Visual Electrodiagnostics: A Guide to Procedures

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Introduction

  Electrodiagnostic testing of vision comprises several technologies which record electrical potentials from the surface of the eyes, the scalp, or adjacent tissues to provide objective indications of the function of various parts of the visual system. This process is in many ways analogous to the role of the electrocardiogram ("EKG") in cardiology for evaluation of the function of the heart. This document has been developed by the International Society for Clinical Electrophysiology of Vision ("ISCEV") to provide a brief introduction for the clinician to the visual electrodiagnostic procedures in widespread use, and to suggest the clinical indications for which these tests are appropriate.

  Detailed specifications for each procedure may be found in the appropriate ISCEV Standards (Links Here) as well as in textbooks and the published literature.

  This document will discuss the following electrodiagnostic procedures:

1. Electroretinogram ("Flash ERG" or simply "ERG")
2. Multifocal Electroretinogram ("mfERG")
3. Pattern Electroretinogram ("pattern ERG")
4. Electro-oculogram ("EOG")
5. Visual Evoked (Cortical) Potential ("VEP")

  In each case, the underlying physiology of the visual system will be briefly reviewed, followed by a brief description of the test procedure, and a summary of the clinical indications and typical test outcomes which are most frequently encountered.

  The complementary relationship between these procedures and clinical methods of *anatomic* assessment (such as Optical Coherence Tomography ("OCT"), Retinal Angiography) and *subjective* methods of visual assessment (visual acuity, perimetry, assessment of color vision, contrast sensitivity) will also be discussed.

Electroretinography (Flash Electroretinography, ERG)

The flash electroretinogram is a recording of the variation in the electrical potential at the surface of the eye in response to stimulation of the eye by a brief, diffuse flash of light. It is a direct reflection of the modulation by light of the extracellular electrical currents within the retina.

The full-field ERG is a global response of the retina and provides an assessment of generalized retinal function under light- and dark-adapted conditions. A ganzfeld (German for "entire field") stimulator which surrounds the eye with a uniformly illuminated sphere is used to deliver a range of full-field flashes that evenly illuminate the maximal area of retina. The ISCEV-standard protocol includes dark adapted recordings to flash strengths of 0.01 and 3.0 cd.s.m^{-2} (DA 0.01; DA 3.0) and recommends recordings to stronger flashes of (DA 10.0 or DA 30.0). The dim flash (DA 0.01) ERG arises in the rod bipolar cells. The bright flash ERG is a mixed rod and cone system response but is normally dominated by the rod system; a cornea-negative a-wave is largely derived from rod photoreceptors; a subsequent cornea-positive b-wave arises largely in the rod On- bipolar cells and reflects function that is post-phototransduction or inner retinal. Photopic 30Hz flicker and single flash ERGs (LA 3.0; 30Hz and 2Hz) are cone-driven but dominated by inner retinal cone bipolar cell activity with a cone photoreceptor contribution to the single flash ERG a-wave.

It should be noted that flash ERG recording with a dim flash under dark-adapted conditions is the only routine electrophysiologic testing modality which selectively monitors the function of the retinal rod photoreceptors.

ERGs are recorded using skin electrodes to serve as "reference" or "ground" connections, with active corneal electrodes (or in some cases, skin electrodes placed in close proximity to the eye) placed on the eye with topical anesthesia. Recordings based on standard ISCEV specifications take about 50 minutes, including 30 minutes for dark adaptation, and 10 minutes for light adaptation. Though corneal electrodes may be somewhat unfamiliar to most patients, they are not uncomfortable.

Indications for ERG:

1. Evaluation of known or suspected generalized dysfunction of the retina or retinal pigment epithelium. Symptoms and/or clinical signs may suggest an inherited or acquired retinopathy but the presence, severity and nature of retinal dysfunction cannot be inferred reliably from the clinical findings alone. For example, severe retinal dysfunction can occur in the absence of fundus abnormality and conversely there may be normal retinal function associated with an abnormal but functionally benign fundus change. Asymptomatic patients with a family history of inherited eye disease may require testing to enable appropriate genetic counselling and management e.g. in forms of retinitis pigmentosa the high sensitivity of the full-field ERG can facilitate early diagnosis in the absence of fundus signs. ERG is very useful in the evaluation of patients with difficulties adapting to dim light (nyctalopia) or bright light (hemeralopia). Electrophysiology can also be used to exclude significant retinal or macular dysfunction in patients with non-organic visual loss.

2. Classification of retinal disease. Flash ERG is useful to distinguish retinal disorders which affect primarily retinal rods from those which affect primarily retinal cones. In rod-cone dystrophy the rod-derived ERG components are more affected than cone-mediated ERGs and vice versa in cone-rod dystrophy. Analysis of multiple ERG parameters including timing, amplitude, waveform shape and inter-ocular symmetry can differentiate between a wide range of disorders. Maximum diagnostic precision requires interpretation in clinical context. Rarely the ERGs have pathognomonic waveform characteristics that specify the diagnosis (see below).

3. Characterization of maculopathy. Macular dysfunction can occur with or without visible evidence of maculopathy. Macular function may be examined using techniques such as the pattern ERG (P50) or multifocal ERG but full-field ERGs are critical for the detection or exclusion of generalised retinal involvement. Common examples include inherited causes of bull's eye lesion which may be associated with macular dystrophy, cone or cone-rod dystrophy. In Stargardt disease there is usually visible signs of maculopathy and flecks but ERGs are required to establish whether dysfunction is confined to the macula or whether there is generalised cone or cone and rod involvement. A combination of standard and large-field pattern ERGs may further characterise macular dysfunction.(Multifocal ERGs offer relatively high spatial resolution and may better localise central, paracentral or radially asymmetrical dysfunction – see below.) The diagnosis of severe color vision defects, as in achromatopsia, is also best performed by ERG.

4. Detection of carrier states of inherited visual disorders. Electroretinography may be used to detect and differentiate carriers of inherited retinal disease. For example, the fundus phenotype in female carriers of X-linked retinitis pigmentosa (RP) is variable; the fundus may be normal or there may be abnormal pigmentation or a "tapetal" reflex but most manifest ERG abnormalities. In contrast, there may be abnormal retinal pigmentation in heterozygous carriers of X-linked choroideraemia but full-field ERG are usually normal. In carriers of X-linked albinism the fundus may show abnormal pigmentation but full-field ERGs are normal. Some autosomal dominant disorders such as Best disease and forms of retinitis pigmentosa exhibit variable expressivity and electrophysiology can detect asymptomatic patients with subclinical disease, helping to establish the inheritance pattern.

5. Detection and characterisation of retinal disease in children or patients unable to accurately describe their symptoms. Accurate diagnosis may be difficult in children or patients who are unable to describe their visual symptoms or who are difficult to examine and ERGs provide an invaluable objective assessment of retinal function. Electroretinography may confirm or exclude retinal dysfunction due to genetic or acquired aetiology or as a manifestation of metabolic or syndromic disease. Babies who not fix and follow and amblyopic patients that fail to respond to treatment may require ERG testing to confirm or exclude retinal pathology. ERGs are frequently valuable in the differential diagnosis of congenital nystagmus, particularly in the absence of diagnostic fundus findings. Early diagnosis of retinal dystrophy may be essential to identify young candidates who are potentially amenable to future experimental treatments. A normal ERG may prompt the need for further investigations e.g. of optic nerve function. Special considerations for ERG testing in infants and young children are discussed separately below.

6. Monitoring of disease stability. Serial full-field ERGs can be of prognostic value by facilitating the distinction between stationary or relatively benign disease from disorders that progress. For example in Stargardt disease pattern ERGs and multifocal ERGs typically show severe abnormalities in keeping with macular dysfunction but some manifest progressive full-field ERG abnormalities in keeping with worsening peripheral retinal function. Serial pattern ERGs or multifocal ERGs may also help predict the relative stability of macular function in progressive disorders such as rod-cone dystrophy.

7. Monitoring treatment efficacy, toxicity, or safety. Electrophysiology can be an essential component in the monitoring of treatment efficacy or toxicity. For example in sub-acute vitamin A deficiency ERGs may be useful diagnostically but may also be used to demonstrate recovery of retinal function following treatment. In inflammatory retinal disorders such as Birdshot chorioretinopathy ERG deterioration may prompt the need for local or systemic treatment and may influence the titration of systemic steroids or immunosuppression. Several medications commonly administered systemically for non-ocular conditions are potentially retinotoxic and pre-treatment assessment and monitoring of retinal and/or macular function may be considered, particularly if patients are considered at high risk of retinal toxicity or

there are clinical changes e.g. a multifocal ERG may reveal annular macular dysfunction that can manifest as an early stage of hydroxychloroquine toxicity.

Electrophysiology has become increasingly important in clinical trials to assess candidates or eyes suitable for experimental therapeutic intervention and to monitor retinal safety of new treatments for retinal or non-ocular conditions. Specific electrophysiological components may be used as an outcome measure in trials that aim to either improve retinal function or arrest progressive retinal degeneration.

8. Phenotype-genotype correlation. To characterise disorders with a known genotype or to guide the screening of genes associated with a known electrophysiological phenotype. Electroretinography is fundamental to defining functional phenotypes and phenotypic variability and accurate ERG characterisation is likely to aid understanding of the underlying genetic defect. Advances in molecular biology have enabled genotyping of many inherited retinal and macular dystrophies but the functional consequences remain difficult to predict due to allelic heterogeneity and other factors. In rare retinal dystrophies the ISCEV-standard ERGs can identify the gene responsible e.g. in enhanced S-cone syndrome (*NR2E3*) and "cone dystrophy with supernormal ERG" (*KCNV2*). In some disorders testing in excess of the ISCEV-standard protocols may be required to reveal the diagnostic or distinctive ERG features e.g. in Bradyopsia" consequent upon *RGS9* or *R9AP* a range of inter-stimulus intervals and additional red flash ERGs may be needed. Prolonged dark adaptation is informative if there is a suspicion of delayed rod dark adaptation e.g. in fundus albipunctatus (*RDH5*).

9. Assessment of the functional significance of fundus/retinal imaging abnormalities. Ophthalmic examination and imaging techniques may be normal in the presence of retinal dysfunction or may reveal abnormalities that do not correlate with the nature or severity of dysfunction. For example, in rubella retinopathy the fundus is abnormal but full-field ERGs are normal. Retinal/RPE imaging techniques such as OCT and fundus autofluorescence can reveal structural or metabolic changes but electrophysiology provides an objective measure that can help establish the functional significance. For example, in retinitis pigmentosa many patients manifest a ring of parafoveal hyperfluorescence, the size of which correlates with pattern ERG and multifocal ERG measures of macular function.

10. To assess retinal function in cases of ocular media opacity. Full-field ERGs can provide valuable information in patients with suspected retinal disease when the fundus is obscured or when the use of retinal imaging techniques is precluded by an opaque ocular media. Bright-flash technique, with flash stimuli brighter than those routinely used, may be helpful. Integrity of the retina and visual pathway may be important considerations prior to treating patients with corneal lesions, cataracts or vitreous haemorrhage, particularly if there is a history of retinal detachment or known retinal disease. A normal or relatively preserved ERG or flash VEP may suggest a better prognosis for improved vision. Note that a total rhegmatogenous retinal detachment can be associated with an absent ERG response, as the retinal break "short-circuits" the retinal currents responsible for the ERG signal, but that this does not preclude recovery of vision of successful retinal detachment repair can be achieved.

11. Assessment of generalised RPE function. An EOG assessment of generalized RPE function is most useful when retinal function (ERG) is normal or relatively preserved. Inherited causes of generalized RPE dysfunction and severe EOG abnormality include the bestrophinopathies; Best disease, autosomal recessive bestrophinopathy (ARB) and autosomal dominant vitreoretinochoroidopathy (ADVIRC). The fundus appearance in Best disease is variable and a common application of the EOG is the exclusion or confirmation of Best disease in patients with autosomal dominant macular dystrophy including adult vitelliform macular dystrophy. Acquired generalized RPE dysfunction has been documented in several conditions including cases of acute exudative polymorphous vitelliform macular dystrophy and some with acute

zonal occult outer retinopathy (AZOOR). Conversely, in the presence of severe ERG attenuation from any cause, the EOG will be abnormal, and not additionally informative.

12. Autoimmune retinopathies. Antibodies to various cancers may cross-react with retinal tissues, causing a paraneoplastic retinopathy. The clinical features depend to some extent on the primary malignancy. Carcinoma-associated retinopathy ("CAR") frequently presents with abnormalities of cone dysfunction, including reductions in photopic ERGs. Melanoma-associated retinopathy ("MAR") resembles congenital stationary night blindness, with characteristic electronegative waveforms.

Multifocal Electroretinography ("mfERG")

Multifocal electroretinography ("mfERG") complements flash ERG by providing a map of retinal function (at least within the posterior pole) with spatial resolution on the millimeter scale, in contrast to the summed response over the entire retina provided by traditional flash ERG. The stimulus is based on a subdivision of a display screen into small polygonal patches (traditionally a tiling of the screen with hexagonal regions), each of which is modulated to display white or black according to a carefully chosen pseudo-random binary control sequence. The control sequence (generally a so-called "m-sequence") has the mathematical property of "orthogonality" – if a copy of the sequence is shifted in time, and the shifted version multiplied with the original sequence, the time-average of the product is zero. As each stimulus region is controlled according to a unique time-shifted version of the same m-sequence, it is possible to recover the response of a particular retinal region by cross-correlating the summed ERG signal taken from the *single* surface electrode with the unique delayed copy of the m-sequence which controls the luminance sequence of the hexagon which projects to the retinal region. In practice, the computation can be streamlined with fast Fourier transform techniques.

One thus obtains an array of response waveforms, each associated with the location of one of the hexagons in the original stimulus array, and with the retinal location corresponding to that stimulus region. The responses can be mathematically stratified into components associated with single illumination events (the "first-order kernel") or with sequences of multiple illumination events (the second-order and higher-order kernels). The first-order response is roughly analogous to a map of the individual "impulse responses" of each retinal locus to the brief illumination of an individual stimulus location.

The mfERG is recorded under light-adapted conditions, and reflects cone-driven responses. Electrodes that contact the cornea or nearby bulbar conjunctiva are required. Good results can be obtained with contact lens, foil, or fiber electrodes. Careful attention must be paid to good image quality and proper refraction. Fixation should be maintained on a central fixation target throughout the study. The stimulus array geometry is often scaled so as to elicit comparable response amplitudes from each stimulus region, resulting in larger hexagons in the peripheral portions of the stimulus pattern. There is a trade-off between spatial resolution (smaller, more numerous hexagons) and the recording duration necessary to complete the entire m-sequence, and to obtain satisfactory responses with a reasonably low signal-to-noise ratio. In many cases, interpretation can be facilitated by averaging together the response waveforms from all the hexagons in each concentric ring in the stimulus pattern (ring-averaging).

Indications for mfERG:

1. Differentiation between retinal and optic nerve disease. As with flash ERG, the mfERG is essentially insensitive to the function of the innermost retinal layers (ganglion and amacrine cells, and the retinal nerve fiber layer). Thus the mfERG is well-suited to compare central vision defects of retinal origin, which produce decreased central mfERG responses, from optic nerve or central nervous system disorders, which generally leave central mfERG responses

unaffected, except for subtle effects, most evident in the second-order kernels. This is particularly applicable to glaucomatous visual field defects, which are not detected in typical mfERg recordings.

2. Correlation of visual field abnormalities with visible fundus abnormalities. Ophthalmoscopic findings in many retinal disorders may be quite subtle, and it is often difficult to predict the extent to which fundus findings explain the loss of vision, or may be benign and purely incidental. mfERG is valuable in confirming the functional visual significance of fundus abnormalities.

3. Monitoring response to therapy. Resolution of fundus lesions, such as serous or rhegmatogenous retinal detachments or intraretinal edema do not necessarily correlate well with recovery of visual function. mfERG can play an important role in monitoring the physiologic response to theryapy and compare the extent of anatomic and physiologic recovery with treatment or spontaneous resolution or exacerbations of disorders of the fundus.

4. Evaluation for occult retinal disorders. On occasion, retinal disorders present with visual impairment in the absence of ophthalmoscopically visible abnormalities of the fundus. Well-known examples include the early stages of Stagardt disease, where visual loss may precede the development of retinal flecks, and so-called occult macular dystrophy, where fundus abnormalities may be evident only with advanced imaging techniques (such as OCT), but visual function may be significantly impaired. mfERG often demonstrates the abnormality of retinal function, which is often localized to the central retina and thus undetectable by full-field ERG techniques. The finding of abnormalities of the mfERG may be valuable in confirming the retinal origin of the visual loss, as well as in confirming the organic nature of the disorder in patients who may have been suspected of malingering or conversion reaction.

Pattern Electroretinogram ("pattern ERG")

The pattern ERG is the recording from the ocular surface of frequency-doubled (non-linear) responses to pattern-reversal stimulation of the central retina. This stimulus paradigm, developed by analogy with visual evoked potential techniques, is designed to suppress the much larger, nearly linear, signals which originate in the photoreceptor and middle retinal layers, and which cancel due to the symmetry of the pattern-reversal stimulus, revealing the non-linear components, which are not subject to this form of cancellation.

Recording techniques are similar to those used for mfERG, with a contact lens, foil, or fiber electrode used to allow high-quality optical stimulation of the retina by a pattern-reversal stimulus, usually a checkerboard, high-contrast stripes, or sinusoidal gratings. The corneal signals are then averaged in synchrony with the pattern-reversal rate (which is double the frequency of the complete cycle of stimulus modulation, suppressing the fundamental and other odd-order harmonic components. Stimulation frequencies are typically either 2 Hz, which allows examination of transient responses, or 8 Hz, which produces a steady-state response suitable for Fourier analysis. The initial cornea-positive deflection is thought to mainly reflect nonlinear components derived from outer and middle retinal layers, followed by a cornea-negative deflection, which reflects primarily activity in the innermost retinal layers, and is sensitive to injury to the retinal ganglion cells and nerve fiber layer.

Indications for pattern ERG:

1. Glaucoma. The pattern ERG is sensitive to ganglion cell and nerve fiber layer loss in glaucoma, and can be of value in the evaluation of "glaucoma suspects" with glaucomatous risk factors (such as elevated intraocular pressure, or optic nerve head changes) prior to the measureable loss of visual field.
2. Other disorders of the optic nerves and nerve fiber layer. The pattern ERG reflects ganglion cell and nerve fiber loss in patients with inherited, compressive, toxic, or metabolic optic neuropathies, including nutritional deficiencies.
3. Inner retinal compromise due to inflammatory disease. Patients with vitritis or more generalized uveitis frequently develop compromise of inner retinal function, which may be poorly reflected in flash ERG recordings, but may produce abnormalities in pattern ERG.

Electro-oculography ("EOG")

The electro-oculogram ("EOG") is a recording of the steady-state resting potential across the retinal pigment epithelium, usually as it is observed using skin electrodes placed at the medial and lateral canthus of each eye during uniform horizontal saccades. Specifically, the resting potential is normally expected to vary slowly with the state of light- or dark-adaptation of the retina, and the EOG is often recorded so as to highlight this effect.

Historically, the recording of the component of the electrical vector (from the back to the front of the eye) which can be recorded using skin electrodes at the medial and lateral canthus, was initially used to record the position of the eye, and to measure the velocity of horizontal eye movements. It was eventually noticed that the calibration of such eye-movement recordings varies with the state of light- or dark adaptation – the signals are of greater amplitude when the eyes are light-adapted. This effect has been ascribed to variations in the resting potential across the retinal pigment epithelium which are modulated by the exposure to light of the overlying photoreceptors. Clinically, one computes the ratio between the maximal voltage excursions during uniform horizontal saccades of the light-adapting eye over 15 minutes to the minimal voltage excursions during dark-adaptation over the next 15 minutes or so. The ratio of the "light peak" to the "dark trough" is known as the Arden ratio, and is used to summarize the result of the EOG study.

Indications for EOG:

1. Known or suspected Best vitelliform dystrophy. In this disorder, metabolites accumulate within RPE cells, often forming a yellow central subretinal mass (which can resemble an egg-yolk, hence the term "vitelloform), and preventing the normal light-rise in the RPE resting potential. Arden ratios are generally less than1.75 (compared with a normal ratio of at least 2.0).
2. Pattern dystrophies and other disorders of the RPE. These funduscopically striking disorders (in many cases due to variant phenotypes associated with the same mutations as Best vitelliform dystrophy) often present with reductions of the Arden ratios. Rarely, inflammatory disease of the RPE or choroid will also selectively reduce the Arden ratios, demonstrating the RPE involvement.
3. Note that the adaptation effect demonstrated by EOG is driven by changes in the light- or dark-adaptation of the overlying retina – any retinal disorder which causes abnormalities in the flash ERG is likely to reduce the adaptation effect on the EOG as well. Thus EOG testing is not separately informative in cases with known ERG abnormalities.

Visual Evoked Potentials ("VEP" or "Visual Evoked Response – VER")

The visual evoked potential test ("VEP") is the recording of electrical currents generated in the visual cortex of the brain in response to visual stimulation which leak to the surface of the scalp. As the brain is constantly active, it is necessary to average the signals from scalp electrodes in synchrony with a repetitive stimulus in order to isolate the signals which represent the specific responses to the visual stimulus – these are the "evoked" responses, to be distinguished from the free-running fluctuations in scalp potential (the electro-encephalogram, "EEG") which form the baseline on which the evoked responses are superimposed.

If the visual system is thought of as a "pipeline" conveying information from the eyes through the optic nerves, through the optic chiasm to the lateral geniculate bodies, and then through the optic radiations to the visual cortex and subsequent visual association areas, the VEP represents a sampling of the visual information near the "output" of the pipeline, which may be compared with samples near the "input" (the flash, multifocal, and pattern ERGs) to evaluate the function of the intermediate structures.

The VEP stimulus is usually in the form of a diffuse flash ("flash VEP") or a pattern stimulus presented on a CRT display or similar device. For most routine applications, a reversing checkerboard or grating stimulus is used, often with a reversal rate of 2/sec. It is possible to measure visual function by varying the spatial frequency (check size or grating size) or contrast of the stimulus pattern. Lesions may be localized to one eye (or optic nerve) or the other by comparing responses driven by each eye separately in turn. In laboratories where pre-chiasmal disease is of primary importance, recording from mid-line scalp electrodes (usually placed on the forehead, at the vertex of the scalp, and over the occiput) is frequently sufficient.

In some cases, more elaborate scalp electrode arrays may be helpful. The abnormal decussation of fibers at the chiasm in patients with most forms of albinism (all or nearly all fibers cross) may be demonstrated by using an occipital R – L derivation, subtracting the signal of the left side of the occiput from the signal of the right side, in response to monocular stimulation. In normal patients, the R- L derivation should produce only noise; in patients with abnormal decussation, the response should be robust, and it should invert when switching to monocular stimulation of the fellow eye. For this test, a pattern on/pattern off stimulation may work better than pattern reversal.

Interpretation of VEP results is based primarily on the latency of the characteristic response peaks, primarily the occiput-positive "P-100" deflection, which is normally seen with a latency of 100+/- 10 msec – response amplitudes are highly dependent on the thickness of the skull and the electrical resistance of the scalp, and are seldom reported. The wiring of the retina to the brain, and the folding pattern of the primary visual cortex, strongly weight the normal VEP in most patients heavily in favor of macular input. (For this reason, it is often difficult to distinguish between macular and optic nerve disease using VEP data.)

The VEP is generally abnormal in cases where vision is compromised by retinal disease or other ocular pathology (even refractive error). For this reason, a competent eye examination is essential for proper interpretation of abnormal VEP findings.

Indications for VEP:
1. Multiple sclerosis (MS). VEP changes typical of demyelination (delayed implicit time without major wave form changes) can be used to support a suspected diagnosis of MS when clinical findings and or other tests are insufficient for certain diagnosis. Pattern stimulation is preferred in this context. VEP changes are, however, no longer included in the primary criteria for MS diagnosis.
2. Optic neuritis and retrobulbar neuritis. VEP delays are typically seen. VEP amplitudes may be attenuated, sometimes greatly, in severe casese. VEP abnormalities persist in about 90% of

cases even after recovery of visual acuity. (Many patients, of course, present with optic neuritis as an early manifestation of multiple sclerosis.)

3. Hereditary, metabolic and toxic optic neuropathies. VEPs are delayed and/or reduced in amplitude in disorders of the optic nerves of most any type. These may include inherited optic atrophy, toxicity from drugs (e.g. ethambutol), toxicity from other ingested substances (e.g. Jamaican "bush tea"), nutritional deficiencies (e.g. Vitamin B12 deficiency in alcoholics), and other toxins (e.g. methanol or ethylene glycol).

4. Compressive and traumatic optic neuropathies. Compromise of optic nerve function following trauma, or compression by mass lesions such as orbital tumors, swollen extraocular muscles in severe thyroid ophthalmopathy, or meningiomas are associated with delays or reductions in VEP responses.

5. Head trauma. A well-preserved VEP response has been shown to be associated with favorable outcomes.

6. Intracranial mass lesions. These are mainly tumors or aneurysms. The pattern of VEP impairment may be localizing.

7. Multifocal VEP. With a suitable modification of the stimulus pattern, replacing solid hexagons with patches of reversing checkerboards, it is possible to use standard mfERG technology to record multifocal VEPs. These recordings are comparable to low-resolution visual fields, and are able to detect glaucomatous visual field defects. The technique is difficult in practice, and is not yet sufficiently rapid or convenient to replace most conventional perimetry.

8. Pediatric vision screening. Dedicated automated instrumentation for vision screening in infants by VEP has recently become commercially available, and in some cases even marketed for use by pediatricians. Statistical analysis of VEP waveforms in response to sequential variation of the VEP stimulus spatial frequency ("Sweep VEPs") has been suggested as a suitable tool to screen for amblyogenic lesions and other vision problems in infants. Sensitivity and specificity data remain sparse.

Special considerations for infants and children.

The power of electrophysiological testing is greatest when done in conjunction with clinical assessment by eye care professional and other medical specialists. The electrophysiologic procedures permit assessment of retinal and visual function in patients who are too young or otherwise incapable of communicating responses to common clinical vision tests.. The electrophysiologic tests yield numeric data which can be valuable in monitoring the course of a patient, including the response to therapies and surveillance for adverse effects of therapy. The array of tests of the retina and visual pathways can be the basis for functional dissection the visual pathways from retina to brain which facilitates diagnosis and discovery of effects of disease on the visual system.

Both ERG and VEP responses normally progress through developmental changes in infants and childhood. Therefore, interpretation of ERG and VEP responses in young patients is ideally referenced to age appropriate norms.

If retinal disease is suspected, or is to be ruled out, an ERG test should be requested. If disease is suspected to affect the brain, and the visual pathways, VEP testing should be requested. If the concern is subnormal vision and the history and physical examination do not limit it to the eye or to the brain, both ERG and VEP tests should be considered.

Infants up to the age of about two years can frequently undergo successful ERG or testing without general anesthesia, while being held in a parents' lap, using only topical anesthetic eyedrops. It may be appropriate to abbreviate the complete ISCEV standard ERG protocol. VEP testing in infants is equally feasible, but may require simple flash stimulation, if steady fixation on the center of the VEP pattern stimulus cannot be induced with a moving toy, jangling keys, etc.

Examination under anesthesia ("EUA") is generally necessary for ERG testing between the ages of two and five or six. General anesthetic agents alter ERG latencies and amplitudes, often to an extent which cannot be accurately predicted or compensated for. (There is no generally accepted way to gauge the depth of general anesthesia.) Interpretation of ERG results obtained at EUA must thus be limited to identification of the grossest abnormalities.

The cortical neurons which drive the VEP are much more susceptible to general anesthesia than the retinal neurons which generate the ERG. It is thus essentially impossible to record meaningful VEPs under general anesthesia.

Indications for ERG and VEP testing in infants and children:

1. Unexplained visual loss – absent or impaired visually-mediated behavior may indicate a disorder affecting any portion of the visual system. A thorough dilated eye exam should be performed in all cases, supplemented by ERG and/or VEP if the diagnosis is not evident ophthalmoscopically.
2. Congenital nystagmus. The differential diagnosis includes several retinal disorders (such as albinism, Leber congenital amaurosis, congenital stationary night blindness, and achromatopsia) in addition to the primary motor causes ("idiopathic infantile nystagmus", "IIN").
3. Known or suspected hereditary disorders. ERG may be helpful in advising families with patients at risk of hereditary retinal disorders. The extent to which the various retinal dystrophies are detectable in early infancy is frequently not known, but a normal ERG at age five or six is thought to rule out most cases of retinitis pigmentosa (with a possible exception for late-onset autosomal dominant cases.)
4. Perinatal brain injury. Infants with known complications including perinatal anoxia, hydrocephalus, and intracranial hemorrhages often present with severe visual

impairments. Though the diagnosis may not be in question, VEPs may be requested to confirm the nature of the severe damage to the visual system, and assist the parents in understanding the limited prognosis.

5. Delayed visual maturation. Infants often present with "visual indifference", showing little or no reaction to visual stimuli for several months. If the eye exam, ERG, and VEP are normal or near-normal, the diagnosis of "delayed visual maturation" is likely, and the prognosis for development of normal or near-normal vision between 6 and 12 months of age is fairly good. Some nystagmus or strabismus may persist.

6. Perinatal infections. Perinatal infections, particularly the "TORCH" agents may attack ocular tissues. Perhaps most common is inflammation of the retinal pigment epithelium in cases of perinatal rubella,which frequently results in mottled RPE pigmentation. In such cases, a normal or near-normal ERG indicates a favorable prognosis.

7. Monitoring for retinal drug toxicity. The most common indication in this category is vigabatrin, which is used as a last-line drug for infantile spasms, particularly in patients with tuberous sclerosis. The drug is known to cause peripheral visual field constriction in adults, and a post-marketing monitoring program is in effect in the USA. ERG is helpful in monitoring patients who are too young or lack the intelligence to perform visual field testing.

8. Pediatric vision screening (see above).

Complementary testing

Electrophysiologic testing plays a complementary role to the imaging studies and subjective tests of visual function which are more commonly employed in the assessment of patients with visual impairment. Among objective studies, electrophysiological methods uniquely assess aspects of function and dysfunction, rather than the anatomic derangements demonstrated by imaging methods. Optimal assessment is obtained with judicious use of subjective, anatomic, and physiologic techniques. A few specific comments are offered below:

Subjective assessments:

Visual acuity. Visual acuity is the workhorse of subjective visual assessment. It has stood the test of time, and does a remarkable job of documenting visual impairment associated with almost the entire range of visual system pathology, from ptosis of the eyelids and corneal epithelial edema to retinal degenerations and optic neuropathies. Acuity may remain normal in a small set of ocular pathologies, including paracentral and peripheral retinal derangements, nerve fiber bundle defects (as in glaucoma), and lesion of the posterior visual pathways which spare the projections of the central retina. Of course, eletrophysiologic testing is helpful in some of these cases, such as the ring scotomas seen in retinitis pigmentosa.

Visual Fields. Visual field testing is widely available, and, with the advent of automated static perimetry, highly standardized and reproducible. Visual fields allow ready localization of visual impairment, with classic patterns of visual field loss associated with localized and generalized retinal disorders, macular and optic nerve disease, chiasmal disruptions, lesions which attack the lateral geniculate body and optic radiations, and cortical lesions. Multifocal ERG can be of great value in distinguishing between macular and optic nerve disease, which often present with similar visual field abnormalities, and are often indistinguishable by VEP. ERG abnormalities are a "leading indicator" of degenerative retinal disorders such as retinitis pigmentosa – staging of these conditions is usually better accomplished by serial visual fields.

Note that peripheral visual fields are often critical in the adequate assessment of degenerative retinal diseases such as retinitis pigmentosa, in which the extent of scotomas, and the presence of residual temporal islands of vision (of great importance to the patient) cannot be assessed by central Humphrey visual fields, and are only poorly assessed by the peripheral automated visual field programs, which are in any event seldom used as they are very lengthy to run.

Contrast sensitivity. Contrast sensitivity is a separate dimension of visual perception from visual acuity, and can be selectively impaired. Loss of contrast sensitivity is readily documented with special eye charts designed for the task, or CRT-based vision testing devices. Abnormality of retinal physiology, such as cone dystrophy, or optic neuropathy, is frequently demonstrated by ERG or VEP. These tests can differentiate these pathologies from simpler optical problems such as corneal haze or cataract.

Color Vision Testing. Color vision is an important visual faculty, and abnormalities may derive from retinal, optic nerve, or (rarely) cortical pathology. The familiar Ishihara plates are highly sensitive to even minor dyschromatopsias, but detect only red-green (protan or deutan axis) abnormalities. Other sets of test plates, such as the H-R-R plates, also detect tritan axis problems. The common x-linked protan an deutan color vision defects are rarely associated with abnormalities in the ISCEV-standard ERG, but can be detected with non-standard chromatic stimuli. Severe loss of color vision suggests more severe pathology, such as achromatopsia or optic nerve disease, which are readily detected by ERG or VEP.

Dark adaptometry. Abnormalities of dark adaptation are difficult for patients and physicians to assess without formal testing, as everyone experiences some degree of difficulty seeing in dim light.

Formal dark adaptometry can be performed with specialized instruments, such as the Goldmann-Weekers Dark Adaptometer. Qualitative assessment can be readily obtained with much simpler materials, such as the Hyvarinen CONE adaptation test, in which the examiner, with presumably normal dark adaptation, compares his/her adaptation with that of the patient, who is asked to sort colored plastic tiles in a very dim room. Abnormalities of dark adaptation generally imply retinal pathology, including degenerative disorders such as retinitis pigmentosa, or perhaps Vitamin A deficiency. ERG testing readily detects these conditions.

Imaging:

Fundus photography has been available as a clinical tool since 1926; fluorescein angiography was introduced in 1959. More recently, advances in fundus imaging have appeared with increasing frequency, not only documenting ophthalmoscopic findings, but extending the range of clinical perception in depth (ICG angiography) and resolution – spectral mode OCT now approaches the resolution of low-power microscopy, without the need to remove tissue from the eye for histologic processing.

It would be unwise to assume that the enhanced capability of fundus imaging has displaced physiologic methods in the armamentarium of the practicing ophthalmologist. The need to complement anatomic methods with studies of visual function is as keen as ever – perhaps even more so as increasing detail in fundus imaging allows ever finer diagnostic distinctions to be made, for which the physiologic consequences must be determined.

Fundus photography documents the appearance of the retina, and allows ready estimation of the size of fundus lesions. Newer cameras provide much wider fields of view than the 30-40 degree fields of traditional fundus cameras, revealing important pathology of the peripheral retina which was previously unappreciated.

Fluorescein angiography documents the extent and integrity of the retinal vascular compartment, and remains an important tool even in the era of advanced OCT imaging, which lacks the dynamic aspect of the evolving fluorescein angiogram. ICG angiography extends the range of angiographic imaging deeper into the choroid, demonstrating vascular structures and abnormalities hidden to traditional imaging with visible light.

Fundus autofluorescence imaging has proven useful primarily in evaluation of the retinal pigment epithelium, allowing the detection of the accumulation of retinal metabolites in the RPE cells. Recognition of this metabolic process often serves as a leading indicator of RPE breakdown, as in retinitis pigmentosa and atrophic ("dry") age-related macular degeneration.

Optical coherence tomography (OCT) has revolutionized retinal evaluation. It is far superior to even the most careful ophthalmoscopy at detecting anatomic disruptions of the posterior pole, such as cystoid edema, vitreomacular traction, or shallow serous detachments of the retina or pigment epithelium. Moreover, the recognition of the role of the line of photoreceptor ellipsoids (previously interpreted as the inner segment/outer segment junction) as an indicator of the integrity of the photoreceptors has clarified the diagnosis of many retinal disorders. For example, in many cases, so-called occult macular dystrophy is no longer as "occult" as was originally thought. Nevertheless, even with the recognition of these subtle fundus lesions, it is as necessary as ever to correlate structure with function. Indeed, the functional significance of the subtlest fundus lesions detected by OCT is seldom immediately clear. Multifocal ERG can be particularly helpful in this regard.

Adaptive optics offer the promise of extending the resolution of fundus imaging to the level of individual photoreceptor cells. Clinical implications are only beginning to emerge.