CHAPTER

22

Visual Evoked Potentials, Electroretinography, and Other Diagnostic Approaches to the Visual System

ARI J. GREEN

Clinical electrophysiology of the visual system provides an important adjunct to the bedside evaluation of patients with neurologic diseases. It provides the only means available for objective assessment of visual function, especially of the retina and optic nerve, and requires less active participation than subjective evaluations such as perimetry and visual acuity testing. Electrophysiologic techniques can also provide localizing information in the visual pathway and—given the functional organization of the visual system—adjustment of stimulus parameters can be used to define the specific cell type or subpathways affected by an injury. Electrophysiologic techniques play an important role in discriminating diseases of the retina and optic nerve when the distinction cannot be made on standard clinical grounds alone. They also may have use in distinguishing types of injuries of the optic nerve (e.g., glaucomatous, inflammatory, or metabolic), based on assessments tailored to the evaluation of particular functional systems (such as motion or color). The utility of visual electrophysiology is established firmly in the diagnosis and monitoring of patients with ophthalmologic conditions, including neurologic conditions with well-recognized ophthalmologic manifestations such as multiple sclerosis (MS). In addition, clinical research suggests that visual electrophysiology could be used to investigate other neuroinflammatory and neurodegenerative diseases, with the visual system used as a model.

ANATOMY OF THE ANTERIOR VISUAL SYSTEM

The neurosensory retina is one of the three traditional anatomic subdivisions of the central nervous system (the others being brain and spinal cord). The projections of the retina are characterized extremely well and make up a significant volume of the cerebral hemispheres. Of our senses, vision has the greatest amount of cortical surface area dedicated to processing its output and up to 40 percent of the brain has been estimated to be devoted to this effort.

At peak function, the human eye can discriminate up to 10 million shades of color, is sensitive to the flux of a

single photon in a darkened room,[1] and can detect flashes of light as brief as 10 to 20 msec. These physiologic features of the human visual system are embedded in the anatomic substrate that makes up the retina, visual pathways, visual cortex, and accessory visual areas. The retina is comprised of 110 million cells divided into at least ten anatomic layers and three primary subsets of neurons. More than 50 different cell types have been described, and ten different neurotransmitters play an important role in retinal physiology.[2–4] Photoreceptors are the primary sensory neurons of the retina and the most abundant of all the retinal cell types (approximately 90 million rods and 5 million cones on average). They are positioned in the deepest layers of the retina (closest to the retinal pigment epithelium, choroid, and sclera), meaning that light has to traverse all the other layers of the retina before interacting with a photoreceptor (Fig. 22-1). Photoreceptors evidence intrinsic photosensitivity and participate in basic phototransduction—turning light into neuronal signal. Photoreceptors respond to light by converting 11-cis-retinal to 11-trans-retinal, resulting in the hyperpolarization of the neuron and leading to a reduction in release of glutamate from its synaptic terminal.[5]

Photoreceptors are subdivided further into two classes of cells: rods and cones (which are distinguished from one another both by the morphology of their outer segments and by the type of opsin they contain). Rods are highly sensitive to light and evidence peak function in low light conditions. Cones, by contrast, are color sensitive and provide their predominant perceptual input under bright-light (photopic) conditions. In normal individuals there are three cone subtypes (short-, medium-, and long-wavelength), each tuned to a different peak spectral sensitivity within the visible spectrum. Cone and rod distribution is not uniform throughout the retina, as cones are concentrated in the fovea, making up nearly all the photoreceptors in the central 1 degree of the retina,

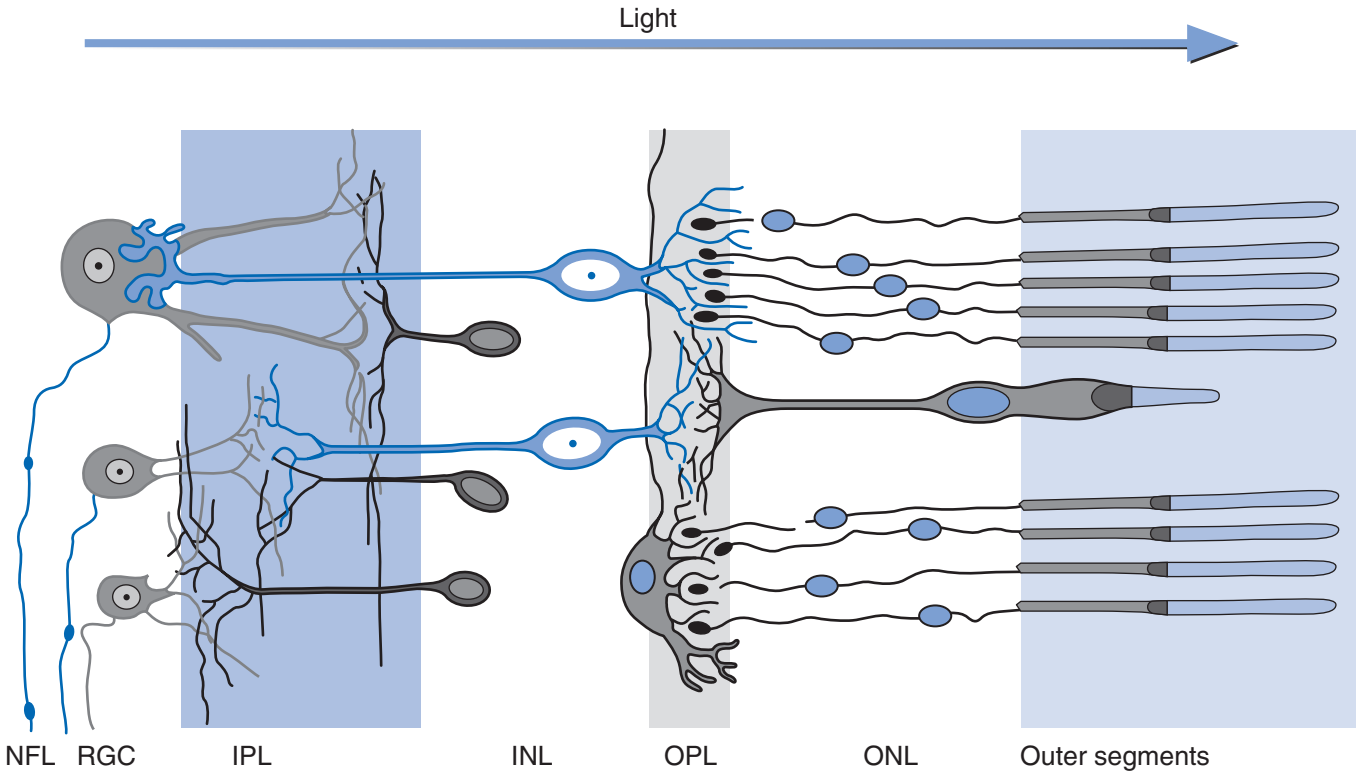

FIGURE 22-1 ■ Classic schematic representation of human retina by Ramón y Cajal. NFL, nerve fiber layer (axons of retinal ganglion cells that become optic nerve); RGC, retinal ganglion cells; IPL, inner plexiform layer (synapses between dendrites of retinal ganglion cells and both amacrine and bipolar cell axons); INL, inner nuclear layer (somata of amacrine, bipolar, and horizontal cells: note how horizontal cells connect across bipolar cell receptive fields); OPL, outer plexiform layer (synapses between bipolar cell dendrites, horizontal cells, and photoreceptor axons); ONL, outer nuclear layer (somata of photoreceptors); outer segments, light-responsive segment of photoreceptors. The shape of the outer segment is the basis of the name "rods" and "cones." Note that the receptive field (dendritic arbor) for the retinal ganglion cells is generally greater than the receptive field for bipolar cells, which in turn is greater than the receptive field for individual photoreceptors. (Instituto Cajal, Consejo Superior de Investigaciones Científicas, Madrid, circa 1900.)

with a steep decline in density out to about 3 degrees eccentricity, beyond which they are distributed evenly throughout the retina. Rods, by contrast, have a peak density around 6 to 8 degrees from the center of the retina, but also show declining density with greater eccentricity outside of this boundary.[5,6]

The middle layers of the retina consist of interneurons that perform the initial processing and organizing of visual information, including the distribution of visual data into parallel processing streams. Photoreceptors synapse with the cells of the inner nuclear layer (bipolar and horizontal cells) in the outer plexiform layer of the retina. Horizontal cells provide a wide neural network for inter-retinal feedback and processing of visual information (see Fig. 22-1). Their organization is likely the basis for the antagonistic, concentric, center-surround response characteristics of bipolar and retinal ganglion cells.[7] Signals arising from photons striking photoreceptors in the receptive field of a single bipolar cell or retinal ganglion cell converge on two separate pools, some of which enhance neuronal firing and others of which inhibit neuronal responses. These stripes of inhibitory and excitatory input are organized in a target-like pattern and their size is not symmetric across the retina. Neurons with larger receptive fields and thereby larger "centers" and "surrounds" can be found at greater eccentricity from central vision. The center-surround organization of retinal neurons likely plays an important part in the sensitivity of the retina to the pattern-reversal electrophysiologic techniques described later.[8] Furthermore, there are many subtypes of bipolar cells, each of which synapses with either groups of rods or cones exclusively. Bipolar cells can be characterized as ON or OFF based on how they respond to photoreceptor hyperpolarization and their response to the reduction of glutamate input that results (depolarizing in the case of ON-bipolar cells).[2,4]

Finally, retinal ganglion cells constitute the primary output neurons of the retina. They receive input from the bipolar cells (via amacrine cells) and synapse primarily in the thalamus, as well as in the tectum and hypothalamus. There are approximately 1.2 million retinal ganglion cells in the human retina, 70 percent of which are found in the central 30 degrees of the retina. It is important to note that retinal ganglion cells typically receive input from a large number of bipolar cells (which, in turn, have received input from a number of photoreceptors).[9,10] As a consequence, the receptive field of retinal ganglion cells frequently is substantially larger than the corresponding receptive field of the photoreceptors or bipolar cells that provide its input (see Fig. 22-1). In addition, ganglion (and bipolar cells) do not respond equally to a stimulus at all points in their receptive field because of their center-surround organization.[11]

There are four primary types of retinal ganglion cells. Magnocellular (also known as alpha or Y-type) retinal ganglion cells have a large receptive field and a large axonal diameter (and hence faster conduction of their action potential). They are concentrated outside of the macula and are tuned primarily for detection of contrast and motion. Parvocellular retinal ganglion cells, conversely, have a smaller receptive field, a smaller axonal diameter, and a relatively slower conduction time, and are concentrated in the macula. Many parvocellular retinal ganglion cells are tuned also for the discrimination of color. Koniocellular retinal ganglion cells are the smallest in size and least well characterized.[11,12] Finally, a class of intrinsically photosensitive retinal ganglion cells containing melanopsin are distributed evenly throughout the retina. These melanopsin-containing retinal ganglion cells likely underlie subjective luminance sensitivity, provide some—if not most—of the afferent input for the pupillary response, and help entrain the circadian rhythm.[13] In addition to participating in the continued segregation and analysis of visual data, retinal ganglion cells carry retinal information to the brain for further processing.

After traversing the inner surface of the retina, retinal ganglion cell axons coalesce into the optic nerve, which carries visual information through the orbit and into the brain. The axons are myelinated once they exit the eye posterior to the lamina cribrosa. Visual information from the two eyes arrives together at the optic chiasm before undergoing an anatomic separation that reflects their functional segregation by hemifield. These axons travel via the optic tract to synapse in the thalamus (sensory visual information), hypothalamus (circadian rhythm), and midbrain tectum (luminance sensitivity and pupillary response). Each of the first three subtypes of retinal ganglion cells synapse in different layers of the lateral geniculate nucleus (LGN) of the thalamus, where visual information is processed further before being taken to the visual cortex for additional processing and decoding.[14,15] Only a small number of melanopsin-containing retinal ganglion cells synapse in the intergeniculate leaflet of the LGN; the majority of them synapse in the midbrain and hypothalamus.[16]

The predominant subnucleus of the LGN (the dorsal LGN) receives retinal input segregated by eye and retinal ganglion cell subtype. Inputs from magnocellular retinal ganglion cells and parvocellular retinal ganglion cells are separated into distinct lamellae, while ON and OFF retinal ganglion cells are also separated in less distinct laminae within these lamellae. The interneurons of the

dorsal LGN are also involved in signal processing of visual information. In contrast to retinal ganglion cells, neurons in the LGN are selectively responsive to stimuli with a particular orientation or direction of motion. However, similar to retinal ganglion cells, relay neurons in the dorsal LGN display a center-surround response profile, which means that the LGN enhances the discriminating power of the retinal input and allows for small variations in the visual scene to be highlighted by the visual cortex.[17,18] Dorsal LGN cells send their axons primarily to the primary visual cortex (Brodmann area 17), which surrounds the calcarine fissure in the occipital cortex. This is also referred to as the striate cortex because of the unique Gennari stripe that can be identified on histologic cross-section and which itself provides horizontal interconnections between areas of the primary visual cortex.[15]

Outputs from the dorsal LGN primarily terminate in layer 4 of the striate cortex (one of the so-called granular cortical layers).[19] The striate cortex (also called V1 or primary visual cortex) dedicates 65 percent of its area to the central 15 degrees of the visual field (out of approximately 150 degrees and 120 degrees across the horizontal and vertical meridians, respectively). Primary visual cortex maintains the general retinotopic organization of visual information with visual information from central vision directly including the depths and banks of the calcarine fissure. Cortex dedicated to the peripheral field includes the surrounding cortical areas anteriorly to the parieto-occipital fissure and posteriorly along the surface of the occipital pole.[15,19] In total, striate cortex comprises approximately 4 percent of the whole human cortical surface, and more than half of this is dedicated to macular vision.[15,20] Visual information arising from the portion of the retina subserving central vision is therefore relatively "over-represented," which has important consequences for the visual evoked potential.

Visual information is deciphered and processed further in accessory visual cortex, which includes a wide swath of neighboring cortex in areas that have been distinguished based on functional determinants (V2–V6). These areas do not have the precise anatomic and histologic landmarks of the Gennari stripe and are characterized best via functional characterization in the primate, although lesional studies demonstrate their existence in humans. Outside V1, the stream of visual information changes significantly and no longer is characterized by the serial relay of visual information and stepwise modulation of visual data. Instead, extrastriate visual processing reflects a loose hierarchy with ample feedback and feedforward loops of interconnection. Although the retinotopic organization is maintained in some of these regions, others demonstrate neurons with extremely large receptive fields tuned for particular features of the visual scene, such as faces (including emotional state), animals, or rates of motion. Two classic pathways arising from the visual cortex include the so-called dorsal stream carrying visual information to the parietal lobes for spatial identification ("Where?") and the ventral stream carrying information to the temporal lobes for object identification ("What?"). In addition, much of the primary visual cortex is comprised of layers (besides layer 4C) that receive inhibitory and modulating inputs from extrastriate areas that help to focus visual processing power on features deemed salient.[14,15,19,20]

When considering the implications of the organizational structure of the visual system for clinical electrophysiology, it is important to remember that visual perception is not the consequence of parallel stimulation of afferent neurons, but that each layer of the visual system influences how much of the arriving visual input is transmitted to the next relay. Furthermore, our visual system is designed to discriminate variation in the visual scene, not strictly to quantify the intensity of visual stimuli. This objective is encoded in the architecture and physiology of the system for processing visual information. Understanding this purpose for our visual system is important in understanding how a particular visual stimulus will drive an electrophysiologic response and how injury might impact the response recorded.

CLINICAL ELECTROPHYSIOLOGY OF THE VISUAL SYSTEM

Visual evoked potentials (VEPs) are cortically generated electrical potentials recorded over the scalp in response to a visual stimulus. Electroretinograms (ERGs) are retinally generated potentials recorded from the cornea or periorbital skin. However, the size of the potentials elicited in both the VEP and ERG is small compared with ambient electrical signals that reflect the ongoing activity of brain, heart, and muscle. Therefore, signal-averaging techniques are employed to help resolve both the VEP and the ERG from background electrical potentials related to nonstimulus activity or ambient conditions ("noise"). The amount of signal averaging required is entirely dependent on the signal-to-noise ratio (SNR), but a reasonable rule of thumb for pattern-reversal full-field VEPs is that 50 to 250 averaged samples are required to achieve an adequate SNR.[21,22] Averaging paradigms are determined partially by the stimulus and specific technique being employed, as averaging is not always required for ERG acquired with a contact lens electrode

(and less averaging typically is required for the ERG than VEP).[23,24] In general, averaging is achieved by recording the responses to repeated stimulation, and clinical studies require several minutes of recording time. The noise reduction provided by averaging can be calculated by the inverse of the square root of the number of averages and there are therefore diminishing returns afforded by increased averaging.[22]

BASIC ASPECTS OF THE ERG

ERG can be recorded from the corneal surface by a contact lens embedded with a corneal ring electrode and a conjunctival reference, or from periorbital skin by small foil electrodes attached at the lateral canthi. Dermal electrodes significantly improve patient comfort and are recommended particularly for children and infants, but usually require additional signal averaging to optimize SNR.[23]

The standard ERG stimulus is a high-intensity light stimulus such as a strobe light or a Ganzfeld (German for "whole-field") stimulator (a hollow dome to which a patient affixes the gaze to obtain a brief but uniform stimulus to the entire retina). The stimulus used can be modulated to optimize assessment of rod or cone response. Cones have a shorter refractory period and therefore a higher-frequency stimulus can be used (30 Hz) to aid in the assessment of their function. (Rods provide minimal response at a frequency greater than 20 Hz.) It is particularly important to utilize methods to optimize cone responses, as there are over ten times more rods than cones, and the rod response on ERG is an order of magnitude greater than the cone response. Colored filters can also be employed to isolate rod and cone responses further. Rod responses have their peak spectral sensitivity in near blue light (510-nm wavelength) and cones as a group have their peak sensitivity in the yellow range (560 nm). Furthermore, red cones exhibit a response with little to no contamination from rods, given the limited overlap in peak sensitivities. In addition, ambient lighting conditions can be varied to help distinguish rod and cone responses. This is significant because the retinal diseases for which ERG is clinically useful have differential effects on rod and cone populations.[24,25]

The ERG typically is recorded with a patient's pupils dilated after the application of mydriatics. This helps to ensure uniform illumination of the retina and prevent pupillary responses from influencing the character of the ERG tracing. The ERG can also be recorded after light adaptation (photopic) to quench the effects of rods, or dark adaptation (scotopic) to enhance rod contribution. There is a fair amount of variability in the protocols employed but, as an example, dark adaptation usually requires that the patient sit in a darkened room for 30 minutes prior to recording.[24,25]

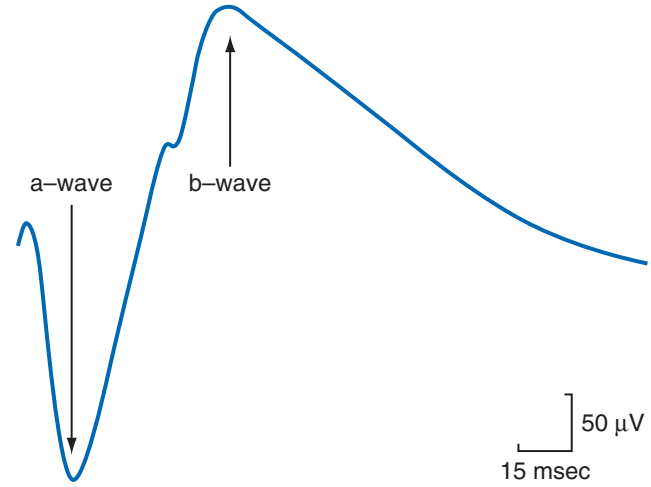

FIGURE 22-2 ■ Schematic representation of dark-adapted electroretinogram at 3.0 candela*seconds/meter^2 (combined cone-rod response). Note the smaller negative a-wave followed by the larger positive-amplitude b-wave.

Although there are differing conventions among ophthalmologists and neurologists, ERG waveforms frequently are described as negative when the tracing dips below the baseline and positive when they cross above it (Fig. 22-2). ERG typically is analyzed by evaluating the first negative deflection (a-wave) and the subsequent positive deflection (b-wave). In photopic recordings, especially with a bright flash as stimulus, a high-amplitude positive wave may precede the a-wave. The a-wave reflects the depolarization of photoreceptors en masse (rods or cones predominantly depending on stimulus parameters and preconditioning state), and the b-wave reflects the activation of the retinal interneurons from the inner nuclear layer.[24,25] The times to peak of the a- and b-waves are referred to as "implicit time" rather than "latency." In normal individuals the a-wave is observed at around 15 msec and the b-wave at around 30 to 35 msec in photopic ERGs. In photopic recordings the implicit times are usually shorter (faster) but the amplitude of the response is usually lower than in dark-adapted ERGs. Additional c- and d-waves have been described and attributed to retinal pigment epithelium and OFF bipolar cells, respectively,[26,27] but these are not assessed routinely in the clinic.

Pattern-Reversal ERGs

The ERG can also be recorded with an alternating checkerboard or other pattern-reversal stimulus. The pattern-reversal ERG (PERG) is described by the same

conventions that govern flash ERG. (Positive deflections are recorded above the baseline, and negative below.) It is characterized by a negative wave at approximately 50 msec (N50) and a positive deflection at around 95 msec (P95). The P95 (also referred to as the PERG b-wave) is thought to reflect activation of the retinal ganglion cells, as some of these cells are tuned to sense spatial contrast, and the implicit time of the PERG implicates neuronal populations downstream from the photoreceptors. In an extremely large retrospective case series, it was reported that subjects with abnormal VEPs and known disease of the anterior visual pathway frequently lost the N95 component of their PERG but almost always showed complete preservation of the P50. However, PERG amplitudes are small and sometimes unreliable and, as a consequence, PERG has found application primarily as a research tool.[24,25,28,29]

FLASH AND PATTERN-REVERSAL VEPs

Prior to 1970, VEPs were only elicited using a diffuse stroboscopic or Ganzfeld flash as the stimulus. Additional stimulus approaches were developed subsequently, including checkerboard pattern-reversal and sinusoidal grating patterns. The flash VEP is much less sensitive than pattern-reversal VEPs for detecting abnormalities such as optic neuritis.[28,30] In addition, flash VEP responses have higher interindividual variation and are more dependent on the patient's state of arousal than pattern-reversal VEP, limiting their routine clinical utility.[30] Their primary clinical use is restricted to patients who are unable to fixate or who are suspected of feigning complete blindness.

Transient and Steady-State VEPs

After stimulation, a transient, cortically generated response is tied to the relevant stimulus (the "transient VEP") and consists of a series of potentials that are alternately positive and negative in polarity. They are labeled on the basis of their polarity and latency. With repeated high-frequency (over 4-Hz) stimulation, however, cortical responses remain constant—or nearly so—with respect to amplitude and phase ("steady-state VEP"). Regan likened transient evoked potentials to providing a "kick" and measuring the response, whereas steady-state responses are similar to "shaking a system gently" and studying the harmonic oscillation that develops.[31] There is some evidence that steady-state and transient VEPs provide complementary data.[30,32–34] The frequency of stimulation in the steady-state VEP can be varied to distinguish responses from the magnocellular (40 to 50 Hz) and parvocellular systems (15 to 20 Hz) in the macaque[31] but this has not been demonstrated to have clinical utility in humans. Interestingly, the observed frequency at which patients with MS appear to have the most profound dysfunction with steady-state VEPs is similar to the frequency at which critical flicker fusion deficits are observed.[30] However, the steady-state VEP is used primarily in evaluating subjects who cannot communicate or otherwise participate in examinations for the assessment of acuity (infants and small children); other applications are restricted largely to the research laboratory at this time.

Interpretation of the Transient Pattern-Reversal VEP

Peak response for the transient full-field pattern-reversal VEP occurs approximately 50 to 250 msec after the stimulus. By convention in clinical neurophysiology (as opposed to ophthalmology) laboratories, the recording arrangements for VEPs are such that electrical potentials that lead to an upward deflection are termed negative, while those with a downward slope are termed positive. There are two primary features to each deflection that can be described: (1) the time elapsed since the stimulus (latency) and (2) the magnitude of deflection from the baseline (amplitude). Normal ranges used for references are dependent on the size, luminance, contrast, and temporal characteristics of the stimulus (see next section). Varying other features of the stimulus, such as the color or shape, have less well-characterized influences on the response but also result in differences.[35–38]

By convention, most recordings are evaluated using the "Queen Square" montage, which includes a midoccipital electrode placed 5 cm above the inion, referenced to a midfrontal electrode placed 12 cm above the nasion (MO–MF). To complete the montage, leads usually are also placed 5 cm to the left (LO) and right (RO) of the MO lead. This placement is obviously very similar to the Fz, Oz, O1, and O2 lead placement from the International 10–20 system and this array can be used as an alternative.

In most individuals, the first response of the full-field pattern-reversal VEP recorded midoccipitally is a negative deflection termed the N75. However, given lack of consistency of both the presence and latency of the N75, by convention full-field VEPs usually are assessed by evaluating the first major positive deflection that occurs at around 100 msec and is therefore designated the P100 component (Fig. 22-3). This positive deflection does not necessarily have the largest amplitude, nor is

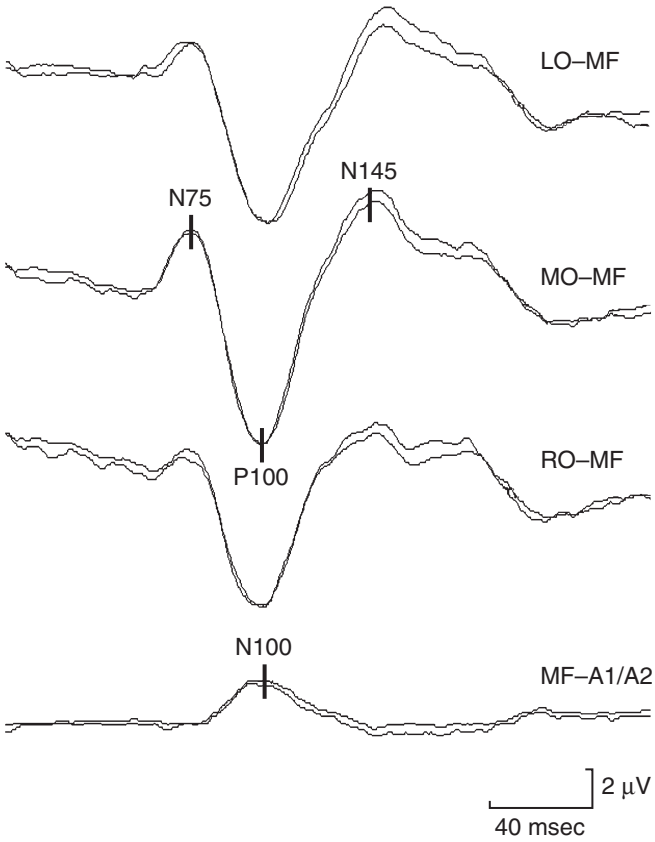

FIGURE 22-3 ■ Full-field pattern-reversal checkerboard visual evoked potential from the right eye of a normal healthy 22-year-old woman (check size 32 minutes of arc). The P100 at the MO–MF channel has a latency of 99 msec.

it always the earliest positive response that is seen, but it is the most reproducible. Following the P100, the next negative deflection is referred to as the N145 (see Fig. 22-3). In patients with hemianopia, stimulation of the affected hemifield leads to absent responses or marked variation in the normal amplitude distribution in the contralateral hemifield (LO–MF or RO–MF), but a good response is seen ipsilateral to the "blind" hemifield (Fig. 22-4, *A* and *B*).[38] However, this method is unreliable compared to dipole source localization, and the ease of obtaining standard automated perimetry has relegated this finding to one of academic interest.

The exact cortical source of the full-field VEP has not been determined unequivocally. It has been suggested that the N75 reflects input from the dorsal LGN to the striate cortex (via the optic radiations), whereas the P100 may reflect a secondary inhibitory response at V1 or excitatory outflow to the accessory visual cortical areas (V2 to V5).[28,38–41] There have been several reports of VEPs persisting even in cases of bilateral destruction of the primary visual cortex, including in 4 of 19 patients with complete cortical blindness.[42]

Latency

Latency of the VEP generally is defined as the time from the stimulus to a prespecified feature of the record, typically the peak of the component of interest. Approaches include measurement of latency to the point of the maximal positive (or negative) deflection but this has the drawback that flat or noisy components may be challenging to characterize. An alternative approach is to measure the latency to peak by interpolation—in the case of the P100, a straight line is drawn from the downward slope of the N75 and the upward slope of the N145, and the P100 latency is measured at the point of their intersection. The delineation of abnormal latency for the P100 on full-field VEP is laboratory specific. It is of critical importance that the same methods used for establishment of laboratory references are employed at the time of clinical analysis. Any deviation from a standard approach should be explained clearly in a laboratory report.

Latency delay of the full-field VEP is often interpreted as evidence of demyelinating injury to the visual pathway (Fig. 22-5). Abnormality of latency is defined routinely as a value exceeding the mean by more than 2.5 standard deviations.[28] Assuming a gaussian distribution for the reference population, this means that 99.4 percent of normal individuals should fall within this reference range. Given this stringent requirement for abnormality, it is important to note that some individuals with injury to the visual pathway still may be classified as normal. As a consequence, most investigators also evaluate interocular latency differences to improve sensitivity. The optimal cut-off for interocular latency should be defined within an individual clinical laboratory but standard values range from 6 to 10 msec.[43,44] Consideration must be given to anterior segment (cataract or other ocular media opacities) or outer retinal diseases (such as diabetic eye disease or myopic degeneration) before changes are attributed to optic nerve disease. This is an additional strength to the combined approach, described later.

Amplitude

P100 amplitude is highly variable and, as a consequence, delineation of amplitude abnormality in the full-field VEP is not based on a simple numerical value. There is a high degree of interindividual variability in amplitude on pattern-reversal VEPs in healthy subjects, and the range of observed values is not subject to a gaussian distribution, making it difficult to establish normal values. Furthermore, there may be interocular differences in amplitude of up to 200 percent and repeated VEPs in the same individual may show variability in

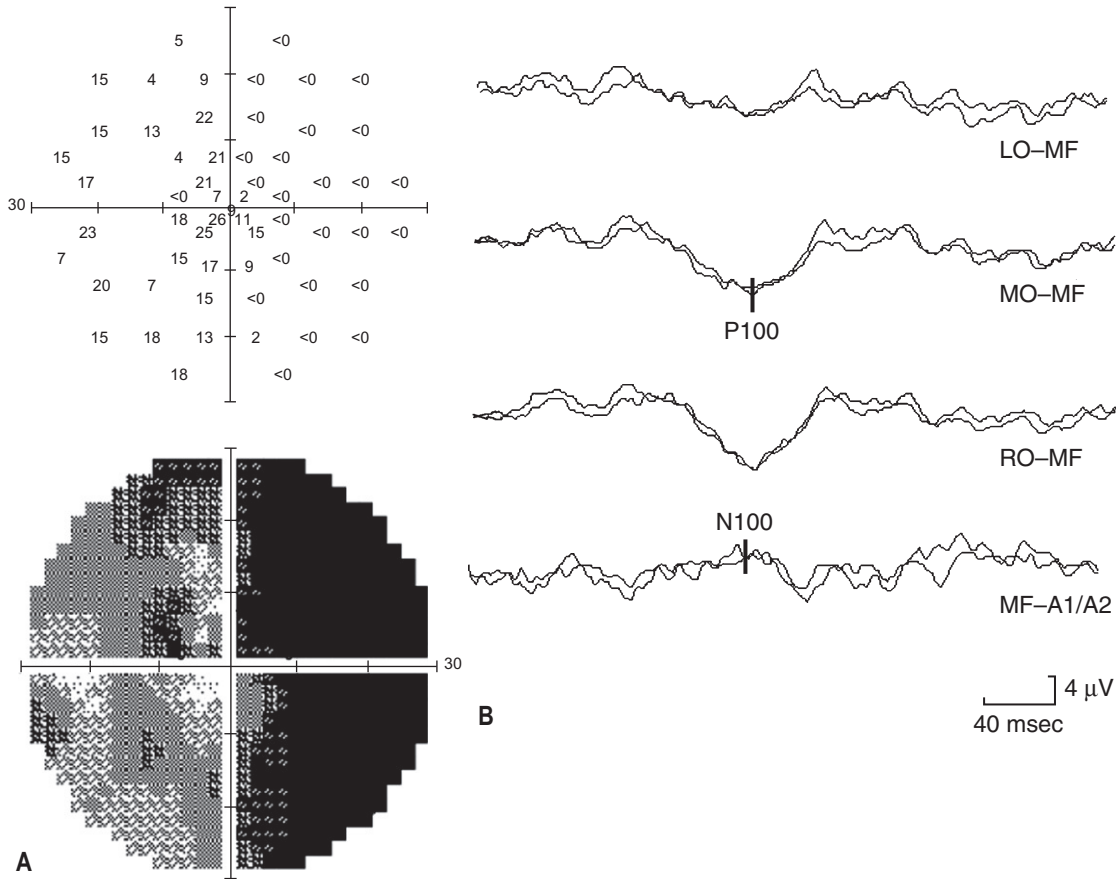

FIGURE 22-4 ■ **A**, Static perimetry (30-2 equivalent from Haag Streit Octopus-900) from a 55-year-old man with a history of demyelinating injury to his left optic radiation (right hemifield defect in addition to reduced thresholds throughout the field). **B**, Full-field visual evoked potential from the same patient showing amplitude loss contralateral to the field loss (LO–MF). Latency is also delayed in the MO–MF recording to 145 msec.

amplitude of a similar extent as well, depending on the subject's state of arousal and other patient- and condition-specific factors.[45,46] Accordingly, caution should be exercised in characterizing a recording as abnormal based on amplitude criteria alone.[47]

Technical Issues for Recording VEPs

As with all clinical electrophysiologic recordings, careful electrode placement with attention to impedance reduction is critical to generating reliable and useful recordings. Because of responses that occur around 60 Hz, bandpass filters at this frequency are not recommended, so ambient electrical noise must be kept to a minimum.[21,28]

Luminance and Contrast

Luminance is defined as the intensity of light from the visible spectrum per unit area traveling in a given direction (usually expressed in candelas/meter^2 [cd/m^2]). Ambient lighting conditions (and preconditioning) can have a significant effect on recordings, and maintenance of luminance conditions is critical for undertaking a reliable study. The luminance of both the stimulus and the ambient conditions should be monitored. The necessary conditions for appropriate ERG recordings are set by the type of study being performed (described earlier). VEPs preferably are recorded under ambient photopic conditions in a standard, normally illuminated room. Patients and normal subjects (laboratory references) should be recorded under the same lighting conditions. The mean luminance at the center of the field is recommended to be at least 50 cd/m^2 but optimally should approximate background luminance. The luminance of the display is also an important factor influencing the VEP, and regular calibration of the system or the use of self-calibrating units is recommended.[28]

Contrast is the luminance difference between two adjacent elements in the visual scene and is defined by the following equation:

$$C = L_{max} - L_{min}/L_{max} + L_{min}$$

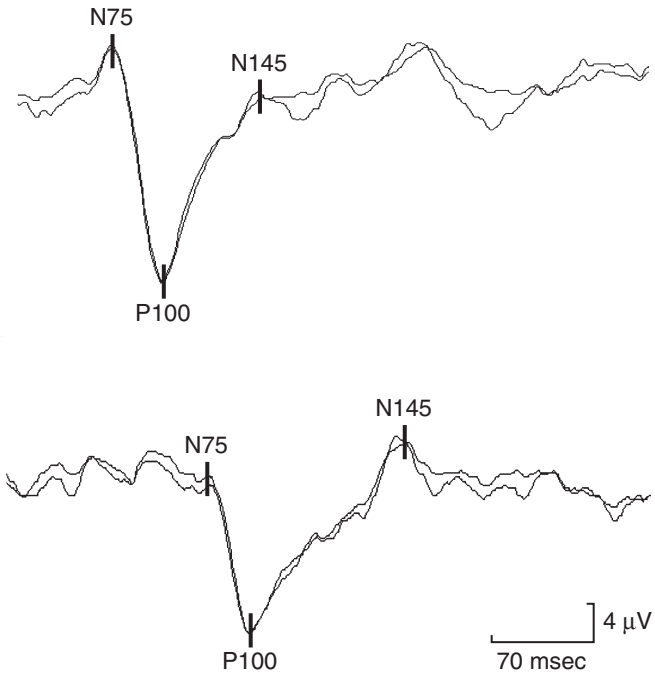

FIGURE 22-5 ■ Abnormal full-field visual evoked potential with latency delay in the right eye of a 25-year-old woman with a history of optic neuritis 1 year earlier. The P100 latency was 104 msec with left eye stimulation, and 165 msec with right eye stimulation. Recording is between midoccipital and midfrontal electrodes.

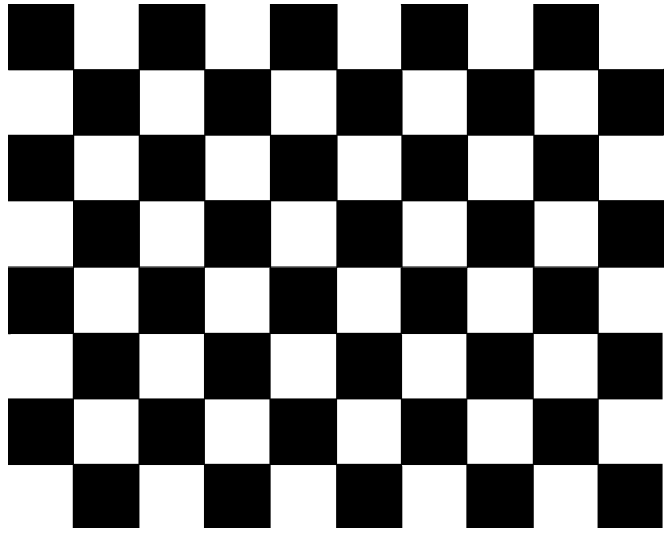

FIGURE 22-6 ■ Full-field visual evoked potential checkerboard stimulus. Each square alternates in tandem, with half the squares black and half white at any one time point. To maintain fixed luminance across the stimulus, either an even number or large number of odd squares is required.

where C indicates contrast level, L_{max} is the brighter luminance element, and L_{min} is the darker luminance element. Contrast is particularly important when considering the electrophysiologic response generated by a pattern-reversal stimulus. Given the sensitivity of the human visual system for detecting differences, pattern-reversal VEP and ERG responses are dependent on contrast. Low-contrast responses have smaller amplitudes and broader peaks than those elicited using patterns with high contrast. Therefore, maintenance of contrast levels in the patterned stimulus used for eliciting VEPs and ERGs is important for ensuring that findings can be compared reliably to laboratory reference ranges, especially at lower contrast levels. In particular, for pattern-reversal VEP, amplitudes decrease with contrast levels below 40 percent.[37]

Stimulus Parameters

Two types of visual stimulus are used commonly in visual electrophysiology: the unpatterned flash or a strongly patterned stimulus that undergoes reversals of its basic elements (typically black and white). Flash stimuli usually are described in terms of stimulus intensity (luminance) and the frequency at which the stimulus repeats. In addition, for ERG recordings, the preconditioning environment is important (as described earlier).

There are two predominant patterns that can be employed: alternating bars or checkerboard (Fig. 22-6). Alternating bars (also referred to as gratings) can have sharp boundaries between the stimulus elements (square wave) or the pattern can blend between regions of high and low luminance (sinusoidal pattern). The shape of pattern elements and their size can impact the response waveform significantly and therefore need to be maintained carefully.[48–50] The size of the stimulus at the retina will depend on its size on the monitor and the distance of the subject from the screen. The total stimulus size will determine the area of the visual field subject to stimulation, and check size will impact the neuronal cell population which is generating the response (especially among ganglion and bipolar cells). Based on the nonuniformity in the size of the receptive fields for ganglion cells across the retina, larger check sizes will generate more of their response from the peripheral retina, and vice versa.

Check sizes that are small run the risk of being confounded by refractive errors,[51] whereas large check sizes will only exhibit alternating luminance in a small number of the total ganglion cells in the field (those with a large enough receptive field or those whose center-surround edge lies at the boundary of the check). Recommendations by the International Federation of Clinical Neurophysiology (IFCN) therefore suggest the use of checks that subtend 24 to 32 minutes

of visual arc. In spite of this, some research suggests that varying check size can enhance the diagnostic yield of VEP.[52]

Regardless of the stimulus parameter employed, maintaining fixed luminance throughout the pattern-reversal cycle is important. Therefore, the mean field luminance should be identified for the patterns that are utilized in the clinical laboratory. Most clinics utilize predesigned all-in-one visual electrophysiology packages, many of which can be outfitted as an extension of a unit devised for other purposes. The use of these systems has the advantage that certain features of standardization, such as the stimulus display and amplifier settings, are preset to meet recommended guidelines for recordings. However, given the potential impact of other laboratory-specific factors, such as background lighting conditions, ambient electrical noise, and distance between the subject and the stimulus display, care still must be taken to ensure reproducible and reliable recordings.

Most of these systems adhere to international guidelines, simplifying the process of standardization and quality assurance in the clinic.[28] However, such guidelines still recommend that every laboratory establish its own specific reference values. Given the dependence of reliable and informative VEPs on these parameters, the IFCN has established a number of recommendations for the practicing clinical electrophysiologist to optimize standardization. These include a description of the stimulus parameter employed, mean luminance of the field, size of the field, and rate of presentation. Additional patient demographic characteristics (age and sex) and ophthalmologic assessments to be documented include: (1) the patient's visual acuity, (2) the patient's ability to fixate, (3) the patient's pupillary size at the time of recording, and (4) a description of known visual field defects or known optical aberrations (such as cataracts or other impaired ocular media) that could influence the patient's ability to visualize the stimulus fully.[28] Adherence to these recommendations helps to ensure that results are interpreted reliably.

Stimulus Options

It has been suggested that, rather than requiring pattern reversal of the stimulus at each sector, displaying the pattern when shown from a neutral gray background (called pattern-pulse) can improve the accuracy of the multifocal technique (discussed later) by reducing false-positive results. In addition, this technique has been employed with larger sectors for multifocal recordings—nicknamed sparse multifocal VEP—allowing for more rapid recording times.[53] Adjustments in contrast level and stimulus color have also been suggested to improve VEP sensitivity, but have yet to be developed for widespread use.[54]

Time Base of Recordings

The relevant epoch (time base) and required filters for recording are determined by the nature of the stimulus employed. For standard full-field VEPs, recording should be made for at least 250 msec after each stimulus. Given that multifocal VEPs are performed with continuous recording, the epoch can be modified during analysis. However, a standard time window of 200 to 250 msec usually is employed and will avoid second-order responses.

COMPARISON OF FULL-FIELD AND MULTIFOCAL TRANSIENT VEPs

Traditional VEPs are recorded in response to a stimulus that varies consistently across a large portion of the visual field (see Fig. 22-6). In contrast, the multifocal VEP technique divides the visual field into a fixed number of sectors, each of which follows its own sequence of stimulus changes. Each sector can have one of two states, which—as with the full-field VEP—are inverted checkerboards (Fig. 22-7). Rather than recording each sector seque-ntially, which would be prohibitively time consuming, in the multifocal approach a stimulation method is employed that allows for simultaneous recording and rapid analysis of the summed response to derive the contribution from each individual sector. In order to achieve this, there are two basic requirements: (1) the stimulation sequence for

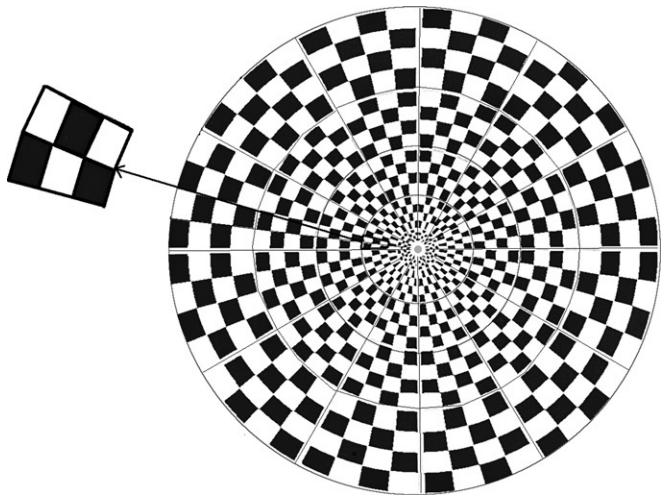

FIGURE 22-7 ■ The multifocal visual evoked potential stimulus, with 120 sectors. Inset of a single sector from the central field second ring (arrow).

each sector must be independent of the sequence for any other sector; and (2) the stimulus state of each sector during any given epoch is independent of its state during any other epoch. Each sector follows the same underlying sequence, but starts and finishes at a different point in the series.[55,56]

The multifocal VEP is recorded using the same electrodes, filters, and amplifier settings as the conventional full-field VEP. The waveforms are generally analogous to those seen in full-field VEP, although there is usually a phase reversal at the horizontal meridian (Fig. 22-8) caused by the involution of the calcarine fissure. However, the standard occipitofrontal VEP montage relatively oversamples the inferior visual field (by use of the midfrontal reference) and therefore sampling of the entire field is optimized by the use of occipital recording electrodes and an occipital reference. Two different montages have been employed to perform multifocal VEP recordings. Standard recording arrangements include four leads: one at the inion, another 2 cm above the inion, and the last two 3 cm to the right and left of the line bisecting these first two electrodes.[57,58] An alternative montage with electrodes placed 2 cm above and 2 cm below the inion ("bipolar occipital-straddle placement") likely results in improved SNR in potentials from the superior visual field[59,60] but may lead to greater contamination with muscle artifact from the neck and shoulders.

Initially, it was hoped that the multifocal VEP could provide an objective means of performing the standard visual field with less participation from subjects. However, intersubject variability caused by differences in the position of the calcarine fissure with respect to external landmarks and variability in the pattern of sulcal arrangement and cortical folding have made it difficult to define absolute normal standard values. To overcome the issues generated by intersubject variability in the multifocal VEP, it has become conventional to compare interocular differences in the multifocal VEP to assess for lateralizing deficits (Fig. 22-9).[61,62] This allows for the detection of deficits that would be missed on standard VEPs[62] or identification of normal areas in a subject who otherwise would be thought to be abnormal across the field (Fig. 22-10).

The macula constitutes approximately 1 percent of the surface area of the retina (10 to 15 mm^2 out of 1,000 mm^2). However, at the cortical level, nearly two-thirds of striate cortex subserves macular vision. Given this tremendous relative cortical "over-representation" of the macula, multifocal VEP sectors are scaled for cortical magnification with smaller check sizes centrally and larger ones peripherally.[63] This scaling of the sectors also necessitates that the multifocal VEP stimulus be concentric rings rather than a rectangular display (see Fig. 22-7). The sensitivity of pattern-reversal VEPs suffers from the limitations imposed by macular over-representation

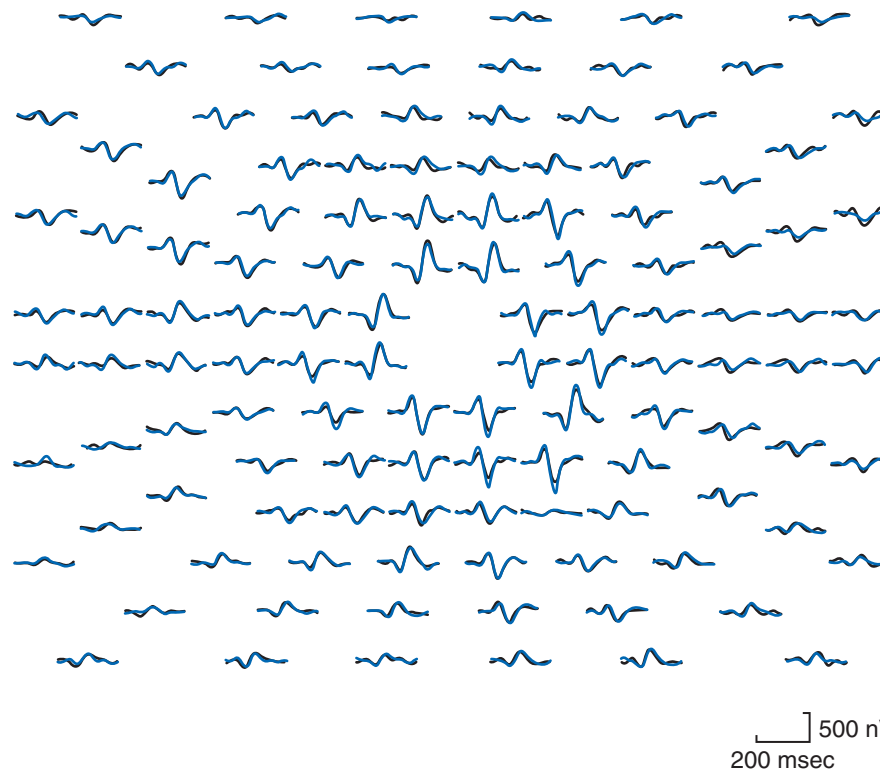

FIGURE 22-8 ■ Normal multifocal visual evoked potential from a 35-year-old healthy man. Right eye represented with black tracings and left eye represented with blue tracings. Notice the symmetry of the waveforms between the two eyes. Also note the phase reversal across the horizontal meridian caused by the calcarine fissure.

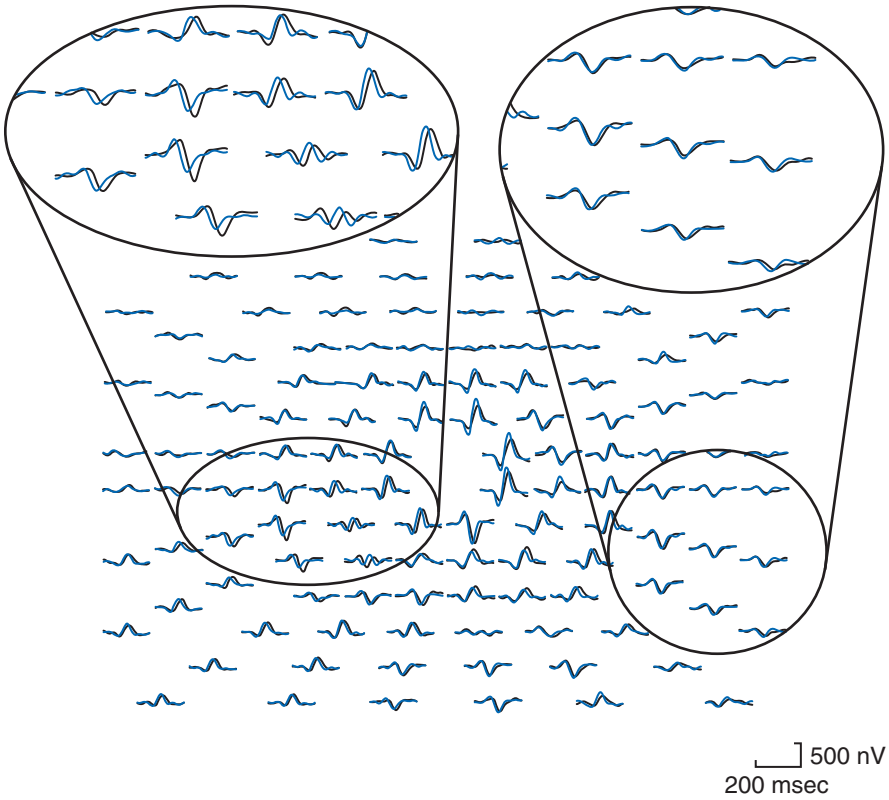

FIGURE 22-9 ■ Abnormal multifocal visual evoked potential with focal areas of latency delay seen in the nasal (left) hemifield of the right eye relative to the left eye (central three rings; left inset) and matched latency (right inset). Right eye represented with black tracings and left eye represented with blue tracings.

(see Fig. 22-10). As indicated by the optic neuritis treatment trial, patients with optic neuritis can suffer injury to any of the topographic areas of the visual field, and by extension, to any of the fiber tracts in the anterior visual pathway.[64] Given the small central checks in multifocal VEP, it is particularly sensitive to refractive error and other optical aberrations.[65] As a result, clinicians must either correct for these deficits at the time of recording or consider them when analyzing a study.

In addition, while concentrating on a stimulus may or may not be important for the reliability of recordings, steady fixation is essential, as derivations of the local response are dependent on the maintained location of each sector in visual space. Therefore, it is unreliable to record from patients with fixation deficits such as primary position nystagmus. Fixation is monitored routinely during multifocal VEP recordings by a pupil camera mounted on the stimulator.

Using source localization procedures and a broader array of electrodes than is used in routine clinical practice, it has been argued the multifocal VEP is derived primarily from primary visual cortex, as compared to the full-field pattern-reversal VEP which has significant contributions from extrastriate cortex.[66] This argument may be undercut by the observation that summed multifocal VEP latencies across the field are longer when compared to full-field VEP latencies across the field.[67] This difference in latency may be explained in part by the increased representation of the peripheral field—which may have slightly longer latencies—in the multifocal VEP. Regardless, given the differences in stimulus, electrode placement, and cortical source localizations, the full-field VEP cannot be considered as the simple summation of multifocal VEPs across the field.[55,57]

The multifocal VEP can be used to monitor for progression within an individual patient. In both normal subjects and patients, the multifocal VEP demonstrates equivalent or superior test repeatability when compared to standard automated perimetry.[68,69] The relatively restricted dynamic range in the superior field with some electrode montages may limit detection of an abnormality in this area.

MULTIFOCAL ERG

In a manner akin to that described above, methodologies can be modified to record ERG responses from local retina areas, as well as the summed response. Using the same pseudorandom sequence, local flashes (rather than small alternating checkerboards) can be used. Unlike the required modification to the recording montage for multifocal VEPs, the same electrode placement is used for

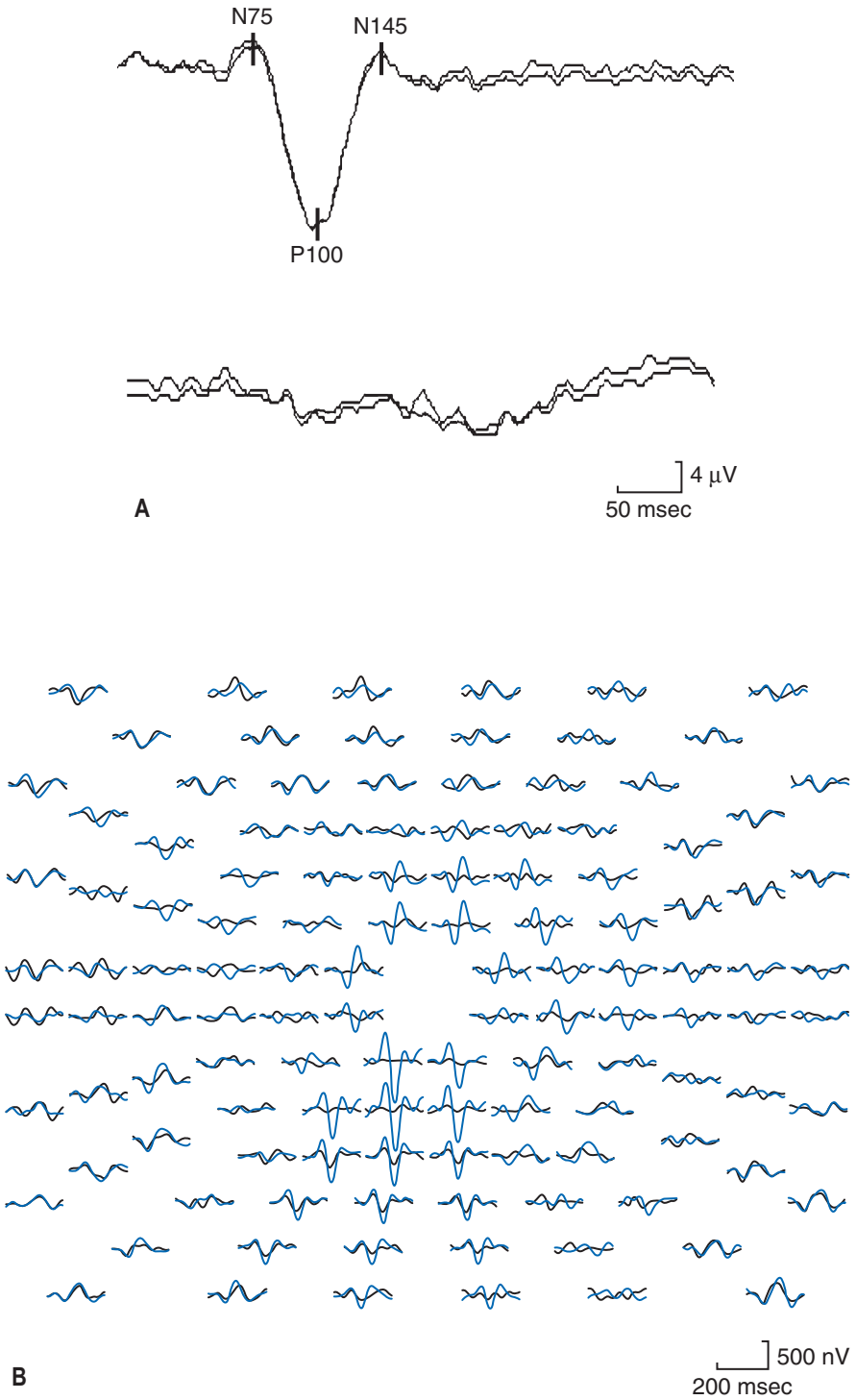

FIGURE 22-10 ■ **A**, Full-field visual evoked potential (VEP) of a 23-year-old woman with a history of optic neuritis, showing normal but delayed (131 msec) responses to stimulation of the left eye (top) and poorly formed, if any, response from the right eye (bottom). Responses are recorded between the midoccipital and midfrontal electrodes to 32-min checks. **B**, Multifocal VEP of the same subject, showing amplitude decrement centrally to right eye stimulation (black tracings) with preserved symmetric responses peripherally. This also demonstrates the macular over-representation of the full-field VEP, as the response is dominated by the central sectors.

multifocal ERG and standard flash ERG. Multifocal ERG amplitudes can be compared across the field, similar to a visual field (Fig. 22-11). The multifocal ERG has less interindividual variability than multifocal VEPs. It is important to note that a dark-adapted state cannot be maintained with the multifocal ERG and therefore this test primarily assesses cone response.[25] In contrast to the standard generation of a multifocal VEP, which is derived from the first slice of the second-order kernel, multifocal ERG is derived from the first-order kernel. This also makes understanding its derivation more straightforward than multifocal VEP.[61]

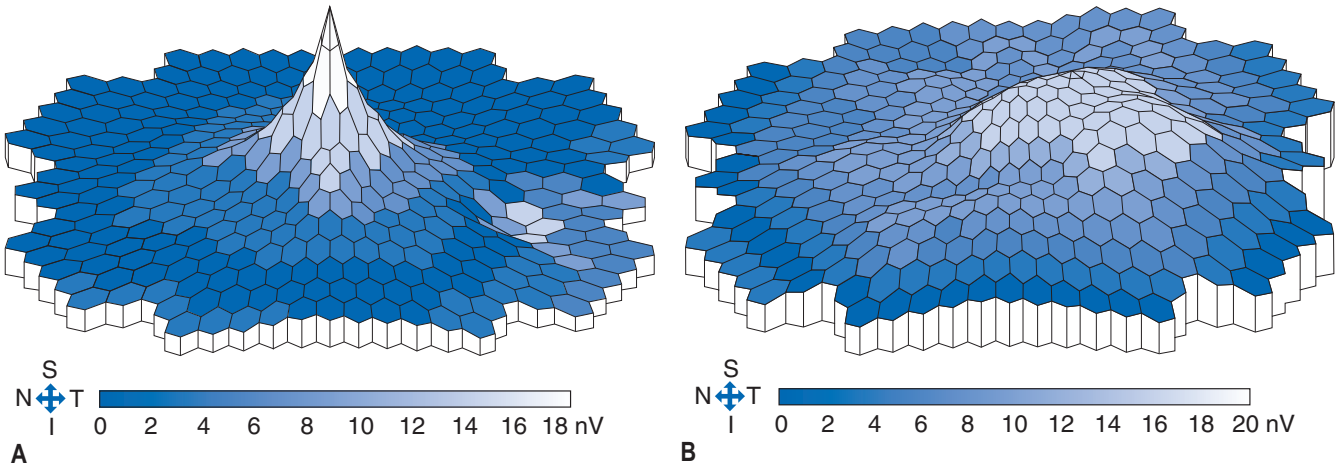

FIGURE 22-11 ■ **A**, Topographic representation of amplitudes from multifocal electroretinography (ERG) in a normal healthy 33-year-old man. **B**, Topographic representation of amplitudes from multifocal ERG in a 38-year-old woman with cone-predominant retinal dystrophy. Note the loss of the sharp central peak and relatively preserved amplitudes in the periphery.

PATIENT FACTORS INFLUENCING RECORDINGS

Head Size and Gender

A number of studies indicate that average P100 latencies are shorter (and amplitudes greater) for women than men. As early as the 1970s, it was suggested that brain volume and pathway length may explain these differences[21,70] However, gender differences may be secondary to differences in head size rather than reflecting a sex-specific effect.[71] Our own experience suggests that this relationship is observed in subjects with multiple sclerosis but no optic neuritis (Fig. 22-12). In spite of this, most laboratories have not used head size to correct for normal referenced latency values.

Age

VEP amplitudes peak in late adolescence and exhibit a modest decline in early adulthood. However, after that point, consistent amplitude is maintained over many years. Latency increases with age, especially for small check sizes and lower total luminance settings. This has been attributed to age-related declines in average pupil size,[72] but contradictory data suggest that other factors

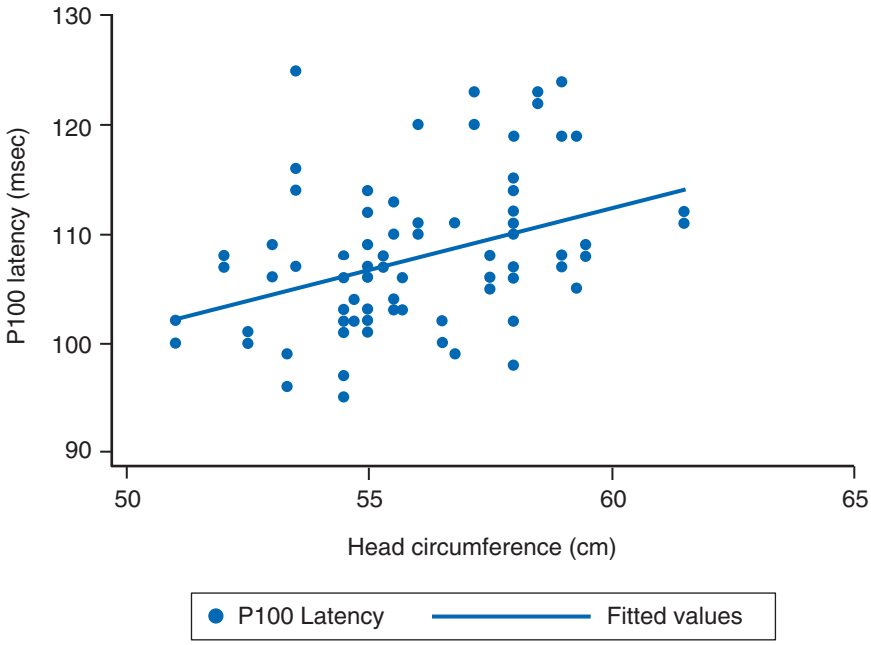

FIGURE 22-12 ■ Data correlating full-field P100 latency to head size in 40 subjects (77 eyes) with multiple sclerosis and no optic neuritis. R = approximately 0.4. (© Ari Green, 2011.)

may underlie this change.[73,74] Our own data suggest that, irrespective of pupil size, multifocal VEP latency increases with age, particularly in men. SNR does not vary with age from the third to tenth decade of life.[75]

Pupil Size

It has been theorized that, because of changes in levels of retinal illumination, large pupils can shorten VEP latency. Pupillary dilatation does not lead to a significant latency shortening of the full-field flash VEP,[76] but it does affect latency of the full-field pattern-reversal VEP.[72] Pupil size has also been shown to affect latency but not amplitude of multifocal VEPs,[77] but both amplitude and latency of the multifocal ERG.[78] It is standard practice for pattern-reversal VEPs to be recorded with normal pupils, whereas ERGs are recorded with pupils pharmacologically dilated.

Temperature

Body temperature has been shown not to influence full-field VEP latencies, except in patients with demyelinating injury in whom the occurrence of temperature-dependent clinical symptoms is well known.[21]

Effects of Anterior Segment Disease

Steady-state VEPs can be used to predict postoperative visual function in patients with a dense cataract.[79] This suggests that the impact of cataract on VEP characteristics is unlikely to be profound. However, it is well known that unilateral central cataracts can lead to interocular latency differences in full-field transient VEPs, and opacity of the ocular media is known to impact both ERG and VEP outcomes.[80] Similar findings have been reported with multifocal VEPs and multifocal ERGs.[63] As a consequence, awareness of large uncorrected refractive errors or anterior segment disease—especially when unilateral—is required when analyzing study results.

CLINICAL APPLICATIONS OF TRANSIENT FULL-FIELD AND MULTIFOCAL VEPs

Multiple Sclerosis and Optic Neuritis

Given the reduced requirement for patient participation in VEP recordings, VEPs sometimes are employed to help in discriminating organic from psychosomatic visual complaints. However, subtle visual impairment may not be detectable with standard VEPs. In addition, there is controversy over whether patients can influence their VEP results by daydreaming or meditation.[81] Technologists need to monitor patient attention and visual fixation, as failure to maintain gaze can influence the VEP findings, especially with multifocal recordings.

VEPs can be used to confirm a diagnosis of acute optic neuritis. The amplitude of the full-field pattern-reversal VEP usually is attenuated and, if present, the response is usually delayed significantly. If vision is worse than 20/80, the waveform is frequently absent. In cases of optic neuritis in which the diagnosis is in question, VEPs can be invaluable (Fig. 22-13). However, the VEP results need to be evaluated in the context of ophthalmologic assessment, as latency delay can be caused by outer retinal or anterior segment disease. With visual recovery, the amplitude returns but prolonged latency with a mean delay of around 35 msec is seen in about 90 percent of patients.[30]

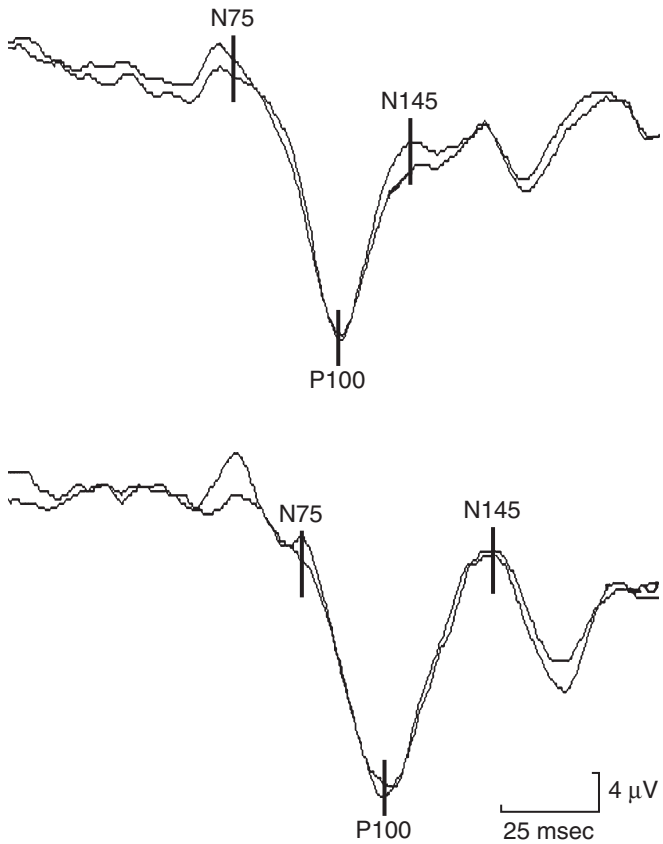

FIGURE 22-13 ■ Full-field visual evoked potential recorded between the midoccipital and midfrontal regions in a 49-year-old woman with complaints of mild eye pain who had slight disc swelling on examination. There was no prior history of optic neuritis. The P100 latency was 99 msec to left eye stimulation (top) and 112 msec to right eye stimulation (bottom). Interocular difference of more than 8 msec is considered evidence of right eye abnormality in our laboratory.

In the period following an acute optic neuritis, VEP latency delays become progressively less pronounced in the involved eye over the following 1 to 2 years. This relative improvement in latency delay is most dramatic in the first 3 to 6 months and is believed to be secondary to remyelination or ion channel reorganization on the denuded axon. Interestingly, in the unaffected fellow eyes of subjects, increasing latency times are observed, especially in individuals who go on to develop MS.[30] Persistent latency delay or amplitude decrement on multifocal VEP after an episode of optic neuritis has been associated with a greater risk of progression to MS.[82,83]

A general review of the literature demonstrates that nearly all subjects with clinically confirmed MS and a history of optic neuritis will have latency delay on pattern-reversal VEP (either in absolute or interocular terms). Older studies reported latency delay among subjects with "clinically definite" MS and no optic neuritis at high rates as well (60 to 95 percent), although, among subjects undergoing diagnostic work-up for MS, these rates were lower (35 to 80 percent, varying with the probability that MS was indeed the diagnosis) and dependent on stimulus method employed (including check size). The author's own experience suggests that rates of latency delay may be even lower when using the VEP to identify patients at the earliest stages of disease.

In older patients, in whom the diagnosis of nonarteritic ischemic optic neuropathy is under consideration, amplitude recovery is less common and latency frequently is delayed by less than 10 msec and almost never by more than 40 msec.[84–88] Therefore, in unusual cases, the VEP can help play a role in distinguishing ischemic from inflammatory demyelinating optic neuropathies. In patients with significant and persistent degradation in visual acuity after an ischemic optic neuropathy (worse than 20/80), the full-field VEP generally is lost completely and not simply delayed.[85,86,88]

Using stimulus patterns of various sizes, it has been reported that a small number of subjects have latency delay in their wider field (approximately 20 degrees from point of fixation), while "central field" full-field VEPs with smaller stimulus and check sizes (central 4 degrees) are normal.[30] This suggests that the location of deficits can influence the sensitivity of the full-field VEP. In a group of patients with recent demyelinating optic neuritis, multifocal VEPs have been shown to be more sensitive for detecting latency delays in the affected eye (89 percent versus 73 percent). This difference may be the consequence of greater detection of latency delays outside of central vision with multifocal VEPs.[89] Optic disc drusen have been reported to impact latency responses on multifocal but not full-field VEPs.[90] This suggests that multifocal VEPs are more sensitive to local injury than full-field VEPs. Our own experience supports this observation, as small, localized, central or peripheral areas of latency delay are missed or difficult to confirm on full-field VEPs. In addition, widened P100 waveforms ("temporal dispersion"), which have been the subject of long-standing controversy in the analysis of full-field VEP recordings, sometimes can be seen to reflect localized defects identifiable on the multifocal VEP (Fig. 22-14).

VEPs and ERGs, especially elicited by the multifocal technique, can improve the sensitivity of subjective visual assessments such as perimetry. Traquair famously described the visual field as representing "an island of vision surrounded by a sea of blindness."[91] Standard automated perimetry is employed routinely to perform standardized, consistent assessments of visual function beyond central vision. It has become the standard measure of disease progression in disorders such as glaucoma and has an important role in measuring visual dysfunction in MS.[64] In patients with visual complaints but normal perimetry, electrophysiologic recordings can be useful in establishing the presence of dysfunction or disease (Fig. 22-15).[54]

Other factors may also influence the difference in sensitivity between the techniques. As mentioned earlier, the full-field VEP is not just the simple sum of the waveforms from the multifocal VEP, given the differences in stimulus parameters and recording paradigms. In patients with optic neuritis, there is a modest but not perfect correlation between full-field VEPs and multifocal VEPs in both latency and amplitude.[89] Patients with an abnormal latency on full-field VEP but unusual waveform morphology sometimes can be found to have entirely normal VEPs using the multifocal technique (Fig. 22-16).

Peripheral Demyelinating Diseases

In addition to demyelinating diseases of the central nervous system (CNS), chronic demyelinating diseases of the peripheral nervous system have been associated with VEP abnormalities. In chronic inflammatory demyelinating polyneuropathy, a number of studies have reported rates of CNS demyelination that vary from 47 to 75 percent.[92,93] These subjects do not always have evidence of additional CNS involvement on magnetic resonance imaging.

Neurodegenerative Diseases

Patients with Alzheimer disease have been reported to complain of visual disturbances without abnormalities that can be identified on standard ophthalmologic

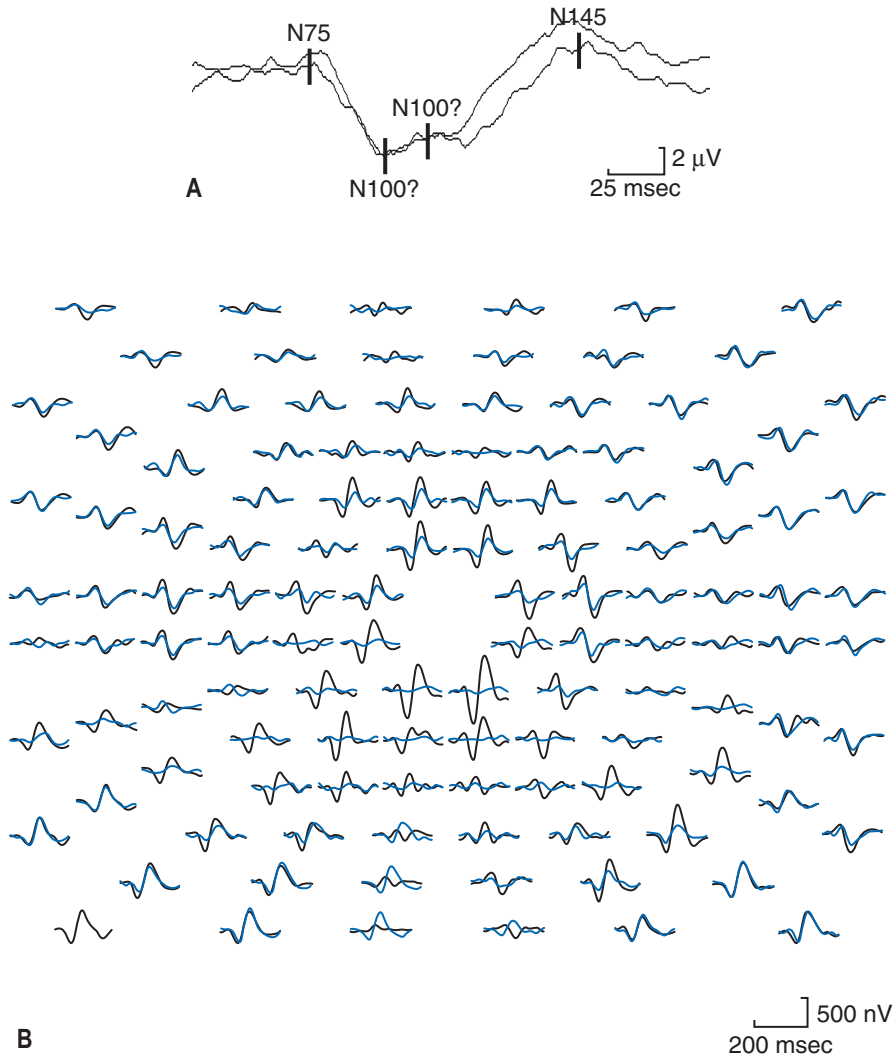

FIGURE 22-14 ■ **A**, Full-field visual evoked potential (VEP) recorded between the midoccipital and midfrontal regions in a 53-year-old woman, with temporal dispersion of the response that is challenging to interpret. **B**, Multifocal VEP confirms abnormality by demonstrating central amplitude decrement in the left eye (blue tracings).

assessment.[94–96] A small but consistent literature suggests that retinal ganglion cell loss can be detected at autopsy in patients with Alzheimer disease[97–101] and that these patients lose axons of retinal ganglion cells during the course of their disease.[100,102,103] Although small studies have reached varying conclusions, the majority of investigations have reported changes on PERG and full-field VEP in patients with Alzheimer disease.[96,103,104] Although statistically significant differences have been reported when comparing groups, these differences are not sufficient to use current electrophysiologic techniques for the diagnosis or monitoring of patients with Alzheimer disease. These findings are consistent with retinal imaging data demonstrating that patients with this disease have thinner retinal nerve fiber layer on optical coherence tomography[97,100–102] and retinal pathology data that document a reduction in retinal ganglion cells at the end of life.[98,99]

Patients with Parkinson disease have been reported to have prolonged latency on full-field VEP, and reduced amplitudes on both scotopic and photopic pattern ERGs, as well as normalization after administration of dopaminergic medications.[105] Similarly, when patients are administered dopamine antagonist medications, they have been reported to demonstrate similar prolongation of VEP latency and reduced ERG amplitudes.[106,107]

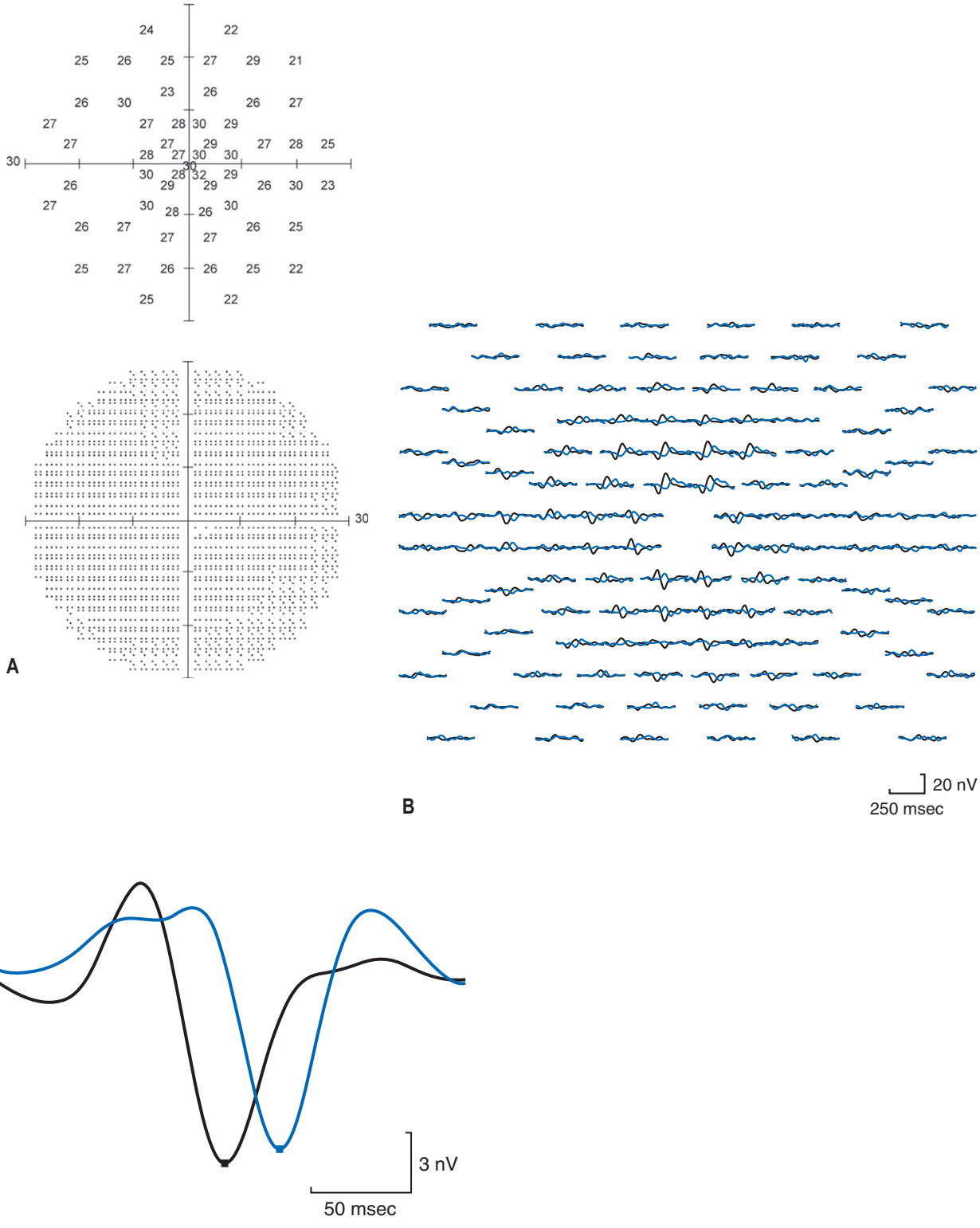

FIGURE 22-15 ■ **A**, Normal visual field (30-2 equivalent Haag Streit Octopus-900) in a 55-year-old man being evaluated for multiple sclerosis with a history of possible optic neuritis in his left eye. **B**, Abnormal multifocal visual evoked potential (VEP) showing diffuse latency delay in the left eye (blue) on the same patient, helping to confirm prior demyelinating injury. **C**, Summed response of multifocal VEP showing a 35 msec difference between the right and left eyes (126 msec and 161 msec, respectively).

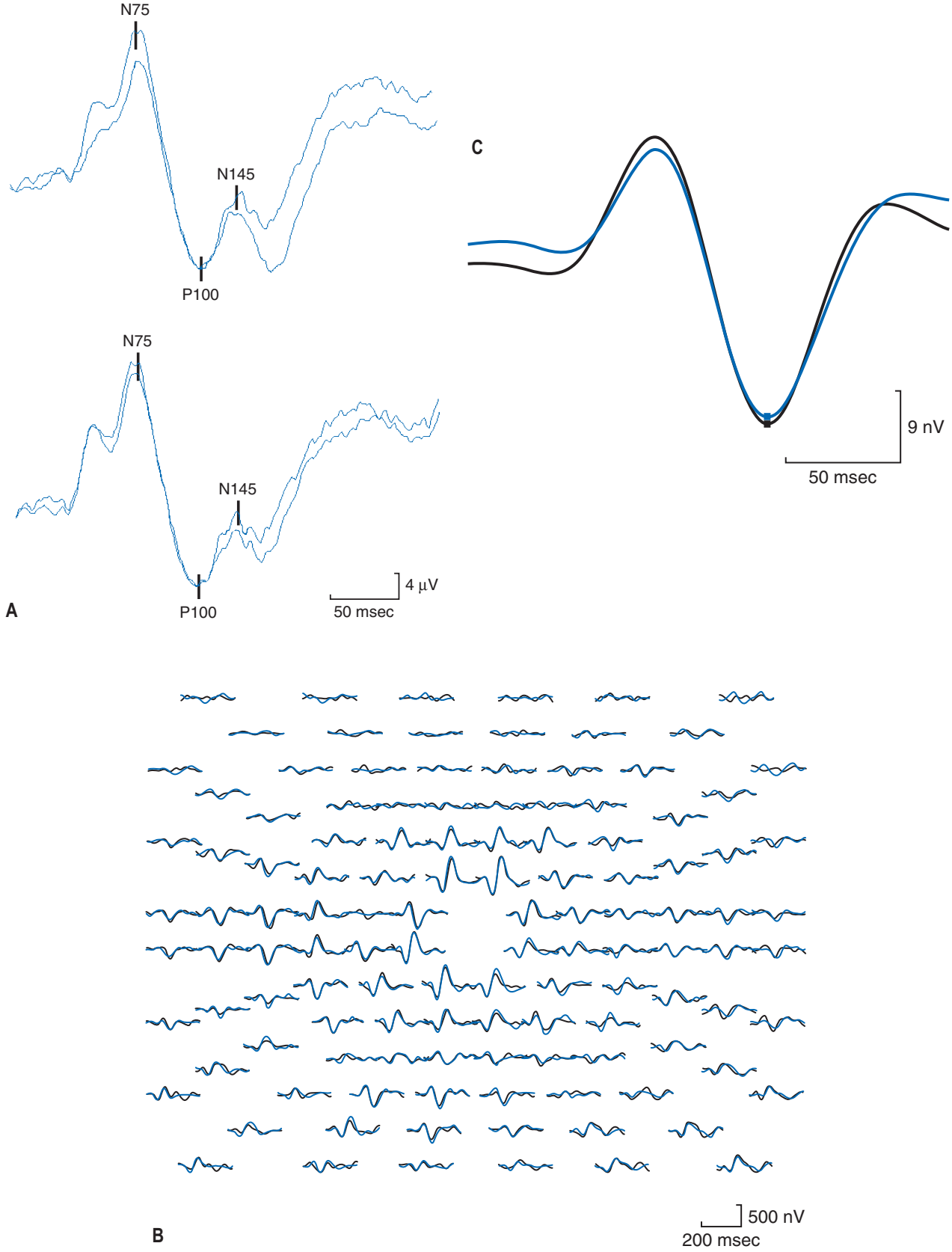

FIGURE 22-16 ■ **A**, Full-field pattern-reversal visual evoked potential (VEP) with unusual waveform from a 26-year-old woman with a history of transverse myelitis. Responses were recorded between the midoccipital and midfrontal electrodes. The P100 latencies were 178 msec and 179 msec to stimulation of left and right eyes, respectively, raising concern about disseminated disease despite a normal brain magnetic resonance image. **B**, Normal multifocal VEP on the same patient. **C**, Summed responses of multifocal VEP on the same patient showing normal morphology, as well as significantly shorter and normal latencies of 125 msec from each eye.

CLINICAL APPROACH TO ERG FOR NEUROLOGISTS

The full-field ERG plays an important role in the diagnosis of a number of conditions encountered by neurologists, including retinal dystrophies, vitamin A deficiency, paraneoplastic conditions (cancer-associated retinopathy; melanoma-associated retinopathy), X-linked retinoschisis (retinal separation), and retinal ischemia (especially old retinal artery occlusions). It is also useful in diagnosing and monitoring retinal inflammatory disorders (e.g., bird shot chorioretinopathy) and medication-induced injury (e.g., hydroxychloroquine toxicity). In retinal dystrophies, the ERG is frequently abnormal even before the patient has any significant visual impairment. In many of these conditions, both the a- and b-waves are attenuated significantly or are absent.[25,108] Retinal dystrophies are encountered most frequently by neurologists when part of a syndrome such as Kearns–Sayre syndrome or the neuropathy, ataxia, and retinitis pigmentosa (NARP) syndrome. Outer retinal degeneration is also significant enough to attenuate the ERG in many disorders involving peroxisomal dysfunction (Zellweger syndrome, Refsum disease, and adrenoleukodystrophy). These conditions are discovered most often in infancy or childhood.[25,108]

In some conditions there is a selective reduction in b-wave amplitude. In these situations, the b-wave is smaller rather than larger than the a-wave, and therefore the recording does not return to baseline after the b-wave. This pattern of abnormality implies that the injury involves the inner nuclear layer with relative preservation of photoreceptor function. It is seen most frequently in cases of old retinal ischemia, retinoschisis, and paraneoplastic conditions. In central retinal artery occlusions, ERG is most useful when the injury is only partial, and it may also provide objective assessment of severity. In this setting, the a-wave amplitude may be reduced as well. In contrast, with central retinal vein occlusions the effect is most pronounced on the b-wave alone.[25,108] Selective b-wave attenuation is usually most evident on the scotopic flash ERG. Finally, the ERG is essential to the diagnosis of paraneoplastic retinal disorders, as structural abnormalities occur late in these disorders and a high index of suspicion is required before ordering the confirmatory serologic tests.[109,110]

ERG can also be useful in (1) subjects with an abnormal VEP but unusual features suggesting primary retinal rather than neurologic dysfunction, and (2) patients with unexplained visual loss in whom examination and retinal imaging cannot distinguish optic nerve from retinal injury.[25,108] It has been suggested that, for diagnostic use, the multifocal VEP should be done in conjunction with a multifocal ERG to determine whether observed localized defects are from optic nerve or retina.[25,58] In our experience, this should also include retinal imaging, which can aid further in properly defining anatomic localization (discussed in the next section).

OTHER INVESTIGATIVE TECHNIQUES

In the modern neuro-ophthalmology clinic, many techniques can be employed to assist the evaluation of patients. As with all clinical diagnostic measures, electrophysiologic studies sometimes fail to detect relevant disease or, conversely, suggest abnormality in a subject who is otherwise normal. VEP abnormalities have been reported in a variety of outer retinal diseases,[111–113] and it has been suggested that unexpected VEP results are best interpreted in combination with the ERG. As a consequence, electrophysiologic studies cannot replace standard clinical examination techniques such as funduscopy, indirect ophthalmoscopy and visual acuity assessments. Furthermore, judicious use of ancillary techniques such as retinal imaging, automated perimetry, and detailed assessments of visual function (color vision performance, low contrast acuity) can help to extend the diagnostic reliability of electrophysiologic investigations. In particular, a combined approach can be valuable to help delineate the potential cause of visual dysfunction in individuals with unusual clinical features.

Optical coherence tomography (OCT) is an important method for the assessment of the structural integrity and health of the visual system. Using an infrared light source in the range of approximately 840 nm, it can be used to image the retina and obtain both cross-sectional and volumetric images of retinal structures. It can serve as an important tool to complement and inform the interpretation of electrophysiologic recordings. OCT can be employed to augment the standard ophthalmologic examination and to quantify retinal structures that otherwise are assessed qualitatively. Recent advances permit image resolution in the axial plane in the order of 2 μm, and extremely high reproducibility makes longitudinal assessments feasible and informative.

In the assessment of patients with possible MS and optic neuritis, for example, OCT can play an adjunctive role in determining whether a borderline VEP abnormality actually reflects disease. During an episode of acute retrobulbar neuritis, patients will often have mild swelling of the nerve fiber layer, beyond the resolution of most trained clinicians (Fig. 22-17). This is especially

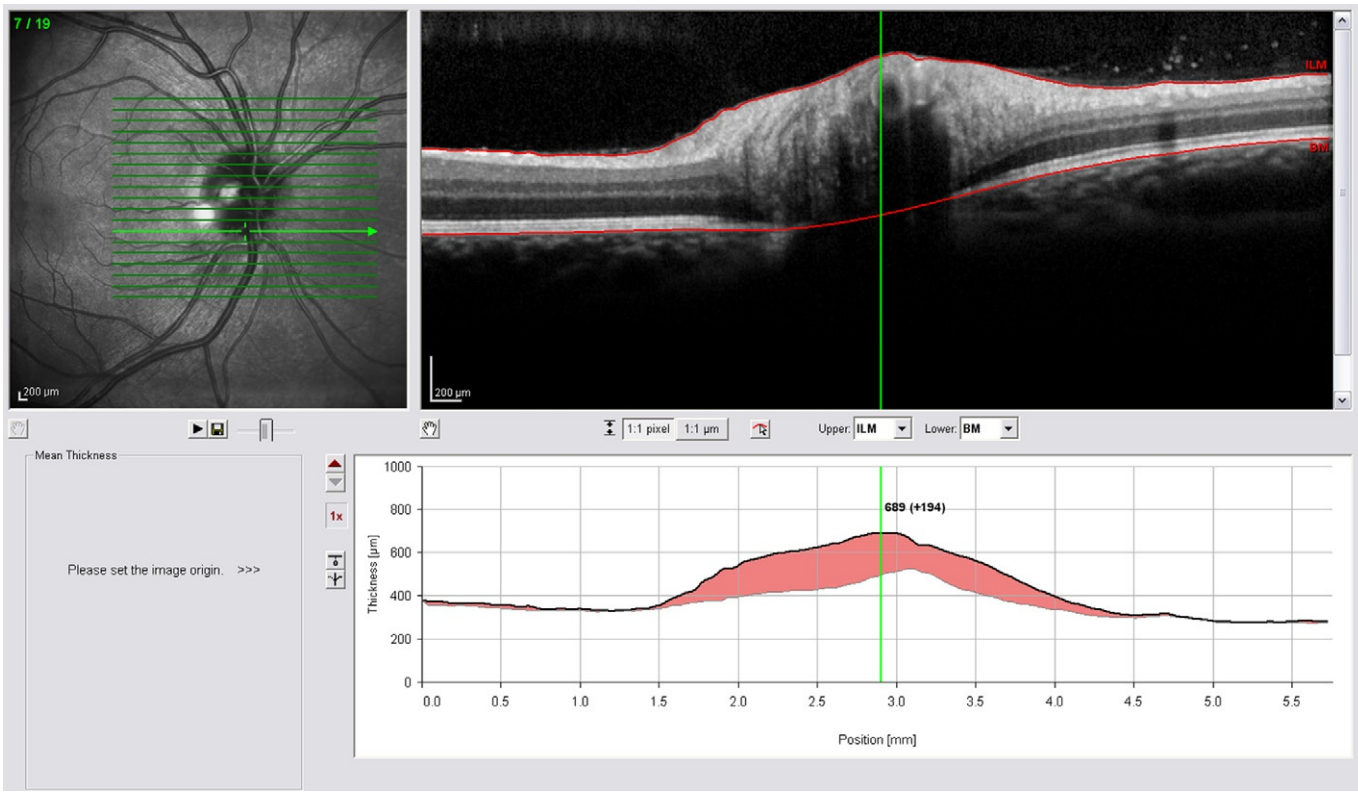

FIGURE 22-17 ■ Optical coherence tomography B-scan through the disc (right) and infrared fundus photo (left) of a 49-year-old woman with eye pain and mild delay of the visual evoked potential (VEP) as indicated by an increased interocular latency difference (the same patient as in Fig. 22-13). Disc swelling evidence of papillitis and VEP prolongation suggests that this is not disc edema but swelling due to anterior inflammatory injury. Note the swelling and the layers of the retina that can be identified.

true in cases where the demyelinating lesion is in the anterior portion of the nerve (typically, anterior to the orbital canal). Conversely, in patients with swelling of the retinal nerve fiber layer on OCT, VEP can help to establish whether the injury is likely to be demyelinating or related to increased intracranial pressure (Fig. 22-18). However, both compressive and infiltrative optic neuropathies can cause swelling and delayed VEP latency. It has also been reported previously that VEP prolongation can be observed in patients with central serous retinopathy,[112] a self-limited condition in which the neurosensory retina suffers a flat serous detachment from the posterior pole and then usually spontaneously re-anneals over weeks to months. Given its clinical characteristics, including the presence of subacute visual blurring in a young patient (albeit without pain), central serous retinopathy can be mistaken for optic neuritis. OCT, ophthalmologic examination, or both can be used to diagnose the retinopathy unequivocally (Fig. 22-19).

In patients with MS, either with or without a history of optic neuritis, nerve fiber layer thinning is observed and usually predominates in the fibers of the papillomacular bundle—that is, the temporal quadrant (Fig. 22-20). This can aid in the interpretation of a borderline VEP finding.

In general, electrophysiologic studies of the visual system can play an important role in the diagnosis and management of patients with a variety of neurologic and ophthalmologic conditions. Their use, in conjunction with other methods for assessing and monitoring visual function and ophthalmologic health, can aid in improving diagnostic accuracy and may come to play an important role in disease prognostication.

ACKNOWLEDGMENTS

The author thanks Chris Songster, Ami Cuneo, and Rachel Nolan for help with the illustrations.

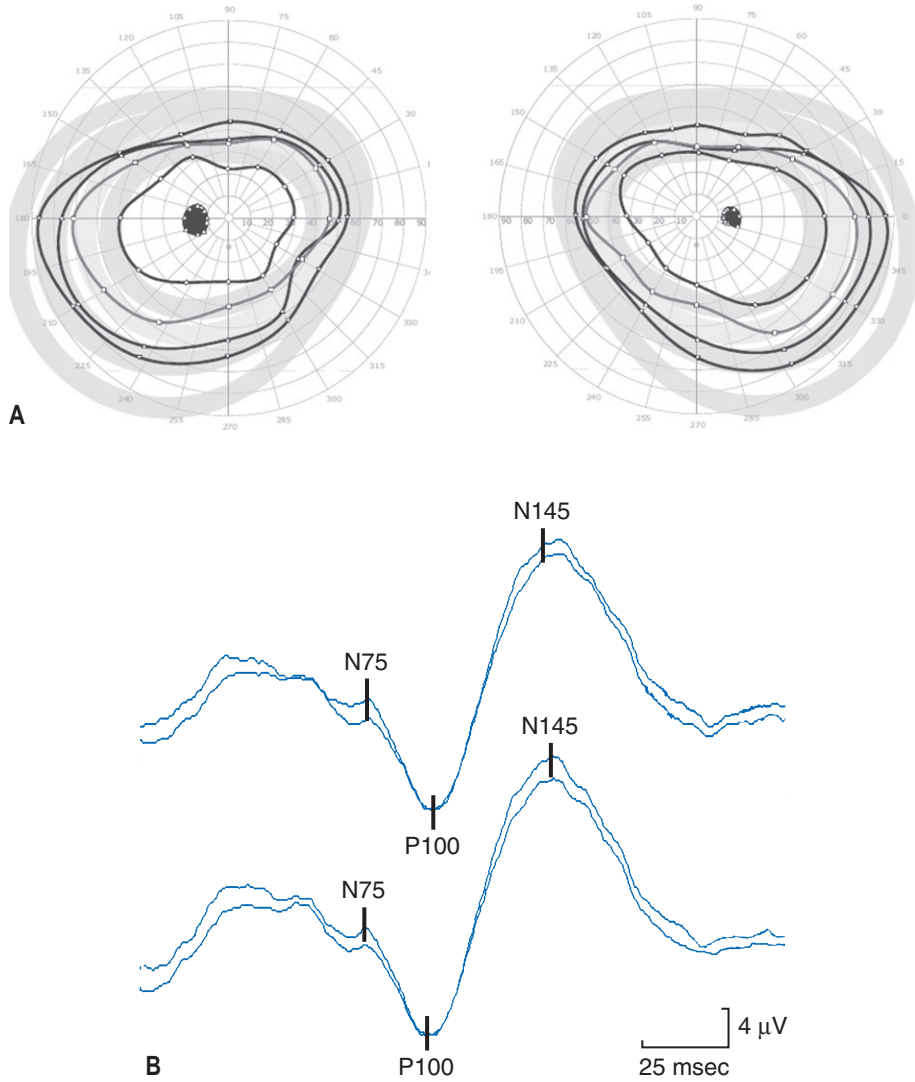

FIGURE 22-18 ■ **A**, Automated kinetic perimetry obtained with a Haag-Streit Octopus-900 in a 33-year-old man with disc swelling or papillitis. Note the enlarged blind spot in the left eye (shaded). Also note relative constriction of isopters in the left eye. **B**, Full-field pattern-reversal visual evoked potential from left (top) and right eye (bottom) shows normal symmetric P100 latency (112 msec) and amplitude bilaterally. This demonstrates that the swelling is likely papilledema rather than papillitis or infiltration.

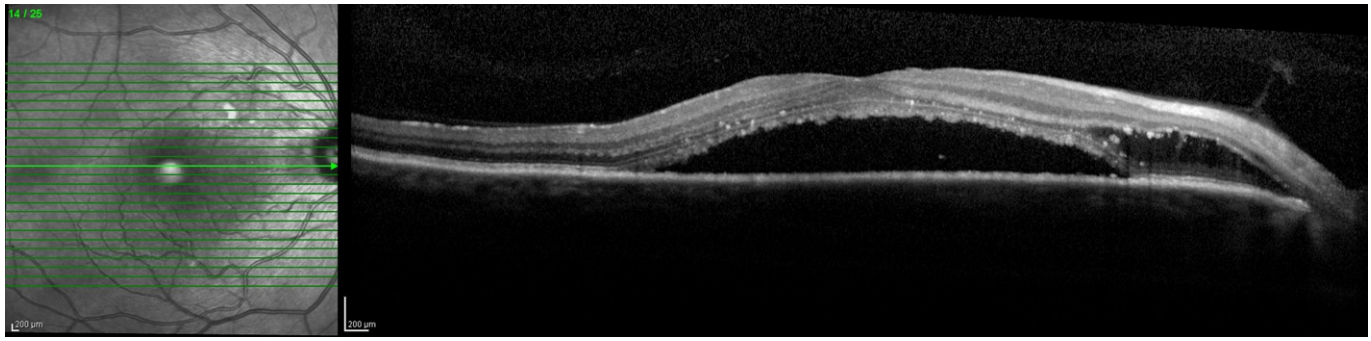

FIGURE 22-19 ■ Retinal photo (left) and optical coherence tomography (OCT) B-scan through the macula (right) of the right eye in a patient with multiple sclerosis and painless visual blurring, confirming a diagnosis of central serous retinopathy rather than optic neuritis. Note the dark fluid-filled space beneath the retina in the OCT. Central serous retinopathy can be worsened by administration of steroids. (© Ari Green, 2011.)

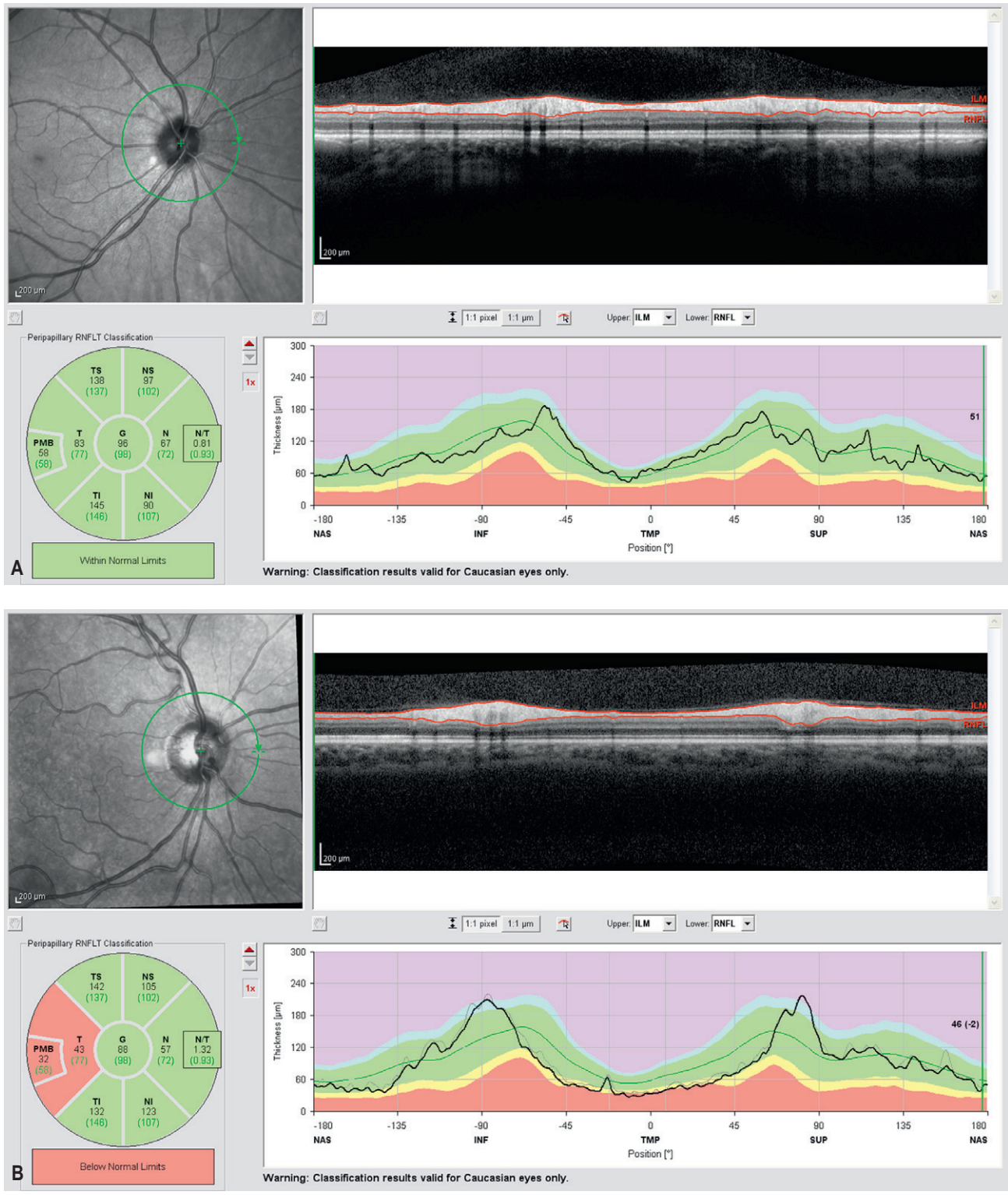

FIGURE 22-20 ■ **A**, Circular circumpapillary optical coherence tomography (OCT) B-scan in a normal healthy subject showing normal nerve fiber layer thickness. Numbers in the clock face represent nerve fiber layer thickness in micrometers. **B**, Circular circumpapillary OCT B-scan in a 32-year-old woman with multiple sclerosis showing characteristic loss of nerve fiber in the temporal quadrant of the OCT.

REFERENCES

1. Rieke F, Baylor DA: Single-photon detection by rod cells of the retina. Rev Mod Physics, 70:1027, 1998
2. Cook T: Cell diversity in the retina: more than meets the eye. Bioessays, 25:921, 2003
3. Stryer L: The molecules of visual excitation. Scientific Amer, 257:42, 1987
4. Vaney DI: Retinal neurons: cell types and coupled networks. Prog Brain Res, 136:239, 2002
5. Masland RH: The fundamental plan of the retina. Nat Neurosci, 4:877, 2001
6. Curcio CA, Sloan KR: Packing geometry of human cone photoreceptors: variation with eccentricity and evidence for local anisotropy. Vis Neurosci, 9:169, 1992
7. Packer OS, Dacey DM: Receptive field structure of H1 horizontal cells in macaque monkey retina. J Vis Sci, 2:272, 2002
8. Derrington AM, Lennie P, Wright MJ: The mechanism of peripherally evoked responses in retinal ganglion cells. J Physiol, 289:299, 1979
9. Wassle H, Boycott BB: Functional architecture of the mammalian retina. Physiol Rev, 71:447, 1991
10. McGuire BA, Stevens JK, Sterling P: Microcircuitry of beta ganglion cells in cat retina. J Neurosci, 6:907, 1986
11. Curcio CA, Allen KA: Topography of ganglion cells in the human retina. J Comp Neurol, 300:5, 1990
12. Rockhill RL, Daly FJ, MacNeil MA et al: The diversity of ganglion cells in a mammalian retina. J Neurosci, 22:3831, 2002
13. Do MT, Yau KW: Intrinsically photosensitive retinal ganglion cells. Physiol Rev, 90:1547, 2010
14. Kupper C: The projection of the macula in the lateral geniculate nucleus of man. Am J Ophthalmol, 54:597, 1962
15. Celesia GG, Demarco PJ: Anatomy and physiology of the visual system. J Clin Neurophys Sci, 11:482, 1994
16. Gooley JJ, Lu J, Fischer D et al: A broad role for melanopsin in nonvisual photoreception. J Neurosci, 23:7093, 2003
17. Singer W: Control of thalamic transmission by corticofugal and ascending reticular pathways in the visual system. Physiol Rev, 57:386, 1977
18. Kaplan E, Purpura K, Shapley R: Contrast affects the transmission of visual information through the mammalian lateral geniculate nucleus. J Physiol, 391:267, 1987
19. Callaway EM: Local circuits in the primary visual cortex of the macaque monkey. Annu Rev Neurosci, 21:47, 1998
20. Horton JC, Hoyt WF: The representation of the visual field in human striate cortex. A revision of the classic Holmes map. Arch Ophthalmol, 109:816, 1991
21. Kriss A: Recording technique. p. 1. In Halliday AM (ed): Evoked Potentials in Clinical Testing. Churchill Livingstone, New York, 1993
22. Hassan U, Anwar MS: Reducing noise by repetition: introduction to signal averaging. Eur J Physics, 31:453, 2010
23. Hidajat RR, McLay JL, Elder MJ et al: A comparison of two patient-friendly ERG electrodes. Australas Phys Eng Sci Med, 26:30, 2003
24. Marmor MF, Fulton AB, Holder GE et al: International Society for Clinical Electrophysiology of Vision: ISCEV Standard for full-field clinical electroretinography (2008 update). Doc Ophthalmol, 118:69, 2009
25. Lam BL: Electrophysiology of Vision. Clinical Testing and Applications. Taylor & Francis, Boca Raton, FL, 2005
26. Samuels IS, Sturgill GM, Grossman GH et al: Light-evoked responses of the retinal pigment epithelium: changes accompanying photoreceptor loss in the mouse. J Neurophysiol, 104:391, 2010
27. Moschos M, Brouzas D: C wave of electroretinogram and visual evoked response in optic neuritis due to demyelinating diseases. Ophthalmologica, 204:149, 1992
28. Celesia GG, Brigell MG: Recommended standards for pattern electroretinograms and visual evoked potentials. International Federation of Clinical Physiology. Electroencephalogr Clin Neurophysiol Suppl, 52:45, 1999
29. Kaufman D, Celesia GG: Simultaneous recording of pattern electroretinogram and visual evoked responses in neuro-ophthalmologic disorders. Neurology, 35:644, 1985
30. Halliday AM: The visual evoked potential in the investigation of diseases of the optic nerve. p. 195. In Halliday AM (ed): Evoked Potentials in Clinical Testing. Churchill Livingstone, New York, 1993
31. Regan D, Lee BB: A comparison of the human 40Hz response with the properties of macaque ganglion cells. Vis Neurosci, 10:439, 1993
32. Milner BA, Regan D, Heron HR: Differential diagnosis of multiple sclerosis by visual evoked potential recording. Brain, 97:755, 1974
33. Vialatte FB, Maurice M, Dauwels J et al: Steady-state visually evoked potentials: focus on essential paradigms and future perspectives. Prog Neurobiol, 90:418, 2010
34. Kirkham TH, Coupland SG: Abnormal electroretinograms and visual evoked potentials in chronic papilledema using time-difference analysis. Can J Neurol Sci, 8:243, 1981
35. Pompe MT, Kranjc BS, Brecelj J: Visual evoked potentials to red-green stimulation in schoolchildren. Vis Neurosci, 23:447, 2006
36. Rudvin I: Visual evoked potentials for reversals of red-green gratings with different chromatic contrasts: asymmetries with respect to isoluminance. Vis Neurosci, 22:749, 2005
37. Spekreijse H, van der Twell LH, Zuidema T: Contrast evoked responses in man. Vision Res, 13:1577, 1973
38. Kuroiwa Y, Celesia GG: Visual evoked potentials with hemifield pattern stimulation. Their use in the diagnosis of retrochiasmatic lesions. Arch Neurol, 38:86, 1981
39. Schroeder CE, Tenke CE, Givre SJ et al: Striate cortical contribution to the surface-recorded pattern-reversal VEP in the alert monkey. Vision Res, 31:31, 1991

40. Givre SJ, Schroeder CE, Arezzo JC: Contribution of extrastriate area V4 to the surface-recorded flash VEP in the awake macaque. Vision Res, 34:415, 1994
41. Kraut MA, Arezzo JC, Vaughan HG, Jr: Inhibitory processes in the flash evoked potential of the monkey. Electroencephalogr Clin Neurophysiol, 76:440, 1990
42. Aldrich MS, Alessi AG, Beck RW et al: Cortical blindness: etiology, diagnosis, and prognosis. Ann Neurol, 21:149, 1987
43. Kupersmith MJ, Nelson JI, Seiple WH et al: The 20/20 eye in multiple sclerosis. Neurology, 33:1015, 1983
44. Robinson K, Rudge P, Small DG et al: A survey of the pattern reversal visual evoked response (PRVER) in 1428 consecutive patients referred to a clinical neurophysiology department. J Neurol Sci, 64:225, 1984
45. Joost W, Bach M, Schulte-Maunting J: Influence of mood on visually evoked potentials: a prospective longitudinal study. Int J Psychophysiol, 12:147, 1992
46. Oken BS, Chiappa KH, Gill E: Normal temporal variability of the P100. Electroencephalogr Clin Neurophysiol, 68:153, 1987
47. Bemelmans NA, Tilanus MA, Cuypers MH et al: Pattern-reversal visual evoked potentials in patients with epiretinal membrane. Am J Ophthalmol, 123:97, 1997
48. Ristanovic D, Hajdukovic R: Effects of spatially structured stimulus fields on pattern reversal VEPs. Electroencephalogr Clin Neurophysiol, 51:599, 1981
49. Sokol S, Jones K, Nadler D: Comparison of the spatial response properties of the human retina and cortex as measured by simultaneously recorded pattern ERGs and VEPs. Vision Res, 23:723, 1983
50. Kurita-Tashima S, Tobimatsu S, Nakayama-Hiromatsu M et al: Effect of check size on the pattern reversal VEP. Electroencephalogr Clin Neurophysiol, 80:161, 1991
51. Sokol S, Moskowitz A: Effects of retinal blur on the peak latency of the pattern evoked potential. Vision Res, 19:747, 1979
52. Neima D, Regan D: Pattern visual evoked potentials and spatial vision in retrobulbar neuritis and MS. Arch Neurol, 41:198, 1984
53. Fortune B, Hood DC: Conventional pattern-reversal VEPs are not equivalent to summed multifocal VEPs. Invest Ophthalmol Vis Sci, 44:1364, 2003
54. Hoffman MB: Investigating visual function with multifocal VEP. p. 139. In Lorenz B, Borruat FX (eds): Essentials in Ophthalmology: Pediatric Ophthalmology, Neuro-Ophthalmology, Genetics. Springer, New York, 2008
55. Baseler HA, Sutter EE, Klein SA et al: The topography of visual evoked response properties across the visual field. Electroencephalogr Clin Neurophysiol, 90:65, 1994
56. Hood DC, Greenstein VC: Multifocal VEP and ganglion cell damage: applications and limitations for the study of glaucoma. Prog Retin Eye Res, 22:201, 2003
57. Klistorner AI, Graham SL, Grigg JR et al: Multifocal topographic visual evoked potential: improving objective detection of local visual field defects. Invest Ophthalmol Vis Sci, 39:937, 1998
58. Klistorner AI, Graham SL, Grigg JR et al: Electrode position and the multi-focal visual-evoked potential: role in objective visual field assessment. Aust N Z J Ophthalmol Suppl:1, S91, 1998
59. Hood DC, Zhang X, Rodarte C et al: Determining abnormal interocular latencies of multifocal visual evoked potentials. Doc Ophthalmol, 109:177, 2004
60. Shimada Y, Horiguchi M, Nakamura A: Spatial and temporal properties of interocular timing differences in multifocal visual evoked potentials. Vision Res, 45:365, 2005
61. Slotnick SD, Klein SA, Carney T et al: Electrophysiological estimate of human cortical magnification. Clin Neurophysiol, 112:1349, 2001
62. Beck RW, Cleary PA, Trobe JD et al: The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. The Optic Neuritis Study Group. N Engl J Med, 329:1764, 1993
63. Winn BJ, Shin E, Odel JG et al: Interpreting the multifocal visual evoked potential: the effects of refractive errors, cataracts, and fixation errors. Br J Ophthalmol, 89:340, 2005
64. Slotnick SD, Klein SA, Carney T et al: Using multi-stimulus VEP source localization to obtain a retinotopic map of human primary visual cortex. Clin Neurophysiol, 110:1793, 1999
65. Klistorner A, Fraser C, Garrick R et al: Correlation between full-field and multifocal VEPs in optic neuritis. Doc Ophthalmol, 116:19, 2008
66. Fortune B, Demirel S, Zhang X et al: Repeatability of normal multifocal VEP: implications for detecting progression. J Glaucoma, 15:131, 2006
67. Fortune B, Demirel S, Zhang X et al: Comparing multifocal VEP and standard automated perimetry in high-risk ocular hypertension and early glaucoma. Invest Ophthalmol Vis Sci, 48:1173, 2007
68. Guthkelch AN, Bursick D, Sclabassi RJ: The relationship of the latency of the visual P100 wave to gender and head size. Electroencephalogr Clin Neurophysiol, 68:219, 1987
69. Gregori B, Pro S, Bombelli F et al: VEP latency: sex and head size. Clin Neurophysiol, 117:1154, 2006
70. Wright CE, Williams DE, Drasdo N: The influence of age on the electroretinogram and visual evoked potential. Doc Ophthalmol, 59:365, 1985
71. Celesia G, Kaufman D, Cone S: Effects of age and sex on pattern electroretinograms and visual evoked potentials. Electroencephalogr Clin Neurophysiol, 68:161, 1987
72. Sokol S, Moscowitz A, Towle V: Age-related changes in the latency of the visual evoked potential: influence of check size. Electroencephalogr Clin Neurophysiol, 51:559, 1981
73. Fortune B, Zhang X, Hood DC et al: Normative ranges and specificity of the multifocal VEP. Doc Ophthalmol, 109:87, 2004
74. Skalka H, Holman J: Effect of pupillary dilatation in flash VER testing. Doc Ophthalmol, 63:321, 1986

75. Martins A, Balachandran C, Klistorner AI et al: Effect of pupil size on multifocal pattern visual evoked potentials. Clin Experiment Ophthalmol, 31:354, 2003
76. Gonzalez P, Parks S, Dolan F et al: The effects of pupil size on the multifocal electroretinogram. Doc Ophthalmol, 109:67, 2004
77. Mori H, Momose K, Nemoto N et al: Application of visual evoked potentials for preoperative estimation of visual function in eyes with dense cataract. Graefes Arch Clin Exp Ophthalmol, 239:915, 2001
78. Galloway NR: Electrophysiological testing of eyes with opaque media. Eye, 2:615, 1988
79. Ruseckaite R, Maddess T, Danta G et al: Sparse multifocal stimuli for the detection of multiple sclerosis. Ann Neurol, 57:904, 2005
80. Arvind H, Graham S, Leaney J et al: Identifying preperimetric functional loss in glaucoma: a blue-on-yellow multifocal visual evoked potentials study. Ophthalmology, 116:1134, 2009
81. Bumgartner J, Epstein CM: Voluntary alteration of visual evoked potentials. Ann Neurol, 12:12, 1982
82. Fraser C, Klistorner A, Graham S et al: Multifocal visual evoked potential latency analysis: predicting progression to multiple sclerosis. Arch Neurol, 63:847, 2006
83. Klistorner A, Graham S, Fraser C et al: Electrophysiological evidence for heterogeneity of lesions in optic neuritis. Invest Ophthalmol Vis Sci, 48:4549, 2007
84. Holder GE: Electrophysiological assessment of optic nerve disease. Eye, 18:1133, 2004
85. Janaky M, Fulup Z, Paiffy A et al: Electrophysiological findings in patients with nonarteritic ischemic optic neuropathy. Clin Neurophysiol, 117:1158, 2006
86. Mukartihal GB, Radhakrishan S, Ramasubba Reddy et al: Statistical analysis of visual evoked potentials in optic neuritis and ischemic optic neuropathy subjects. Conf Proc IEEE Eng Med Biol Soc, 2:1193, 2005
87. Parisi V, Gallinaro G, Ziccardi L: Electrophysiological assessment of visual function in patients with nonarteritic ischaemic optic neuropathy. Eur J Neurol, 15:839, 2008
88. Wilson WB: Visual evoked response differentiation of ischaemic optic neuritis from the optic neuritis of multiple sclerosis. Am J Ophthalmol, 86:520, 1978
89. Klistorner A, Fraser C, Garrick R et al: Correlation between full-field and multifocal VEPs in optic neuritis. Doc Ophthalmol, 116:19, 2008
90. Grippo TM, Ezon I, Kanadani FN et al: The effects of optic disc drusen on the latency of the pattern-reversal checkerboard and multifocal visual evoked potentials. Invest Ophthalmol Vis Sci, 50:4199, 2009
91. Scott GI: Traquair's Clinical Perimetry. 7th Ed. Henry Kimpton, London, 1957
92. Stojkovic T, de Seze J, Hurtevent JF et al: Visual evoked potentials study in chronic idiopathic inflammatory demyelinating polyneuropathy. Clin Neurophysiol, 111: 2285, 2000
93. Uncini A, Gallucci M, Lugaresi A et al: CNS involvement in chronic inflammatory demyelinating polyneuropathy: an electrophysiological and MRI study. Electromyogr Clin Neurophysiol, 31:365, 1991
94. Cronin-Golomb A, Corkin S, Rizzo JF et al: Visual dysfunction in Alzheimer's disease: relation to normal aging. Ann Neurol, 29:41, 1991
95. Jackson GR, Owsley C: Visual dysfunction, neurodegenerative diseases, and aging. Neurol Clin, 21:709, 2003
96. Katz B, Rimmer S: Ophthalmologic manifestations of Alzheimer's disease. Surv Ophthalmol, 34:31, 1989
97. Berisha F, Feke GT, Trempe CL et al: Retinal abnormalities in early Alzheimer's disease. Invest Ophthalmol Vis Sci, 48:2285, 2007
98. Blanks JC, Torigoe Y, Hinton DR et al: Retinal pathology in Alzheimer's disease. I. Ganglion cell loss in foveal/parafoveal retina. Neurobiol Aging, 17:377, 1996
99. Blanks JC, Schmidt SY, Torigoe Y et al: Retinal pathology in Alzheimer's disease. II. Regional neuron loss and glial changes in GCL. Neurobiol Aging, 17:385, 1996
100. Danesh-Meyer HV, Birch H, Ku JY et al: Reduction of optic nerve fibers in patients with Alzheimer disease identified by laser imaging. Neurology, 67:1852, 2006
101. Guo L, Duggan J, Cordeiro MF: Alzheimer's disease and retinal neurodegeneration. Curr Alzheimer Res, 7:3, 2010
102. Lu Y, Li Z, Zhang X, Ming B et al: Retinal nerve fiber layer structure abnormalities in early Alzheimer's disease: evidence in optical coherence tomography Neurosci Lett, 480:69, 2010
103. Paquet C, Boissonnot M, Roger F et al: Abnormal retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. Neurosci Lett, 420:97, 2007
104. Krasodomska K, Lubienski W, Potemkowski A et al: Pattern electroretinogram (PERG) and pattern visual evoked potential (PVEP) in the early stages of Alzheimer's disease. Doc Ophthalmol, 121:111, 2010
105. Archibald NK, Clarke MP, Mosimann UP et al: The retina in Parkinson's disease. Brain, 132:1128, 2009
106. Bartel P, Blom M, Robinson E et al: Effects of chlorpromazine on pattern and flash ERGs and VEPs compared to oxazepam and to placebo in normal subjects. Electroencephalogr Clin Neurophysiol, 77:330, 1990
107. Stanzione P, Fattapposta F, Tagliati M et al: Dopaminergic pharmacological manipulations in normal humans confirm the specificity of the visual (PERG-VEP) and cognitive (P300) electrophysiologic alterations in Parkinson's disease. Electroencephalogr Clin Neurophysiol, 41:216, 1990
108. Gouras, P: Electroretinography. p. 427. In Aminoff MJ (ed): Electrodiagnosis in Clinical Neurology. 5th Ed. Elsevier Churchill Livingstone, Philadelphia, 2005
109. Thirkill CE: Cancer associated retinopathy. Neuro-ophthalmology, 13:297, 1994

110. Berson EL, Lessell S: Paraneoplastic night blindness with malignant melanoma. Am J Ophthalmol, 106:307, 1988
111. Janaky M, Palffy A, Horvath G et al: Pattern reversal electroretinograms and visual evoked potentials in retinitis pigmentosa. Doc Ophthalmol, 177:27, 2008
112. Lennerstrand G: Delayed visual cortical potentials in retinal disease. Acta Ophthalmol, 60:497, 1982
113. Weinstein GW, Odom JV, Cavendar S: Visually evoked potentials and electroretinography in neurologic evaluation. Neurol Clin, 9:225, 1991