Handbook of Pediatric Retinal Disease

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Preface

Pediatric ophthalmology is a broad field encompassing many diverse topics including embryology, chromosomal abnormalities, neurology, craniofacial abnormalities, systemic diseases, retina disease, and strabismus. This variety makes pediatric ophthalmology interesting and intellectually stimulating, but at the time somewhat daunting. The handbook series is designed to give the practitioner an easy to understand, succinct yet detailed reference on various subjects related to pediatric ophthalmology.

The *Handbook of Pediatric Retinal Disease* is a practical resource on the diagnosis and management of both the most common and more esoteric retinal disorders. An in-depth chapter on electrophysiology of the eye (with an emphasis on hereditary retinal disease) is included. This chapter provides important information for deciding which tests to order and how to interrupt electrophysiology results. Children with retinal disorders often are faced with irreversible visual loss and even blindness. In these cases, even a seasoned physician often feels uncomfortable when speaking with the family. A beautifully sensitive chapter, "Breaking the News," provides practical points to help the physician communicate both clearly and empathetically with the family.

A broad range of retinal disorders are covered in this volume, with many color photographs to demonstrate the ophthalmoscopic findings. Chapters in the handbook are reader friendly and are organized with clear sub-headings to guide the reader to their areas of interest quickly. Excellent color photographs and diagrams illustrate the clinical points and help establish firm diagnosis parameters. Extensive use of tables and information boxes simplify and summarize complex topics. Each chapter is fully referenced to provide evidence-based practice guidelines and further in-depth reading.

Another important use for the *Handbook of Pediatric Retinal Disease* is to serve as a basis for patient and family education. Information including diagrams and photographs from the handbook about their child's specific retinal disease can be shared with the families. This important information is often lacking in general texts on ophthalmology and pediatrics.

I hope you will find the *Handbook of Pediatric Retinal Disease* to be an invaluable adjunct to your pediatric practice.

Kenneth W. Wright, MD

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Pediatric Visual Electrophysiology

Anthony Kriss* and Dorothy Thompson

Visual electrodiagnostic tests can contribute significantly to pediatric ophthalmology. The tests are objective, safe, relatively swift, and easy to administer. They can give unique insight into the functional integrity of different levels of the visual pathway. The *electroretinogram* (*ERG*) indicates retinal function, the *electro-oculogram* (*EOG*) expresses pigment epithelium function, and the *visual evoked potential* (*VEP*) reflects optic pathway function beyond the eye to the visual cortex. These tests complement, and supplement, other visual methods of assessment. Thus, depending on the clinical context, an abnormal ERG may suggest the necessity for metabolic screening, and an abnormal VEP in association with a normal ERG can indicate the need for structural imaging studies.

There are advantages to being able to use visual electrodiagnostic tests in preliminary disease stages in young infants. This practice enhances the chances of successful surgical or clinical intervention and allows genetic counseling when it is most pertinent to young parents. It can also ease emotional acceptance and allow for more opportune implementation of

In Memoriam: On October 5, 2001, Dr. Kriss passed away after a long illness. Despite the gravity of his ill health, Dr. Kriss worked hard to finish this chapter and submitted it one week before his death. His tenacity in completing this definitive work on Pediatric Electrophysiology is a testament to his passion for this field. I have known Dr. Kriss professionally for almost 20 years and have the highest respect for his research, teaching, and clinical abilities. This chapter exemplifies Dr. Kriss' commitment to excellence, attention to detail, and his world-class expertise in the field of Pediatric Electrophysiology. It is my honor and privilege to include his chapter in this second edition by Kenneth W. Wright, MD.

educational programs. In many ways, the functional sensitivity of electrodiagnostic tests is not yet rivaled by functional imaging techniques. Despite advances in statistical manipulation and faster resolution, the application of imaging methods to young children is still a daunting challenge.

When ERG and VEP are tested together, they can help determine whether a baby's nystagmus or failure to fix and follow are a result of dysfunction of the anterior visual pathway. Together, they can help distinguish if the basis of the clinical problem lies with cones, rods, the inner retinal layer, optic nerve, or at the chiasm or postchiasmal pathway. In older infants, testing can help establish if there is an underlying reason why an eye is not responding to patching and can provide an objective indicator of the presence of posterior hemisphere dysfunction with an associated visual field loss. In older children, visual *electrophysiology* can be a useful complement in investigating headaches, malingering, or possible functional visual loss. Pattern VEP findings can also provide a helpful measure of the level of visual acuity, especially in preverbal children. Visual electrophysiology in the future will offer a key measure of the functional outcome of human gene therapy.

The results of visual electrophysiological tests are usually displayed as graphs of voltage (in microvolts) plotted against time (in milliseconds). These graphs have characteristic waveforms, and the constituent positive and negative peaks are quantified by their latency (called implicit time by some), relative to the onset of stimulus delivery, and their size (amplitude) relative to the previous peak or an estimated baseline. Formal identification usually recognizes the polarity and latency of a component; for example, P100 of the pattern reversal response refers to the positive component that peaks 100 milliseconds (ms) after the pattern reverses. Response measures are also altered by technical and physiological factors, which can mimic response changes associated with pathology. Therefore, it is important to be aware also of the effects of nonpathological factors, as they could lead to misinterpretation of recordings by the unwary. To reduce the possibilities of these types of error, international professional bodies have prescribed standards [e.g., ISCEV (International Society for the Electrophysiology of Vision) or International Federation of Clinical Neurophysiology].[35,36]

This chapter is a distillation of visual electrophysiology [ERG, EOG, pattern electroretinogram (PERG), and VEP]. It describes the physiological basis of responses with emphases on

responses used clinically and on the application of visual electrophysiology to pediatrics. Details of the ISCEV recording standards are given also. These standards relate mainly to the testing of older children and adults; pediatric standards are being discussed at present. The authors have described testing protocols for young children that they found to be valuable in a pediatric practice dealing with both ophthalmologic and neuro-ophthalmologic problems (to about equal extents), testing approximately 1500 children per year.

THE ELECTRORETINOGRAM

Types of Electroretinograms

Flash ERG, Pattern ERG, and Multifocal ERG

Some retinal cells hyperpolarize, others depolarize in response to changes in retinal illumination. The gross effect of these summed biopotentials is recordable at the front surface of the eye as a series of negative and positive voltage changes (peaks) in the first 200 ms after the light stimulation. These series of peaks are the ERG. The form and timing of the ERG is related to the eye's state of light adaptation and to the intensity, spatial, chromatic, and temporal characteristics of the stimulus. The *flash electroretinogram* (*F.ERG*) is generated by a uniform flash of light (e.g., from a strobe light flashed in a Ganzfeld or by LEDs) that reflects electrical activity from most of the retina. A *pattern electroretinogram* (*PERG*) is recorded when structured stimuli are used; for example, checkerboards or gratings. Usually, PERGs are recorded using stimuli localized to the macular and paramacular areas. Pattern stimuli contain equal numbers of black and white elements (usually checks) that counterphase, or appear from a background of uniform gray field of equal mean luminance (pattern onset). With these stimuli, there is no overall change in mean retinal luminance, and light scatter within the eye is minimized. A localized flash ERG can be applied if a bright stimulus surround is used to reduce the effect of scattered light (called focal ERG).

Multifocal ERGs (mfERGs) are obtained by stimulating the central 30° to 50° of the retina with a contiguous array of flickering hexagons. Each element is independently alternated

between black (off) and white (illuminated) according to a pseudorandom binary order called the m-sequence. Multiple hexagons are simultaneously alternated, but the m-sequence determines that no pattern of simultaneous hexagon stimulation is repeated twice in the sequence. Cross-correlation techniques associate ERG activity with localized retinal areas and provide a topology (map) of the test field's retinal sensitivity.[150]

Separating Rod and Cone Activity

There are important clinical advantages in separately assessing rod and cone activity. Rods and cones can function separately or interactively, depending on the level of overall illumination. During light adaptation, the retinal circuitry alters to cater for a million-fold change in visual sensitivity (6 $\log_{10}$ unit). The cone pathways are preferentially stimulated by high-intensity white light and longer-wavelength (red) flashes presented under photopic conditions, as well as by fast flash rates delivered above 15/s. The rod pathway is preferentially activated by dim, short-wavelength (blue-green) light stimuli or by very dim white flashes presented at less than 10/s under fully darkened (scotopic) laboratory conditions.

Rods can detect single light quanta in dark backgrounds. Rod ERGs are slower responses than cone ERGs, as they are reflecting a longer pathway through the retina. Rods contact one bipolar type only: the "On" rod bipolar, which directly links to a rod amacrine cell that, in turn, feeds back to contact cone "On" bipolars. Cones are involved in analysis of spatial contrast discrimination mechanisms and detect decrements ("Off" changes), as well as increments ("On" changes) of light against an illuminated background. Cones directly contact both cone "On" and "Off" bipolars.[190] Other more direct rod-to-cone gap junction pathways and also an "Off" bipolar pathway have been described.[187] Electroretinography can help dissect these pathways and improve our understanding of retinal dysfunction.

Origins of the ERG

Retinal Response to Light

Light stimulation of both rods and cones causes transient and sustained changes in the extracellular ion composition, particularly of potassium ions (K^+ ions). Müller cells, which are of glial

origin and span the depth of the retina, have variations in their surface conductivity for K^+ ions. This variation causes localized buffering of K^+ ions and induces radial currents involving the length of the Müller cell. The movement of these ionic currents through the membrane and interstitial resistance of Müller cells give rise to an associated voltage change [V = current (I) × resistance (R)], and this mass dipolar response is detectable at the front surface of the eye as the ERG.

Component Origins

Granit, in 1933, suggested that three processes are involved in generating the flash ERG: process I (PI) is the main contributor to the c-wave (EOG), PII to the b-wave, and PIII to the a-wave.[70] Granit surmised that the ERG is an algebraic summation of these positive- and negative-going processes with different timing and size and that the processes are generated by different retinal structures. ERG analysis continues to be a lively area of research some 70 years later. A variety of neurotransmitter analogues, and antagonists, are now available to pharmacologically dissect out the various contributions of the different retinal networks whose function also contribute to the resultant ERG.[191] New components (e.g., the scotopic threshold response elicited by markedly dim flashes) have been discovered.[193] New analysis techniques (algorithms) have been applied to studying phototransduction,[171] and methods of assessing the different contributions of On and Off pathways have been elaborated.[193] Paired-flash ERGs have been used to study inactivation mechanisms and recovery rates of rhodopsin via the dynamics of the rod a-wave.[92] The lifetime of activated rhodopsin in normal human rods has been estimated to be 2.3 s.[167]

Three main features of the flash ERG are usually analyzed for clinical purposes:

- Size or amplitude of the negative and positive peaks (a- and b-waves)
- Latency or implicit time of these peaks
- Waveform, in particular, the relative size of each wave that determines the shape of the ERG (e.g., as when describing the "negative" ERG)

Cone-driven ERGs are smaller, with components of shorter latency, compared with rod-mediated ERGs. Cone-driven ERGs can be distinguished by b-wave latencies around 30 to 35 ms,

prominent a-waves, and "spikier" morphology. The rod ERG is rounder, with later and larger b-waves, around 50 to 60 ms, and the a-wave is less prominent, or may be nondetectable depending on stimulus intensity (Fig. 1-1).

The *a-wave* is the main corneal negative wave with a peak latency of 15 to 25 ms (depending on stimulus intensity and whether it is mainly being generated by cones or rods). In the dark, an influx of cations through channels kept open by cGMP depolarizes the rods, resulting in release of the neurotransmitter glutamate. Light stimulation causes closure of cation channels, resulting in diminution of the dark current, receptor hyperpolarization, and reduction of glutamate release. The a-wave is a reflection of the mass hyperpolarization of photoreceptors. The maximum amplitude of the photocurrent response is determined by the upper limit of dark, or circulating, current available. On illumination, the catalytically active form of rhodopsin, metarhodopsin II, binds to the membrane G-protein

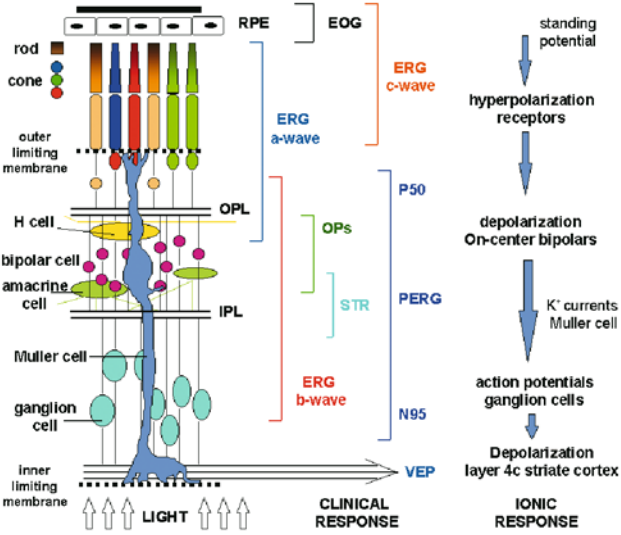

FIGURE 1-1. Schematic retina showing level of electroretinogram (ERG) component generators. Diagram represents ionic changes occurring in retinal thickness after light stimulation. The summation of these changes over time results in the ERG. The different parts of the ERG waveform are generated in different retinal levels.

(Gt) and initiates a signal-amplifying cascade of reactions.[163] Changes in the slope of the a-wave with intensity have been quantitatively related to the mechanisms involved in the G-protein-triggered phototransduction amplification cascade. Differences in amplification and maximal a-wave amplitude have been noted between retinitis pigmentosa (RP) and cone dystrophy.[28,29,91,171,178,197] Recent work has attempted to relate differences in the behavior of these parameters with RP genotypes.[222]

The *b-wave* is a corneal-positive component. Its latency is between 30 and 80 ms, depending on the relative contribution of cones and rods. b-wave activity is associated predominantly with depolarization of on-center bipolar cells. However, Sieving et al.[191] have recently demonstrated that the size and shape of the photopic ERG b-wave is limited by hyperpolarizing bipolars and represents the algebraic sum of both depolarizing and hyperpolarizing activity. The size of the b-wave changes systematically with stimulus intensity and can be approximated mathematically by the Naka–Rushton function, which is a derivation of the Michaelis–Menten equation and describes a saturating nonlinearity as follows:

$$\frac{V}{V_{max}} = \frac{Int}{Intensity + K}$$

where V = trough-to-peak amplitude of the b-wave
V_{max} = maximum value of trough-to-peak amplitude
Int = flash intensity in td-second
K = semisaturation value, i.e., when I = K V is $V_{max}/2$

Oscillatory potentials (OPs) are a series of high-frequency positive wavelets (four are usually discernible, but sometimes a late fifth wave is present also). OPs overlap with the rising phase of the b-wave. These wavelets are thought to reflect synaptic activity of inhibitory feedback pathways in association with retinal amacrine and ganglion cell activity. Early wavelets of OPs reflect rod function and "on" pathways, and later wavelets are linked with the cone system and "off" pathway activity.[225] OPs are most readily recorded under mesopic conditions. They represent both photopic and scotopic processes and the interaction between cone and rod pathways. They are sensitive to chemical agents that disrupt retinal inhibitory mechanisms (dopamine-, GABA-, and glycine-mediated) but are not selectively altered by excitatory amino acids.

The *c-wave* is a slow positive-going wave that is best recorded over several seconds using DC amplification. It shows variable presence among healthy controls, mainly as it represents the interaction of two retinal potentials with opposite polarity and similar time course. One is a slow positive retinal pigment epithelium (RPE) signal and the other a negative response caused by the presence of K^+ ions in subretinal space. The c-wave is difficult to record reliably and is little used clinically.

The *d-wave* is a positive wave that is closely associated with a reduction in light under photopic conditions. When very brief flashes are used, this component is not obviously discernible as it merges with the b-wave. It can only be isolated by separating on and off stimulation by 50 to 150 ms.

Flicker ERGs elicited by stimuli rates greater than 20/s reflect cone photoreceptor activity. Rods are unable to respond to activation at these stimulation rates. There appears to also be an inner retinal contribution to the flicker response.[107] Stimulation rates of 8 to 10/s are used to elicit sinusoidal rod-mediated ERGs.

Scotopic Threshold Response (STR)

The STR is a slow negative response generated at the inner retina and peaking around 100 ms. It is elicited from a dark-adapted eye using very dim light at intensities lower than that which elicits the b-wave. Experimental evidence suggests that it is generated at the inner retina, most probably by amacrine cells.[193]

Pattern ERGs (PERGs)

PERGs are usually elicited for clinical purposes by using a reversing checkerboard, stimulating macular/paramacular retinal areas. The PERG has typically a biphasic configuration with a positivity at 50 ms (P50) and a negativity at 95 ms (N95). Clinical and experimental evidence indicates that the P50 reflects macula function and the N95 reflects ganglion cell function.[51,90] PERGs are small, of the order of 0.5 to 8 μV peak amplitude. They are best recorded with corneal electrodes that do not impede the eye's optics (e.g., DTL fiber, gold foil, HK silver wire electrodes). Interestingly, infraorbital skin electrodes pick up PERGs at about half the size of those detected by corneal electrodes, whereas, for flash stimulation, ERGs are about 80% to 90% smaller. ISCEV recommends a check size of 0.8°, presented

in a field size of 16°.[12] Clear focus response, averaging up to 50 to 100 averages, and minimal blinking are needed to optimally record PERGs. This level of cooperation is more likely to be achieved in children aged 6 years and older.

ERG RECORDING METHODS

Electrodes

ERGs are recorded clinically from metal electrodes placed on, or very close, to the cornea. The electrode conductor may be mounted in a contact lens, or directly touch the eye's tear film (as with gold foil and DTL electrodes). There are warnings against multiuse contact lenses, and several guidelines are published regarding the risks of cross-contamination from electrodes used for clinical electrophysiology purposes. The greatest known risks are from AIDS, hepatitis B, and prions associated with Creutzfeld-Jakobs Disease (CJD) and human variant CJD. In clinical visual electrophysiology, disposable electrodes are strongly advocated. Single-use, contact lens JET electrodes and DTL fiber electrodes are favored for corneal ERG recordings and sticky pad electrodes for infraorbital recordings. Sterilizable silver/silver chloride EEG electrodes are commonly used to record VEPs.

Some centers routinely use contact lens electrodes to record flash ERGs from babies and young children. The recording is obtained while the child is unconscious, either under sedation or anesthetized as part of a fundus examination. Other centers find that reliable recordings can be obtained in most young children while the child is conscious but physically restrained. Very little has been published on the risks of corneal abrasion or serious damage associated with sedation or anesthesia for ERG recording in children. Indeed, there are medical practitioners and parents who feel the risks associated with induced unconsciousness are unacceptable when used to obtain the ERG only. Some departments use skin ERG recordings as "a last resort" when sedation is not an option for reasons of patient size or weight. Other departments (including the authors') find that, with signal averaging, reliable flash ERG recordings can be obtained from skin electrodes positioned immediately below the lower eyelids; this method allows the VEP to be recorded at the same session and has strong diagnostic advantages. The authors

use DTL electrodes and ISCEV standard recordings for experimental purposes on cooperative older children and adults.

ERG amplitude is related to the type of recording electrode used. It is important for laboratories to standardize on one type. The authors compared six different forms of electrode in the same subjects. The Burian–Allen contact lens (with lid speculum) electrode gave the largest a-b amplitude for the mixed rod/cone ERG, which measured 470 μV on average. Relative to this, the amplitudes of the same component recorded from the other electrodes were as follows: Jet, 89%; C-glide, 77%; gold foil, 56%; DTL fiber 46%; and lower lid skin ERG, 12%.[53]

Physiological and physical factors also have important effects on the ERG. Physiological factors to consider include these:

1. Gender differences (females tend to produce larger and shorter latency responses compared with males).
2. Age.
3. Fundal pigmentation (light fundi are associated with larger b-wave amplitudes compared with darkly pigmented fundi).
4. Pupil size.
5. Refractive error.
6. Drugs (treatment and anesthesia).
7. Circadian rhythm.

Physical (stimulus) factors having important effects include these:

1. Intensity: illuminance rather than stimulus intensity, per se, should be used to study retinal responses. Illuminance depends on pupil size, which is small (around 3 mm diameter) in infants. In adults, however, it can vary between 5 mm and 9 mm after dilation. This variation of pupil area is significant, and it is important to note pupil size or, more pertinently, illuminance, especially if the pupils are unusually large or small.
2. Duration.
3. Interstimulus interval (ISI).
4. Color.

Technical Equipment

Amplification

ERGs and VEPs are relatively very small signals (5–10 thousandths of 1 volt). Differential amplification is needed to visu-

alize responses. This technique involves recording the *voltage difference* between two points on the head (one "active," recorded over or very near where the response is generated, and the other relatively "inactive," little influenced by activity at the active site). The method is an effective way to remove background activity (called noise), common to both active and inactive sites. Differential amplifiers have filters to restrict the amplified range of high and low frequencies, which helps to distinguish response activity from electrical activity of other physiological and extraneous origins. DC amplifiers have no lower limit to their frequency response and can record both steady and fluctuating potentials. They are preferred for recording very slow potential changes (e.g., EOG fluctuations and the c-wave). AC amplifiers allow filtering of low-frequency activity, which can cause significant distortions in the recording of the ERG and VEP. Low-frequency interference mainly arises from eye movements and from ionic interactions at the electrode and body surface interface. Recent advances now permit digital DC amplification to be used, and with this technique corrections of slow potential changes can be made online while signal acquisition is taking place.

Averaging

Individual small evoked responses such as the PERG and VEP are often almost invariably difficult to discern, as they are intermixed with "noise" arising from physiological (usually muscle, heart, or spontaneous brain activity) and extraneous sources (power lines, hospital equipment, communication frequencies). The technique of signal averaging offers a powerful means to systematically add activity occurring immediately after each stimulus delivery; this has the effect of clarifying the signal and reducing background noise activity. The background noise reduces approximately in relation to the square root of the number averaged; for example, averaging 100 responses reduces background noise amplitude to one-tenth of the size of the response. Although children tend to produce larger VEPs than adults, they tend to be more restless (i.e., produce more eye movements and muscle activity), and a greater number of responses need to be averaged to achieve a good discrimination between the response and background activity.

THE ELECTRO-OCULOGRAM

Granit's process PI contributes to the c-wave of the ERG, and is also reflected in the standing potential of the electro-oculogram (EOG)[70] (see p. 91). Steady ionic currents flow between the pigment epithelium and the photoreceptors and generate the standing potential that is positive at the cornea relative to the posterior pole. ISCEV standards for the EOG, published in 1994 and reissued in 1998, are found on their Web site (www.ukl.uni-freiberg.de/aug/iscev)

The EOG is usually recorded using skin electrodes (nowadays, mainly EEG or sticky pad type) placed close to the inner and outer canthi of each eye. The potential difference between these electrodes is recorded, using DC or near-DC amplification, when the eye makes a saccade between two preset fixation points. This recording technique can also be used to depict and monitor nystagmus.

The amplitude of the EOG is closely linked with the size of the saccade and with the state of light adaptation of the eye. Patients are asked to alternate fixation between two lights placed centrally (commonly LEDS), with an angular separation at the eye between 20° and 30°, every 2 min or so. Eye movements are performed in the dark, when the EOG reaches a minimum amplitude, normally after 8 to 10 min (dark trough). Lighting conditions are then made strongly photopic and, after 8 to 10 min, the EOG usually increases to a maximum size (light peak), which is about twice the dark-trough size.[9]

Clinically, the ratio between the light peak against the dark trough is used as an index to gauge photoreceptor/pigment epithelium function. This is called the Arden index and, in many laboratories, values greater than 1.8 are considered normal.[9] In practice, children of approximately 6 years of age and older have the tolerance and discipline to reliably make saccades every 2 min, for a total of 30 min.

Fulton et al.[63] have described a technique for obtaining an EOG in younger children. A rotating chair (as used for eye movement studies) is utilized to elicit the vestibulo-ocular reflex (i.e., doll's head response). The child's fixation attention is held on a toy target while the chair rotates the child's body by a fixed amount (e.g., 30°). However, the technique is not widely applied because, in practice, it is difficult to reliably hold a child's attention for the long half-hour period required to gauge the light peak and dark trough.

THE VISUAL EVOKED POTENTIAL

Types of VEP: Transient, Steady State, Sweep, and Multifocal

The VEP is normally largest in the midline, around 3 to 5 cm above the inion. VEPs are elicited to stimulate a wide central area of the visual field, most commonly at stimulation rates less than 5/s; this ensures that all components of individual responses are clearly distinguished (the transient VEP). For clinical purposes, uniform light flashes and checkerboard pattern stimuli are usually used. Patterns either reverse (pattern reversal) or abruptly appear from a uniform background of the same overall stimulus luminance as the pattern and then disappear (pattern onset/offset). Recently, the technique of *multifocal VEP* has been introduced. The stimulation technique is similar to that used for multifocal ERG studies, but the VEP is usually recorded from a single midoccipital site following stimulation of small, well-localized areas of the visual field. Steady fixation during signal acquisition is vital, making its application to pediatrics very limited at this time.

When the stimulation frequency is increased so that the VEPs merge and appear to maintain a consistent sinusoidal waveform (noted at rates around 8–10/s or more), then responses are said to be "steady state." Steady-state techniques are used to elicit sweep VEPs where a predetermined range of different pattern sizes, or contrast levels, are presented sequentially. The changes in response amplitude and phase are analyzed using Fourier techniques, and the results are presented graphically (usually approximating a bell shape). Computations of the maximum and measures of regression relating to the rate of change of the rising and falling slopes are often used to summarize results.

Cortical Origins of the VEP

VEPs reflect surface activity of cortical gyri and, therefore, mainly reflect activity of areas of the visual field represented at the surface of gyri. Parts of the visual field represented within fissures are weakly recorded at the surface, at least by electrical means, and are best picked up using magnetic techniques. Experimental evidence indicates that the P100 component of the flash VEP arises from cortical activation by the retinogeniculate

pathway. The arriving afferent volley causes depolarization in lamina 4c of the striate cortex (area V1).[68,184] Studies in the monkey indicate that pattern reversal stimulation activates the same cortical areas as diffuse flash stimulation but additionally activates supra- and infragranular layers of striate cortex. Other specialized visual areas are also activated, in particular, the V4 complex, which is also involved in generating later components of the flash VEP.[68] Topographic studies in adult humans suggest the pattern-onset VEP has spatially separate generator sources for its main three components, labeled CI, CII, and CIII.[98,99] The CII negativity, and probably CIII positivity, have an extrastriate origin whereas CI positivity arises from striate cortex. However, others have used dipole localization models and suggest that Cl originates in peristriate Brodmann area 18 and CII in a peripheral area adjoining.[162] In children, CI is the most prominent component and shows sensitivity to changes in contrast and luminance. CII shows sensitivity to the "contour" features of pattern (i.e., edges, corners), and inward, starting around 8 years of age and older. These maturational changes in the onset waveform can confound its application in the clinical context.

Flash VEPs

Bright-flash stimulation is used mainly when visual acuity is poor or when cooperation is limited. In patients with cataract, corneal opacity, severe retinal dystrophy, optic atrophy, or marked cortical defects, it is not possible to elicit pattern VEPs reliably. The flash VEP has a complex waveform and can show more variability across patients than pattern VEPs. This difference limits its clinical usefulness, as bright flashes must be markedly dimmed before significant changes in flash VEP are detected. This is the case also for changes in pupillary size.

Pattern Reversal VEPs

The *pattern reversal VEP* (*P.VEP*) is usually elicited by checks that alternate from black to white and vice versa. Some prefer to use vertical or horizontal gratings going through the same cycle. Horizontal gratings can be advantageous when nystagmus is present because stimulation is in the plane orthogonal to the eye movement. The P.VEP has a stereotype triphasic waveform, dominated by a major positive component at about 100 ms (P100), preceding (N80) and succeeding (N145) negative components.

PATTERN-ONSET VEPS

Pattern-onset VEPs are elicited by the brusque appearance of a pattern usually lasting between 100 and 300 ms. When onset durations are longer than about 80 to 100 ms, then VEPs both to the onset and offset are discernible; at shorter intervals, the VEPs merge and it is difficult to distinguish particular individual components. Interestingly, the waveform and response properties of the offset VEP are similar to those of the pattern reversal VEP (although component latencies are consistently about 10 ms later for offset VEPs).[188]

The pattern reversal VEP is used more widely in clinical assessment, as its waveform is maintained across the lifespan, and half-field abnormalities are more reliably detected with this stimulus mode. Pattern onset is valuable for assessing acuity in the older child, particularly if nystagmus is present. In older children, it is useful in identifying the abnormal pathway projection associated with albinism.[8] It is also more difficult to actively defocus the pattern with onset stimulation, and this stimulus mode is also valuable when assessing patients suspected of malingering or having hysterical visual loss. In their laboratory, the authors routinely perform both pattern reversal and onset/offset stimulation on patients with nystagmus and those who may be feigning visual loss, as the tests can be done rapidly, and complementary information is obtained in a recording session lasting approximately 35 to 40 min.

COLOR, MOTION, BINOCULAR, AND VERNIER VEPS

There are two main projecting systems from the retina: these parvocellular (P) and magnocellular (M) systems appear to maintain partial segregation in their projections to the many specialized cortical areas.[56] Although there is functional overlap between M and P systems, stimulus properties can be targeted so as to bias the contribution from one of these processing streams.[132,142,216] Isoluminant chromatic patterns, or high-contrast, high spatial frequency patterns, presented at low temporal rates preferentially stimulate the P system. The M system is more responsive to low-contrast, low spatial frequency stimuli presented at high temporal rates.[211] Stimuli at velocities less than 4°/s appear to preferentially elicit VEPs from cortical areas concerned with motion processing.[50,119,137,156]

The use of these specific stimuli has not yet significantly enhanced routine pediatric electrophysiological assessment.

However, experimental studies have reported interesting findings about normal visual development. Skoczenski and Norcia[195] have shown that vernier VEPs are strikingly immature, agreeing with what is found in psychophysical studies of vernier acuity. The slower normal maturation of the nasotemporal optokinetic nystagmus (OKN) (compared with temperonasal OKN) and the persistence of this asymmetry in infantile esotropia shows moderately good correlation with the degree of asymmetry in motion VEPs, eye alignment, fusion, and stereopsis.[20]

Paradoxical Lateralization of the Pattern Reversal VEP

It is well recognized that the posterior scalp distribution of the pattern reversal VEP is strongly asymmetrical if only one occipital hemisphere is activated; this occurs during half-field stimulation, or if a hemianopia is present. Half-field stimulation activates the contralateral striate visual area, represented at the occipital pole and medial surface on each side of the calcarine sulcus, near the pole (i.e., the right half-field activates the left hemisphere). The P.VEP P100 component is commonly largest over the midline and occipital scalp ipsilateral to the field (i.e., to right half-field). Stimulation P100 is largest over the right occiput, especially when moderate to large checks (>30′) are presented in a wide lateral half-field (>6° out from central fixation). Recording electrodes over the hemisphere ipsilateral to the stimulated field therefore are optimally placed to pick up the dipole-like activity generated by activation of the visual area of the contralateral hemisphere.[14] This has been called "paradoxical" lateralization, because the P.VEP P100 is mainly being recorded over the nonstimulated hemisphere.

It is very important to be aware of the changes in VEP distribution associated with hemianopia when clinically interpreting VEPs, particularly in pediatrics, when the abnormality may be unsuspected. The authors have described in several studies[97,125,166] how the detection of VEP asymmetry associated with hemianopia led to confirmation by imaging studies of unsuspected posterior cortical abnormalities in young infants. They disagree with others[37] who have asserted that VEP is not reliable in demonstrating hemianopia. When there is a P100 over one occiput and N100 over the other, the authors find that this is a strong and reliable indication of posterior hemisphere dysfunction (Fig. 1-2).[22,26–28]

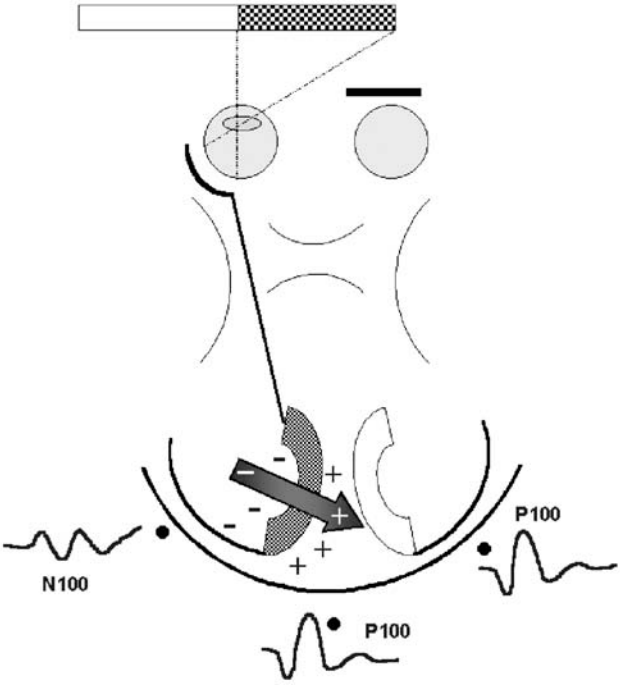

FIGURE 1-2. Diagram of paradoxical lateralization. The stimulation of the right half-field mostly activates the left hemisphere from the occipital pole along the calcarine fissure. If this hemisphere is regarded as a flat battery, the direction of the bioelectrical dipole (*arrow*) points to the opposite hemisphere. Thus, the electrode on the hemisphere ipsilateral to the field stimulated (contralateral to the activated hemisphere) is best placed to pick up the P100. This would be the occipital distribution if there were right hemisphere dysfunction and a homonymous left half-field defect. The distribution would be the same for each eye: an uncrossed asymmetry.

Macular and Paramacular P.VEP Components

As indicated previously, half-field stimulation in healthy controls and full-field stimulation in patients with hemianopia will produce asymmetrically distributed VEPs over the occiput, with the P100 component being largest on the side of the scalp ipsilateral to the stimulated or preserved half-field and an N100

component largest over the contralateral scalp. There is strong experimental and clinical evidence that activation of the macula area (up to about 6°) elicits P100 and its accompanying negative components at around 80 and 145 ms. However, activation of the paramacular areas of cortex (from about 6°–10° from central fixation) elicits a contralateral N100 (and its accompanying components, P75 and P145).[79] Patients with discrete central scotomas, such as those found with tobacco-alcohol amblyopia, will produce P.VEPs with an attenuated P100 but with relatively well-preserved N100 components best recorded over each side of the occipital midline.[78]

Recording VEPs in Children

VEPs are altered by the state of arousal and defocusing, more markedly so for P.VEPs elicited by smaller checks (<20′). Anesthesia and deeper levels of sedation can lead to all forms of VEP becoming broader, smaller, and later. However, Wright et al.[236–238] have described that P.VEPs obtained under chloral hydrate sedation can be useful in assessing interocular differences in amblyopia.

The authors much prefer to record from alert young children. Infants and toddlers sit on a parent's lap but are most likely to require encouragement to attentively fix on the stimulus target; this also helps to reduce myogenic activity associated with movement. The advice of parents is usually sought to help decide whether an older child should sit on a lap or sit independently. A large stimulus screen (about 10° to 15° out from central fixation) is important to ensure stimulation of both macular and paramacular cortical representations. It is useful to have the ability of switching from music videos or cartoons to pattern stimulation (but keeping the audio track constantly on). Toys making attention-grabbing noise and when dangled across the upper part of the stimulus field are also useful, as the cortical representation of the lower visual field is more represented mainly in occipital/parietal areas and predominantly contributes to full-field VEP recordings.

Closed-circuit television is valuable in helping to monitor fixation, and interrupted averaging, which acquires data only when fixation is adequate, greatly helps to obtain more reliable results. Repeated runs are necessary to confirm response consistency. The authors recommend using a series of different check sizes to assess consistency and subtle variations in

response amplitude and latency. This methodology will also help give an indication of vision and refractive error (if P.VEPs become larger and of shorter latency when larger checks are used). Spectacles should be worn, but this is not always possible. Therefore, it is important to present an adequate range of check sizes that can withstand moderate refractive error. The authors use check sizes ranging from 400′ to 6.25′ presented in a 28° field, starting with a medium check size (50′), which is relatively robust to moderate refractive error and provides an indication of the general quality of P.VEPs likely to be recorded from that patient.[78] Marked changes in pupil size and eyelid droop will also deleteriously affect P.VEP amplitude and latency. Pattern-onset stimulation is the preferable stimulus mode when nystagmus is present or fixation is otherwise unstable. Slow stimulation rates (about 1/s), and longer acquisition times (about 500 ms) are more suitable when recording immature VEPs of infants less than about 8 weeks of age.

A transoccipital montage of at least three electrodes is essential for VEP detection of chiasmal or hemisphere anomalies. A monopolar recording derivation, in which a common reference is placed near the midfrontal location, is preferable for more optimal visualization of occipital VEP half-field asymmetries. Bipolar derivations, where separate references are placed at parietal/central location of each hemisphere (favored by some workers), can have the effect of reversing the apparent localization of the VEP.[78] Monocular stimulation should be part of the routine testing protocol, and pattern-onset stimulation used if latent nystagmus becomes evident. When cooperation is very limited, binocular and monocular ERG and VEP flash stimulation should be tried first, followed by attempts at pattern stimulation (onset and reversal). Many children are calmer by the end of this stage, and some may accept eye patching for monocular testing. If not, the session can be abandoned, having obtained useful details about retinal and postretinal function, and another appointment is given for 3 to 6 months later for another attempt at getting more detailed information using pattern stimulation.

STANDARDS AND GUIDELINES

Subcommittees of the International Society for Clinical Electrophysiology of Vision (ISCEV) have recommended standards for electroretinography, electro-oculography, and visual evoked

potential recording. There are also guidelines for multifocal ERGs, and, as indicated earlier, guidelines for pediatric visual electrophysiology are in preparation. The International EEG Federation has endorsed the ISCEV standards (see also American EEG Society EP Guidelines, 1994).

ISCEV ERG Standards

These standards define a standard flash to be 1.5 to 3.0 photopic cd/m^2 intensity at the surface of the Ganzfeld stimulus bowl with a maximum duration of 5 ms. Use of a contact lens electrode with speculum is strongly advocated together with artificial pupillary dilation, a full-field Ganzfeld sphere, and at least 20 min of dark adaptation. The recording of five standard responses is recommended in the following order:

Dark-adapted responses:

1. A rod response from dark-adapted eyes, elicited after at least 20 min of dark adaptation by a dim white flash (2.5–3 log units dimmer than standard flash); the a-wave should be barely detectable and the b-wave should have a slow onset and be relatively large (200–400 μV).
2. Next, a maximal mixed rod/cone ERG recorded from a dark-adapted eye using the standard flash with well-defined a-wave, b-wave, and oscillatory potentials.
3. Finally, oscillatory potentials (OPs) are recorded to repetitive standard flashes, presented at 15-s intervals to the dark-adapted eye (the first few trials are discarded as OPs will become more conspicuous to later flashes). The slow activity of a- and b-waves is preferentially filtered (amplifier settings of 100–300 Hz), making OP high-frequency wave-lets more conspicuous. The number, size, and latency of OPs are noted.

Light-adapted responses:

1. The eye is then light adapted (rods saturate at levels above 30 cd/m^2) for at least 10 min as the patient stares into the internally illuminated Ganzfeld bowl. The cone-mediated ERG to the standard flash is then recorded.
2. Last, the cone-mediated ERG to the standard flash flickering at 30 Hz is acquired.

Recording from Young Children

ISCEV Approach

The ISCEV standards advocate that a contact lens, with lid speculum, also be used in young children. They indicate that for "unusually noncompliant" children (most often between 2 and 6 years), restraint may be necessary, or alternatively induced sedation or anesthesia (often linked with fundal examination) may be needed. It is acknowledged that heavy anesthesia can change the ERG. Light anesthesia is likely to have a small effect, compared with the variability expected in pediatric recordings. However, there is no discussion of the possibility of corneal abrasion and the rare, but potentially very serious, risk associated with general anesthesia or sedation. These issues are discussed from time to time on the ophthalmology Internet mail base (ped-ophth@ucsd.edu). The guidelines also acknowledge that the standard ISCEV protocol may need to be abbreviated and, when cooperation is poor, it may be possible to obtain only the ERG responses most pertinent to the diagnostic question (Fig. 1-3).

GOS Pediatric Protocol: Combined ERG/VEP Recording

Recording the ERG and VEP at the same session greatly enhances the diagnostic power of visual electrodiagnostic testing, particularly when assessing young children who appear to have poor vision. It is possible to rapidly and reliably gauge if the basis of the visual problem is retinal (involving predominantly cones, rods, or both), or whether it is postretina, primarily affecting the optic nerve, chiasm, or pathway beyond the chiasm (if multichannel recording and monocular stimulation are adopted). There is a degree of complementarity between the tests; thus, cone or macular abnormalities will be associated with poor VEPs also.

As mentioned previously, the authors do not routinely sedate or anesthetize young children, and still manage to achieve a low recording failure rate (about 2–3/1000 where no ERGs and VEPs could be recorded); this is accomplished by entertaining and encouraging children, and using the assistance of parents throughout the recording session. Skin ERG electrodes are positioned within 1 cm of the lower eyelid margin (this is comfortable for the child, and ERGs are relatively large). The authors