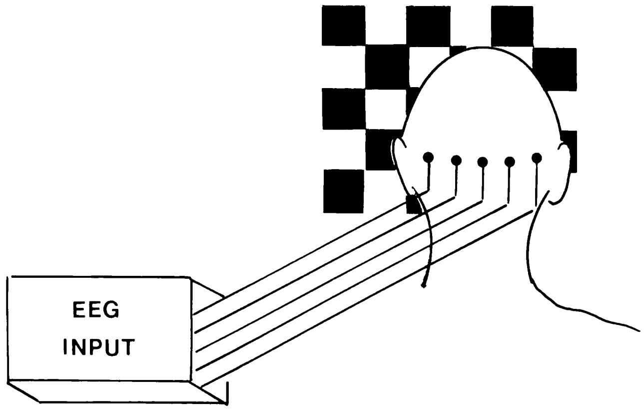

FIG 54–2.
Schematic of the electrode montage for evoked potential recording in albinos; tinned copper cup electrodes (8-mm diameter) are positioned with an equal spacing of 3 cm in a horizontal row 1 cm above the inion. The reference is either linked ears or a frontal electrode.

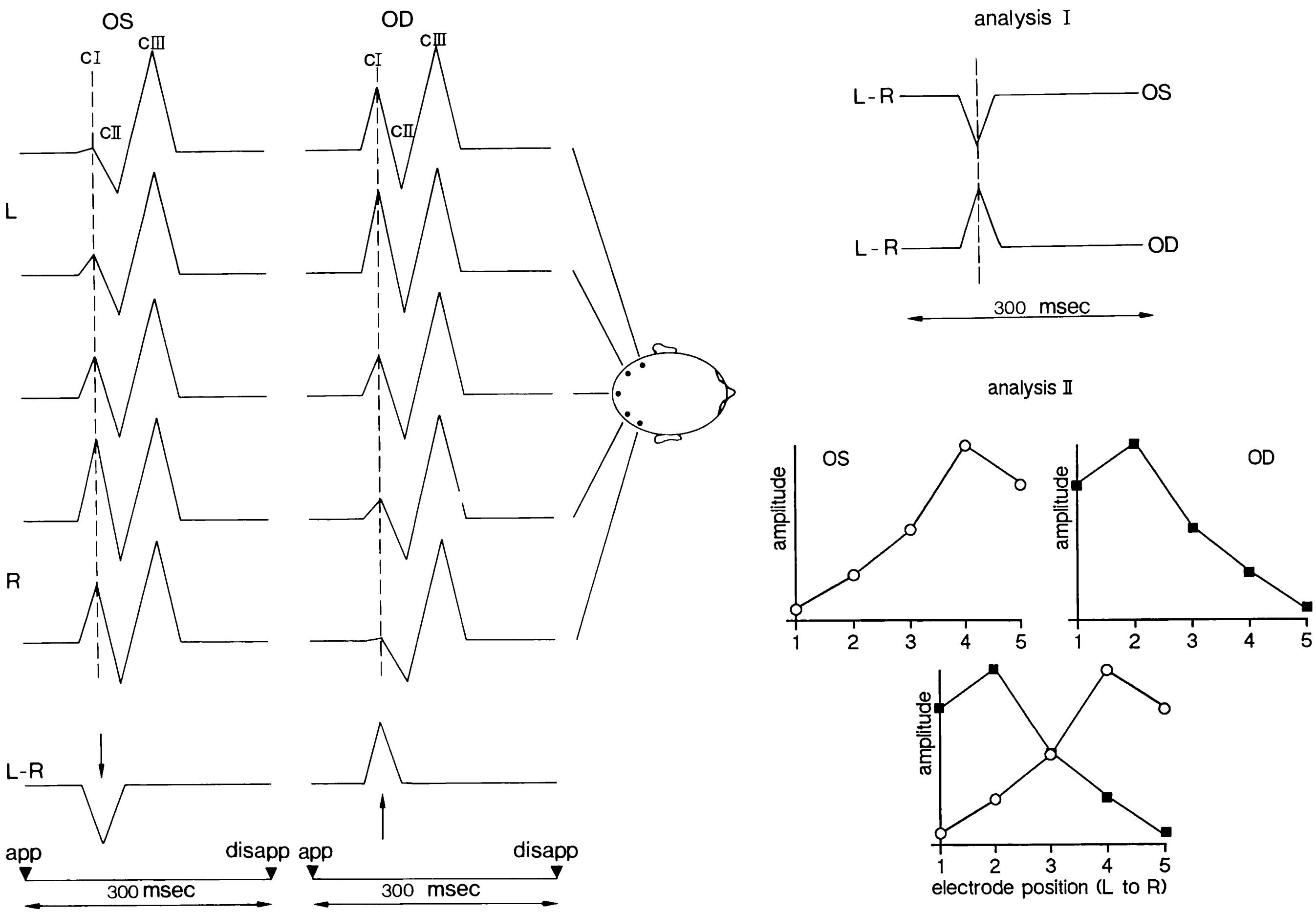

FIG 54–3.
Schematic of analysis procedures for determining left *(OS)* and right *(OD)* eye response asymmetry in the pattern-onset response. The *dashed line* is drawn at 90 ms after pattern onset. Visual inspection within an early latency window reveals the contralateral hemispheric asymmetry. Hemispheric laterality can also be seen by a bipolar derivation obtained by subtracting trace 4 from trace 2. The polarity reversal denoted by the *arrows* and the *dashed line* under analysis 1 are indicative of the albino VEP feature. A quantitative approach to determine asymmetry is depicted under analysis II *(lower right),* where the amplitude of the response at 90 ms is plotted as a function of the electrode. Note the characteristic crossover pattern when the left eye and right eye functions are combined in a single graph. (Adapted from Apkarian P, Reits D, Spekreijse H, et al: *Electroencephalogr Clin Neurophysiol* 1983; 55:513–531. Used by permission.)

mum of C_I is a useful measure. Once such a plot for both the left and the right eye is obtained, a "lateralization index" can be defined, that codes where the potential is greatest across the electrode array (0 = left hemisphere, 2 = right hemisphere, and 1 = midline). With a lateralization index for each eye, interocular comparisons across a number of recording conditions and/or patient groups are greatly facilitated. Application of a comparable analysis in a group of albinos confirms the suggestion that reliable VEP albino asymmetry is found for the C_I component.[1] Thus, stimulus and recording procedures that optimize the C_I response should be employed. The C_I component in the pattern-onset VEP is typically considered to primarily reflect local luminance variation in the response. The second negative component, C_{II}, reflects contrast mechanisms and as such is particularly sensitive to pattern size and defocus.[10, 11] Because of the foveal hypoplasia and reduced acuity in albinos,[13] it is common to find an absent or relatively weak C_{II} and a robust, readily identifiable C_I component, at least in mature albino VEPs.

If the limitations of the albino visual system are taken into account, optimization of albino VEP test procedures is straightforward. Because of the relatively low visual acuity and high incidence of substantial refractive error, element sizes of the test pat-

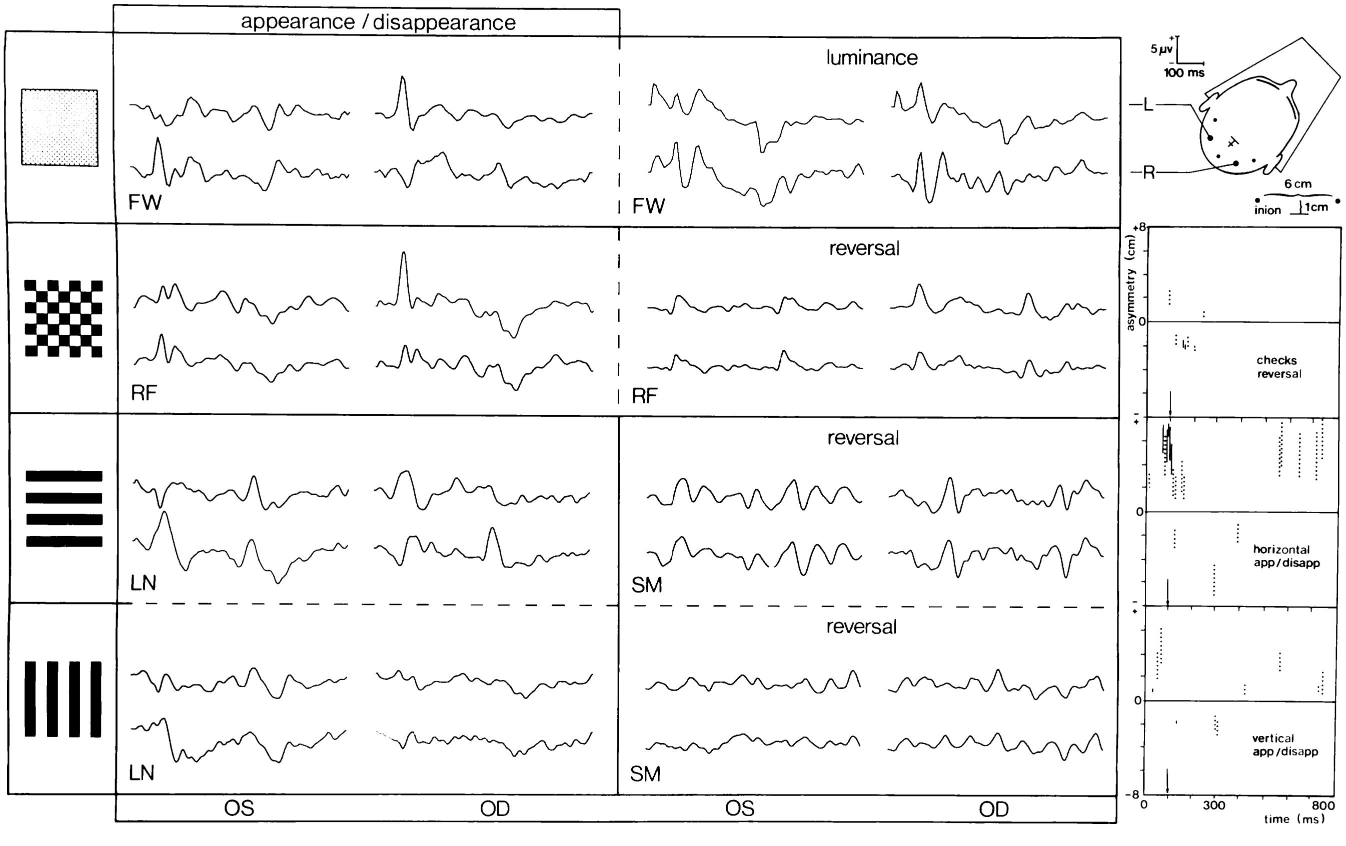

FIG 54–4.

Albino VEP responses following pattern onset (appearance, 300 ms) and offset (disappearance, 500 ms) in columns 1 (OS) and 2 (OD) are compared with stimulus conditions of luminance or pattern reversal (400 ms reversal rate) in columns 3 (OS) and 4 (OD). The *upper* traces of each set represent a left *(L)* hemispheric response, *lower* traces a right *(R)* hemispheric response. In the *upper row,* pattern-onset responses are compared with luminance stimulation. In the remaining rows, pattern appearance is compared with pattern reversal for checkerboard *(row 2),* horizontal *(row 3),* or vertical *(row 4)* gratings. On the *right* are group average (left minus right eye location) analyses for check reversal *(top),* horizontal grating *(middle),* or vertical grating *(bottom)* pattern onset. The mean of the left-minus-right locations across subjects is at the midpoint of each vertical line. The length of the line represents ±1 SE. *Dotted lines* indicate a confidence level of 95% and solid lines, 99%. The *vertical arrow* is placed at 100 ms. Positive values indicate contralateral localization and negative values, ipsilateral. (From Apkarian P, Spekreijse H: The VEP and misrouted pathways in human albinism, in Cracco RQ, Bodis-Wollner I (eds): *Evoked Potentials.* New York, Alan R Liss, Inc, 1986, pp 211–226. Used by permission.)

tern should be large and the contrast high (about 80%). High-contrast patterns from about 50 to 110 minutes typically fall within the albino acuity range and are relatively unaffected by minor errors in optical defocus. While all pattern VEP testing should proceed following proper refractive correction, this task is frequently difficult in albino infants and young children, particularly if they have nystagmus. In these cases larger pattern sizes (110 to 220 minutes) may prove more appropriate. Albinos can be comfortably tested with a stimulus distance of about 150 cm. In some infants and very low vision patients (Snellen acuity less than 20/200 or 0.1), this distance may be reduced (if so, remember that the poor resolution of some commonly used TV monitors will degrade the image quality and as a result yield poor response waveforms and reduced amplitudes in eyes with good acuity). An appropriate field size for albino testing with pattern stimulus is about 15 to 20 degrees; the distance should be properly adjusted to accommodate these field requirements.

About 90% of albinos present with oculomotor anomalies including nystagmus and strabismus,[7, 13] and therefore pattern-reversal stimulation is inappropriate. This is depicted in Figure 54–4, which shows left and right hemispheric responses from four adult albinos tested under various stimulus conditions. The pattern-onset response with a duty cycle of 300-ms pattern onset and 500-ms pattern offset (although a much shorter appearance is just as effective) is compared with the pattern reversal (1 Hz) for three pattern configurations, i.e., checkerboard, horizontal bars, and vertical bars. Regardless of pattern configuration, the pattern reversal does not evince reliable asymmetry. However, for the pattern-onset condition, horizontally oriented gratings yield better responses than do vertical ones, although a checkerboard pattern that contains all stimulus orientations is still optimum. If a checkerboard pattern is not available, the results presented in Figure 54–4 suggest that horizontal gratings are a better candidate for testing albinos than are vertical ones. The high incidence of astigmatism in albinos should also be taken into account if gratings are to be used as stimuli. A quantitative assessment of the various pattern configurations and stimulus modes is presented at the right of Figure 54–4. In this analysis of interocular hemispheric lateralization, the location of the peak of the potential distribution from the left eye minus the location of the peak of the potential distribution of the right eye is determined for every time instant of the response. Quantitative analysis confirms the qualitative impression.

While the poor reversal response in albinos is attributed primarily to the degree of nystagmus, in Figure 54–4 albino R.F., who has no nystagmus, also does not show contralateral asymmetry with pattern-reversal stimulation. This emphasizes that although with pattern-reversal, contralateral asymmetry may be elicited in some albinos, when compared with pattern-onset stimulation, the pattern reversal is highly unreliable in detecting albino misrouting. This is not surprising in light of the fact

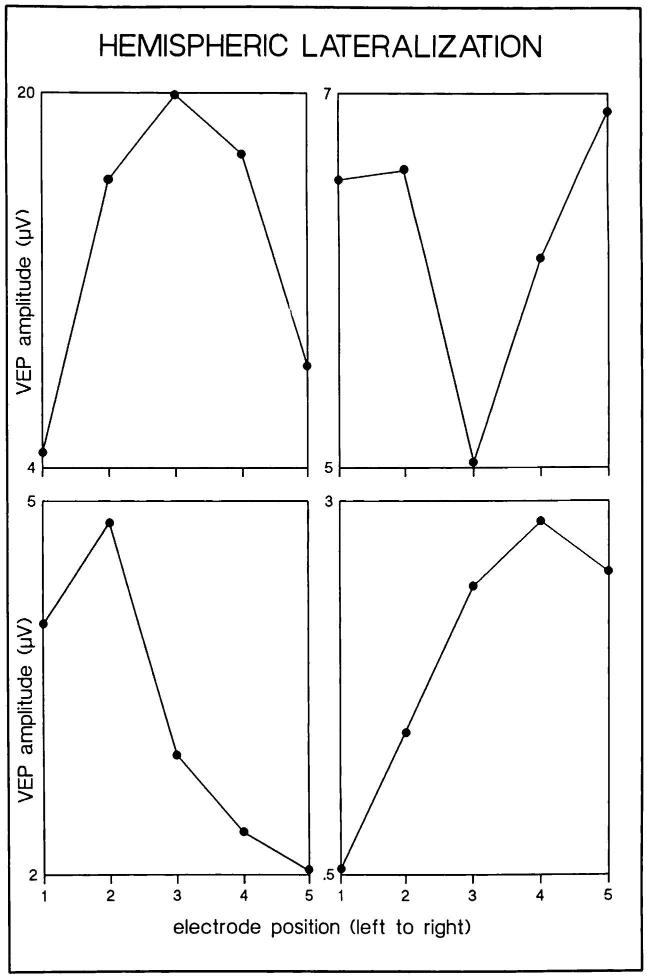

FIG 54–5.
Binocular VEP amplitude of the pattern-onset C_I component (peak to baseline amplitude measurements) as a function of electrode from the left (nos *1* and 2) to the right (nos. *4* and *5*) occiput in four normal adult controls shows intersubject variability in hemispheric lateralization (pattern size, 48 minutes; onset/offset, 300/500 ms). (From Apkarian P, Spekreijse H: The use of electroretinogram and visual evoked potentials in ophthalmogenetics, in *Desmedt JE* (ed): *Visual Evoked Potentials.* Amsterdam, Elsevier Science Publishers, 1990, pp 169–223. Used by permission.)

that albino VEP contralateral asymmetry shows a high degree of component specificity.

The "luminance flash" (increase in the luminance of an unstructured stimulus) may also be used in infants but its efficacy in detecting misrouting in adults is significantly reduced. As shown in the uppermost traces of Figure 54–4, when pattern onset is compared with luminance flash in an adult albino, clear contralateralization is found only for the pattern onset/offset condition (labeled in Figure 54–4 as appearance/disappearance).

While the pattern of hemispheric asymmetry described is specific to albinism, it should not be confused with VEP asymmetry resulting from optic pathway lesions, malformations, tumors, or other non–albino-related pathway anomalies. Nor should albino response asymmetry be confused with normally occurring hemispheric response dominance due primarily to individual variation in cortical neuroanatomy. In Figure 54–5, the VEP was evoked binocularly, and the amplitude of the pattern-onset C_I component is plotted as a function of electrode position from left to right occiput. The subjects were four normal adults. In the upper left plot the distribution of response is symmetrical, with the peak of the potential distribution located at the midline. However, the midline response may be significantly attenuated as shown at the upper right, possibly due to thickening of bone at the midline. The normal control can also present with varying degrees of hemispheric lateralization, with the peak of the potential distribution located either to the left (lower left) or to the right (lower right). Similar variation in hemispheric response dominance can also be observed in albinos. In Figure 54–6, the binocular responses from four albinos show hemispheric symmetry (upper left), midline attenuation (upper right), left hemispheric response dominance (lower

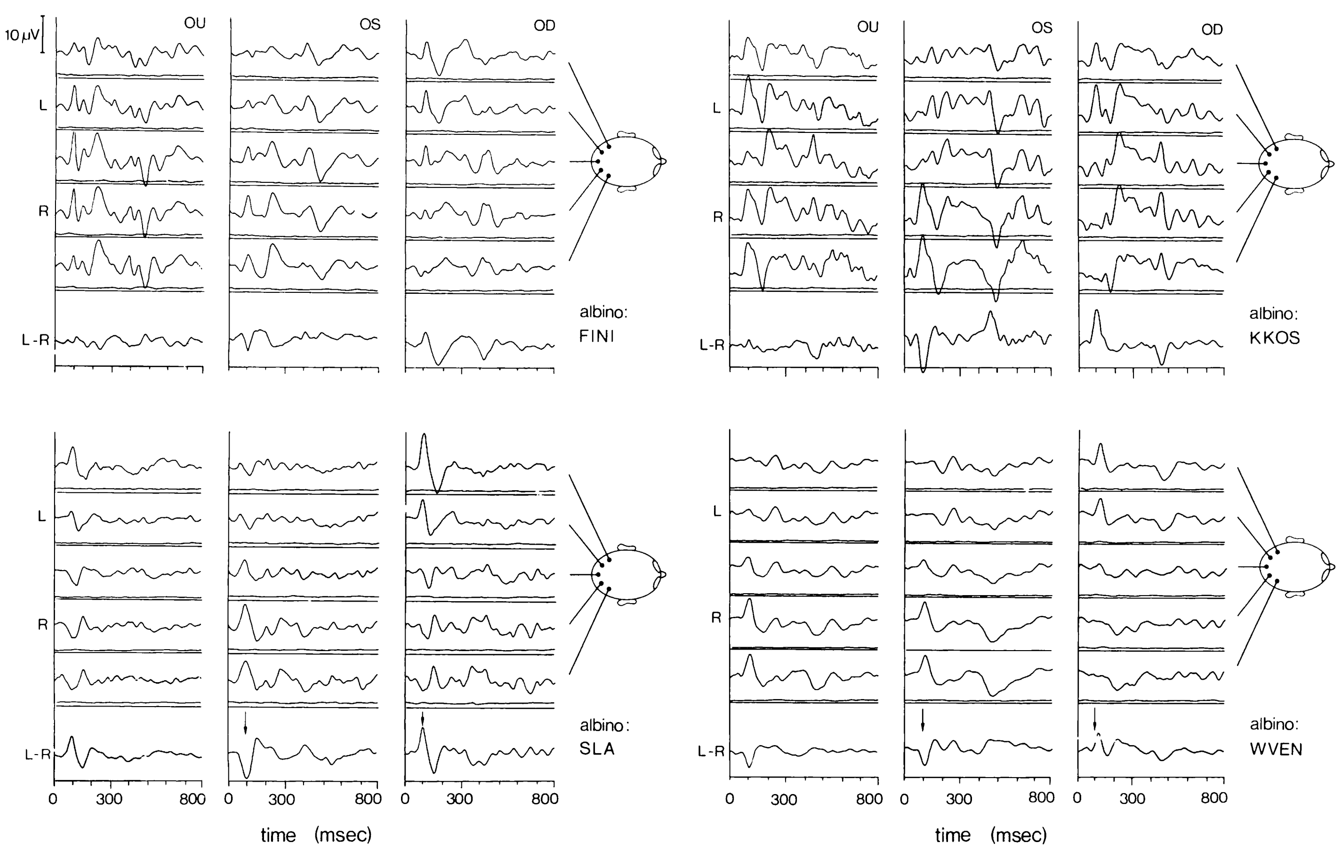

FIG 54–6.
*Variable binocular VEP topography (first column of each triad) in four albinos with midline symmetry *(upper left)*, midline attenuation *(upper right)*, and left *(lower left)* or right *(lower right)* hemispheric lateralization. The standard error of the mean at every time instant of the response is drawn below each trace. Interocular comparison between the two eyes (second and third columns) reveals the albino VEP contralateral asymmetry. (From Apkarian P, Reits D, Spekreijse H, Van Dorp D: *Electroencephalogr Clin Neurophysiol* 1983; 55:513–531. Used by permission.)

left), and right hemispheric dominance (lower right). Despite the wide variation in hemispheric lateralization, in each of these cases a left eye-to-right eye comparison demonstrates the albino VEP defect. Since in albinos the responses from each eye reflect primarily the decussating retinal fiber projections, the albino binocular VEP can readily reflect ocular dominance. It is therefore essential that misrouting detection be based on an interocular comparison.

With appropriate pattern-onset stimulation and recording procedures, VEP topography can reveal the condition of misrouted optic pathway projections of the type described with virtually 100% accuracy and with zero false-positives in patients about 3 years of age or older. To achieve comparable sensitivity and specificity in the albino infant and toddler, luminance flash stimulation is introduced into the test paradigm.[5]

VEP testing in pediatric populations is complicated by the fact that the pattern-onset response is immature and lacks the adultlike triphasic waveform as shown in Figures 54–7 and 54–8 (see also Spekreijse[12] and Apkarian et al.[6]). The immature pattern-onset waveform consists primarily of a single positive peak with a latency of about 150 ms. Because reliable asymmetry in adults is restricted to the early C_I component, what might one expect from the immature response profile? If the albino is around 3 years of age or older, despite the lack of adult waveform complexity, latency-specific asymmetry can still be observed. The dashed line in Figure 54–7 has been placed at about 100 ms. Visual inspection of the raw traces reveals that the early portion of the single positive peak corresponding to the C_I latency reflects contralateral asymmetry while at later times the longer latency portion, seemingly independent, does not. Thus at around 100 ms, VEP misrouting can be detected in the response profiles of the young albino child. However, in albinos below the age range of about 3 years, specificity in albino asymmetry is no longer evident as shown in Figure 54–8 for the pattern-onset responses from two albino infants. Instead, broad response peaks with long latencies appear to lateralize but do so inconsistently. Contralateral asymmetry is observed in the pattern responses of one of the albinos (upper left) but is difficult to assess in the other (lower left). The luminance flash response, however, yields a clear

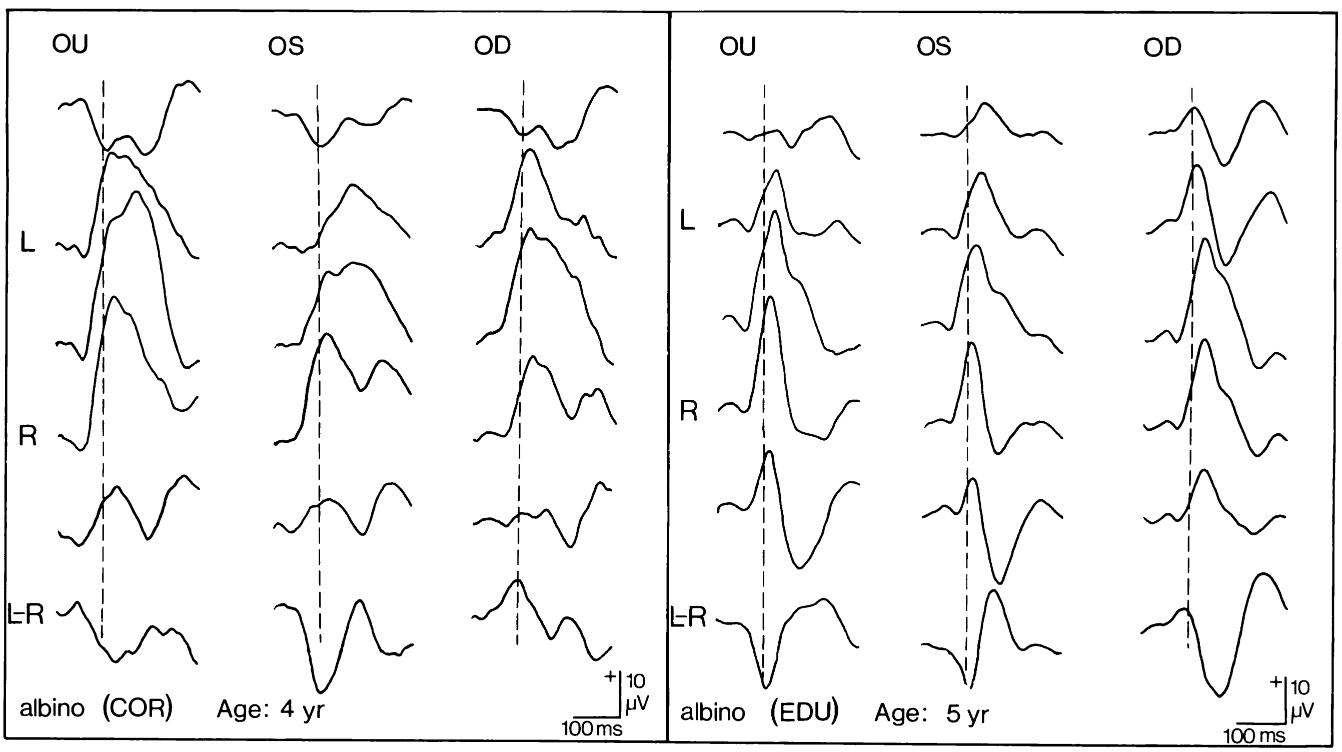

FIG 54–7.
Binocular *(OU)*, left eye *(OS)*, and right eye *(OD)* pattern-onset responses for two albino children. Contralateral hemispheric asymmetry is revealed in the monocular responses at about 100 ms *(dashed line)*. (From Apkarian P, Reits D, Spekreijse H: *Exp Brain Res* 1984; 53:285–294. Used by permission.)

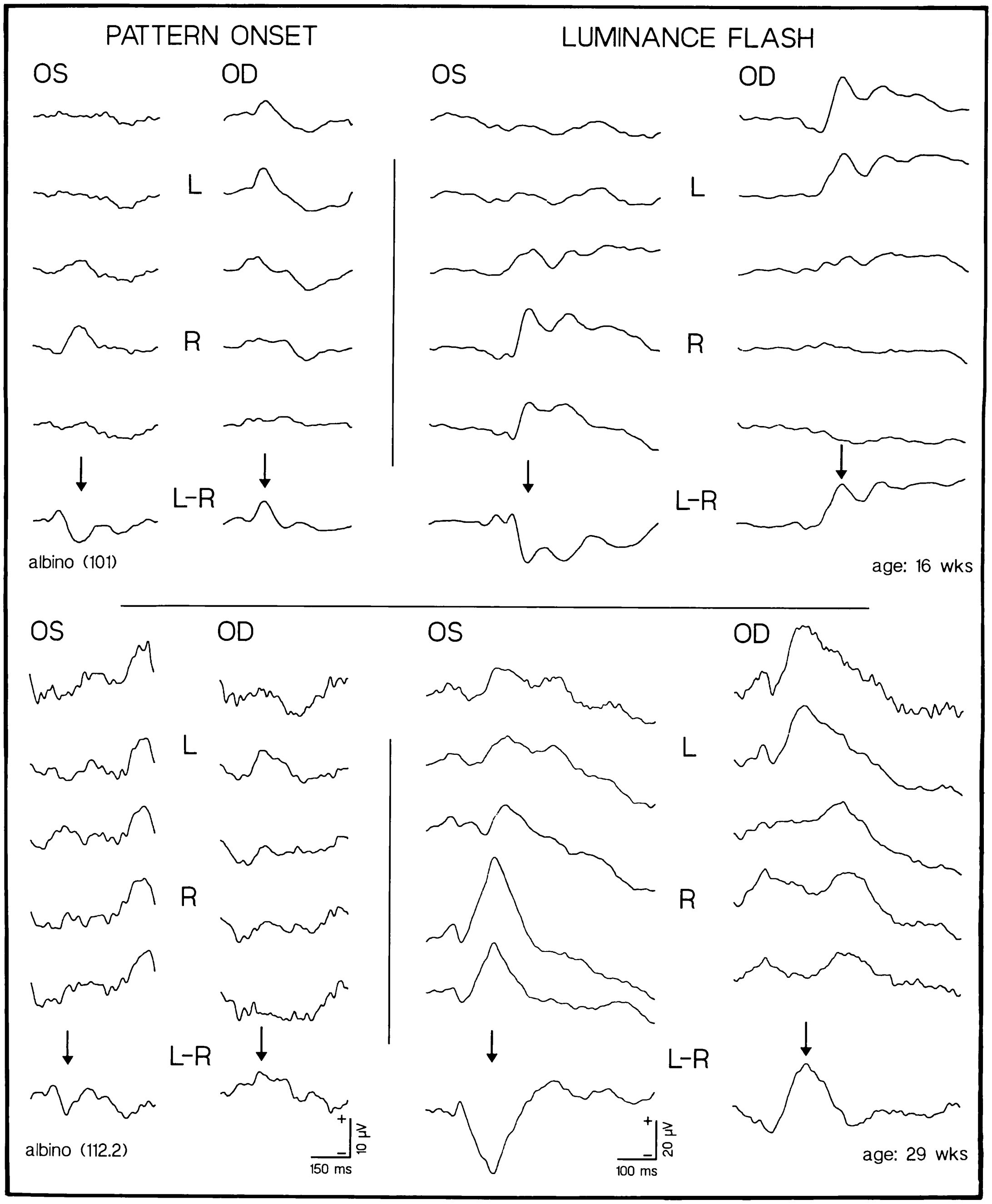

FIG 54–8.
Left eye *(OS)* and right eye *(OD)* pattern-onset/offset (40/460 ms) and luminance flash (1 Hz, 0.6 J) responses for two albino infants. *Arrows* are positioned at the maximum contralateral asymmetry, which, when present, does not show clear component specificity. The whole single positive peak appears to shift from the right occiput to the left following left and right eye stimulation, respectively. Note the presence of clear asymmetry for the flash response.

indication of misrouting in both infants. An important point to consider is that, just as with pattern-onset responses, the luminance flash response also undergoes a maturational process. While the immature flash response in the infant supports the detection of misrouting, in older children and adults the situation reverses. Thus, when appearance and disappearance of a test pattern is employed, one should check that no overall luminance change occurs. Hit rates and test reliability are reduced significantly when misrouting detection is attempted with luminance flash in the older albino. The transition period between the first months of life, when flash stimulation is indicated, to adulthood, when its usefulness is minimal, is not yet defined. As such, for practical purposes all misrouting tests should be performed with both luminance flash and pattern onset.

OVERVIEW OF ALBINO VISUAL EVOKED POTENTIAL METHODS

VEP albino testing can be summarized by the following outline of optimum test procedures.

Electrode Montage

At least five electrode derivations should be employed with the montage described above. A more extended montage has been shown to be unnecessary,[3] whereas fewer than five active electrodes across the occiput reduces the test sensitivity. If only limited recording channels are available, this disadvantage should be borne in mind. If four-channel recording is used, the recommendation is for three electrodes placed across the occiput: at the left, midline, and right hemisphere; the fourth channel is best reserved for the interhemispheric difference potential. If only three-channel recording is available, one electrode can be placed at the left occiput and the second at the right; the third channel is best reserved for the difference potential. Reference and ground configurations are discussed above.

Stimulus Mode

With pattern stimulation the onset/offset mode is advised. A stimulus-onset duration of 300 ms and an offset of 500 ms will clearly distinguish between the two response complexes. However, since the albino VEP correlate is most reliably detected within an early time window of the response, the effects of contamination of the onset waveform complex by the off-response complex for detecting misrouting is negligible. For practical purposes, a pattern onset of 40 ms and an offset of 460 ms is quite appropriate. The brief stimulus duration has several advantages, including avoiding afterimage problems, facilitating testing in pediatric populations, and yielding relatively larger amplitude responses. The optimum configuration of the pattern stimulus is a checkerboard. The optimum size for the screening pattern is about 60 minutes. If reliable VEPs are obtained, the element size can be reduced. If a response cannot be elicited with the 60-minute pattern size, larger checks should be used. An adequate mean luminance of the screen is about 100 cd/m^2, and contrast is best tested at about 80% or greater. The optimum field size is about 20 degrees at a distance of about 150 cm.

With luminance stimulation a 1-Hz flash with an intensity of about 0.6 J is adequate. The source can be placed at a distance of about 30 cm.

Test Protocol

Monocular testing with total occlusion of the fellow eye is obligate. Binocular testing is optional, although quite useful in determining ocular and/or hemispheric dominance. In albinos 3 years of age or younger, it is advisable to begin the test session with the luminance flash conditions. It is crucial that no light leakage occurs from inadequate occlusion during monocular testing. If the young patient remains cooperative, pattern conditions can be added to the protocol. In older patients, pattern stimulation can proceed first.

Data Analysis

The VEP correlate of aberrant retinogeniculocortical projections is detected by visual inspection of the raw traces including an interhemispheric difference potential. The albino visual pathway anomaly is evinced in VEP topography distributions by the presence of contralateral hemispheric asymmetry following full-field monocular stimulation of pattern onset for the older albinos and/or luminance flash for the very young albinos. Albino asymmetry is expressed as a shift in occipital lateralization of the VEP from the left hemisphere following full-field right eye stimulation to the right hemisphere following left eye stimulation. This VEP profile is pathognomonic to albinism.

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