

Visual Evoked Potentials

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Summary: The recording of visual evoked potentials (VEPs) is an important means of obtaining reproducible, quantitative data on the function of the anterior visual pathways. In this review, the technical aspects of recording VEPs are briefly discussed, components of the VEPs are described, and the clinical uses of VEPs are considered. It is concluded that VEPs are useful in providing information concerning the functional integrity of the anterior visual pathways. They are especially useful in evaluating patients with visual symptoms but no objective findings on examination and in patients without visual symptoms but with diseases that are known to involve the visual pathways commonly and subclinically. Lastly, the utility and limitations of VEPs in various neurological disorders are summarized, bearing in mind the widespread availability of advanced neuroimaging techniques. **Key Words:** Visual evoked potentials—Anterior visual pathways—Clinical uses—Diagnosis.

Electrophysiologic techniques, including the recording of visual evoked potentials (VEPs) and electroretinograms (ERGs), have been used extensively to evaluate patients with known or suspected visual problems. In particular, such methods have been used to investigate patients with ocular disorders or diseases affecting the optic nerves, optic tracts, or geniculostriate pathways. They have been especially helpful in the evaluation of patients with suspected multiple sclerosis (MS), in whom demyelinating lesions (often asymptomatic) are frequent in the anterior visual pathways. Since the early studies by Halliday and others (1972, 1973a, 1973b) on the utility of VEPs in optic neuritis, the introduction of magnetic resonance imaging (MRI) has greatly facilitated the evaluation of MS patients, especially when performed with the use of gadolinium enhancement. As a result, the role of VEPs in the diagnosis and management of patients with MS as well as in patients with other disorders needs reevaluation. It is the purpose of this

review to consider broadly the current role of VEPs in the diagnosis and management of patients with diverse neurological diseases.

VISUAL STIMULI AND THEIR PHYSICAL CHARACTERISTICS

Any repetitive visual stimulus can be used to elicit a VEP, although the most widely used in clinical practice have been patterned or unpatterned achromatic stimuli delivered monocularly. Pattern stimuli are typically checkerboard patterns that alternate the light and dark squares, but alternating sinusoidal gratings or bars have also been used. Checkerboard stimuli are quite complex because, in addition to the fundamental spatial frequency, multiple harmonics of this frequency are also present and are oriented in orthogonal (predominantly diagonal) directions (Kelly, 1976). By contrast sinusoidal gratings have a single spatial frequency that is oriented in only one (usually horizontal) direction. Although some authors have argued that the greater simplicity of a sinusoidal grating makes this a preferable stimulus for eliciting the VEP (Bobak et al., 1987), the issue has not been well stud-

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TABLE 1. Latency of visual evoked potential components following stimulation by pattern reversal or flash

Author	TV pattern-reversal		Flash	
	N75	P100	I	IV
Wilson et al., 1980	56 ± 1.3	95 ± 1.4	53 ± 2.2	114 ± 1.8
Bajalan et al., 1986	Not reported	105.7 ± 7.4	Not reported	113.1 ± 10
Hughes et al., 1987	59.0 ± 10.9	100.3 ± 6.5	64.6 ± 10.5	103.9 ± 9.2
Sandford et al., 1988	74 ± 5.0	100.7 ± 6.3	Not reproducible	Not reproducible

ied clinically. Most laboratories use checkerboard stimuli and, considering the sensitivity of the visual system to complex lines and edges (see article by Celestia, this issue), it may be that the more complex stimulus is actually preferable for detecting subtle deficits in visual function.

Unpatterned stimuli generally consist of brief flashes of white light. Such stimuli usually produce reproducible responses although the latencies of the different components of the response are more variable than those elicited by pattern stimuli (Table 1). The VEP elicited by pattern reversal has been found to be slightly more sensitive than flash-elicited VEPs in detecting pathology of the optic pathways, but flash VEPs can, in some patients, be abnormal when pattern reversal VEPs are normal (Bajalan et al., 1986).

Hemifield stimulation is performed with use of a reversing pattern stimulus that is confined to either the right or left visual hemifield. Some computer programs allow for a randomized presentation of the right and left hemifield stimuli so that visual fixation is more easily maintained by subjects.

Visual stimuli are characterized by several physical parameters that need to be understood when comparing the findings in different laboratories as well as to appreciate the utility of the VEP in different clinical settings.

Luminance

Luminance (L) or brightness is measured in candela per square meter (cd/m^2). For a checkerboard or a bar stimulus, the average screen luminance is defined as the mean of the luminance of the light and dark squares [i.e., $(L_{\text{light}} + L_{\text{dark}})/2$] except when the number of light and dark squares or bars on the screen is unequal. In this latter circumstance the average luminance will be changed when the pattern is reversed so that a "flash" stimulus will be delivered in addition to the pattern. Similarly if VEPs are recorded to pattern onset, this may be accompanied by a luminance

change and therefore by an accompanying flash stimulus (so-called "flash pattern") unless the background luminance is the same as the average luminance of the pattern stimulus. There is little agreement with regard to the optimal luminance for eliciting the VEP; typical mean values (when reported) for pattern stimuli range from 100 to 1,000 cd/m^2 (Czopf, 1985; Bodis-Wollner et al., 1987; Wright et al., 1987), whereas flash stimuli are generally delivered at $>3,000 \text{ cd}/\text{m}^2$ (Czopf, 1985; Wilson and Keyser, 1980).

Visual Angle and Spatial Frequency

The size of an object in the visual field is measured either in terms of its visual angle or its spatial frequency. Visual angle (in degrees) is calculated as the arc tangent of the ratio of the check size (or bar width) to the distance between the eye and the screen (each measured in the same units). The result is generally converted into minutes of arc (i.e., multiplied by 60) rather than being expressed in degrees. The spatial frequency is calculated as the number of cycles (one light/dark pair of either checks or bars) in each degree of visual angle. Thus, spatial frequency and visual angle are inversely related; higher spatial frequencies are associated with a smaller visual angle subtended by each check or bar.

The size of the check or bar used for clinical purposes varies in different laboratories, but check (bar) size usually ranges between 10–60 min of arc (3–0.5 cycles/degree). The optimal check size for clinical recordings is unclear. Any variability of amplitude and latency of the VEP with changes in visual acuity is less conspicuous with use of check sizes larger than ~50 min of arc (Harter and White, 1970; Collins et al., 1979), so that the test may theoretically be more specific with checks of this size in some clinical settings. However, some authors have argued that, because the contrast sensitivity function for the foveal part of the retina is maximal at 4–5 cycles/degree, the best stimuli are small checks (Bodis-Wollner et al.,

1987). Indeed, small checks often appear to be more sensitive than large ones in detecting abnormalities, but it is necessary to have normal values for each check size that is used.

Contrast

Contrast is defined as the difference in luminance between the dark and light squares divided by the sum of these luminances [i.e., $(L_{\text{light}} - L_{\text{dark}})/(L_{\text{light}} + L_{\text{dark}})$]. It is generally expressed as a percent value (i.e., multiplied by 100), and typical values in VEP recordings range from 50 to 80%.

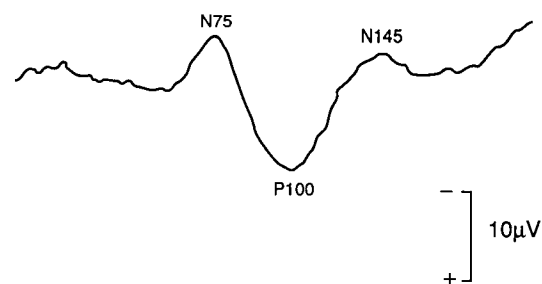
Television Monitors

Early VEP recordings were made with projection devices that allowed almost instantaneous reversal of the patterns. Most modern laboratories now use a television monitor for generating the visual stimulus. Such monitors take 16.7 ms (at 60 Hz) to make one raster sweep and thus to complete the pattern reversal. As a result, component latencies for pattern reversal VEPs that use television monitors are generally longer than those recorded with use of other projection devices.

RECORDING ARRANGEMENTS

Responses are recorded from electrodes placed 5 cm above the Oz site (International 10:20 system) as well as 5 cm lateral to the right and left of this location. These electrode sites are designated midoccipital (MO), right occipital (RO), and left occipital (LO) respectively, and each is referred to a midfrontal (MF) electrode placed 12 cm above the nasion. Depending upon the number of channels available for recording, responses may also be recorded between the MF or MO electrode sites and linked mastoid electrodes to help resolve ambiguous wave shapes (Shih et al., 1988). The reason for this is that the MF electrode site is active and records a negative potential (N100) that occurs at about the same time as the major occipital positivity (P100). If the latencies of these two components are disparate, a W-shaped response can result, in which the identity of the P100 component is unclear; such ambiguity may be resolved with use of a less-active reference, such as the linked mastoids. Responses to hemifield stimulus may also be helpful in clarifying an ambiguous waveform. Responses are recorded for 250 ms following stimulus onset, and stimuli are presented at a rate of ~ 2 Hz. Responses are

PATTERN REVERSAL



FLASH

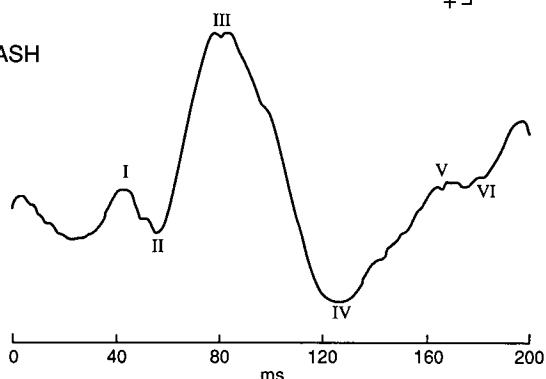


FIG. 1. Monocularly elicited VEPs [midoccipital (MO)] to pattern-reversal (top trace) and flash stimuli (bottom trace) delivered at 1.8 Hz in a normal subject. Only one trial, which is the average of 128 responses, is shown for illustrative purposes. See text for further details.

filtered with use of a band pass of 1–100 Hz before being averaged and displayed. Responses to 128 pattern reversals per trial are generally sufficient to define the signal. This is because the amplitude of the occipital P100 is generally on the order of $10 \mu\text{V}$, and therefore the initial signal-to-noise ratio is high enough to define the signal in only a few trials. Recordings should be repeated at least once to ensure replicability of the findings.

COMPONENTS OF THE VEP AND PRESUMED GENERATORS

Patterned Stimuli

The VEP to patterned stimuli recorded over the midoccipital electrode (Fig. 1, Table 1) consists of an early negativity (N75) followed by a large positive wave (P100) and a subsequent negativity (N145). The generators of the N75 and P100 components are probably in the primary visual (striate) cortex (Corletto et al., 1967). In lesions restricted to this area these potentials are generally absent or abnormal (Aldrich et

al., 1987), and in lesions involving the visual association cortex these potentials are spared (Bodis-Wollner et al., 1977). A few cases of large lesions in area 17 with associated blindness but sparing of the occipital P100 have been reported (Celesia et al., 1980, 1982). In these cases, however, small areas of functioning striate cortex have been demonstrated or presumed to account for the findings (Celesia et al., 1982). These two components of the VEP do not arise from the same generators because some patients have an abnormal P100 with no concomitant abnormality of the N75 (Ghilardi, 1991). In addition, physostigmine has been shown to have a differential effect on the amplitudes of these two components in cats (Arakawa et al., 1993). Further support for the occipital cortex as the generator of the P100 is derived from hemifield stimulation, which produces largest P100 components over the hemisphere ipsilateral to the stimulated field. This paradoxical lateralization has been attributed to the location of primary visual cortex on the mesial surface of the hemisphere, and generators in this region have been confirmed with use of equivalent dipole mapping methods to define the origin of the P100 component in humans (Brigell et al., 1993). The generators of the N145, by contrast, are largely unknown although they are presumably located in association areas of cortex (Corletto et al., 1967).

The portion of the retina responsible for the VEP depends upon the spatial frequency of the stimuli. For high-frequency stimuli the parafoveal region accounts for almost all of the response, whereas for low-frequency stimuli (such as large checks) the more peripheral retinal areas make major contributions (Armington and Brigell, 1981; Meredith and Celesia, 1982).

Unpatterned Stimuli

The VEP to unpatterned flashes of light is somewhat more complicated and variable than the response to patterned stimuli (Fig. 1, Table 1). Usually a series of alternating negative and positive waves (labeled I, II, III, IV, V, and VI) can be recorded over the midoccipital region. Wave IV is the most conspicuous positivity and seems to be analogous to the P100 of the pattern VEP. The generators of these components are not as well understood as those of the patterned VEP. Presumably, however, the generators of wave IV and P100 are not identical because patients may have abnormalities of the flash-elicited wave IV but a normal P100 to patterned stimuli (Wright et al., 1984; Bajalan et al., 1986; Ray et al., 1991).

CLINICAL USES OF THE VEP

It is important initially to consider the clinical role of VEPs in general terms and to define those circumstances in which the VEP is likely to provide information of the greatest clinical value. An abnormal VEP provides evidence of functional disturbances in the afferent pathway being stimulated. It also provides some information regarding the site of any functional disturbance, although this information is often based more on knowledge of neuroanatomy than on any understanding of the generators of the VEP. For example, although the P100 is thought to be generated in the striate cortex, a unilateral (monocular) delay in P100 latency is regarded as evidence of a functional disturbance in the anterior optic pathways because visual information is known to be binocularly represented posterior to the chiasm. When the VEP is delayed bilaterally, such localization is not possible.

The role of the VEP as a means of testing visual function is clearly important and complementary to other tests such as MRI that provide detailed information on structure but not function. Thus it is important to use the VEP in those circumstances where the information desired concerns function rather than structural integrity. For example, in a patient with slowly progressive loss of vision from a compressive optic neuropathy, the VEP will be less helpful in evaluating the patient than an MRI. By contrast, in a patient with ill-defined visual complaints and a normal examination, the VEP will be more useful than the MRI because it specifically assesses vision and can provide objective evidence of an organic disturbance of visual function.

The VEP can also be used both to monitor patients and as an aid in diagnosis. However, if the VEP is to be used to monitor patients for early (preclinical) changes that might lead to some therapeutic intervention, it is essential to document not only that a visual disturbance is common in the condition being monitored but also that changes in visual function predict future clinical deterioration. Similarly, if the VEP is to be used to diagnose a particular condition, then the occurrence of a visual disturbance in that disorder (but not in alternative conditions) should be well established.

Lastly, unless the VEP is being used to monitor patients longitudinally, it will generally provide more useful information when patients do not have clear evidence of visual dysfunction on clinical examination. Thus, when a deficit is already evident clinically,

the VEP findings are usually just confirmatory and provide little additional information.

Multiple Sclerosis

Although the use of MRI has largely overshadowed the role of evoked potentials in documenting a multiplicity of lesions in patients with suspected MS, electrophysiological tests, which are complementary to MRI, still have an important role in the diagnosis and management of MS patients. For example, Paty et al. (1988) studied a group of 200 patients suspected of having MS but in whom a diagnosis of clinically definite MS could not be made. They found that the MRI showed one or more white matter lesions in 62% of the patients, whereas the VEP was abnormal in 43% of the patients who did not have optic neuritis. It is important to note the VEP was abnormal in 23% of the patients who had normal MRIs. Moreover, when these same patients were evaluated 2 years later, MRI and VEP abnormalities were equally predictive (44%) of those patients who would evolve to clinically definite MS at follow-up (Lee et al., 1991).

In addition, it is widely recognized that white matter hyperintensities can be seen in the MRIs of normal subjects and that these changes become both more severe and more prevalent with advancing age (Hunt et al., 1989; Kozachuk et al., 1990). The prevalence of such MRI abnormalities in young adults is on the order of 20% (Kozachuk et al., 1990). Thus, it is clear that an important role of evoked potential testing in general, and for VEPs in particular, is to establish the significance of any changes seen on MRI, particularly if these changes are few or patients are middle-aged. In patients with a diagnosis of definite MS, based on the history and physical examination, neither MRI nor recording of the VEP is required to establish the diagnosis. However, now that effective therapies are available for MS (IFNB Study Group, 1993), it is important to be certain that a patient has definite MS before initiating a long-term treatment program that is both expensive and potentially toxic. The VEPs, as other evoked potentials studies, have an important role in this context. In addition, these studies have been used by some to observe patients receiving treatment in order to monitor the effectiveness of therapy.

Degenerative Neurological Disorders

The VEP can be abnormal in a variety of degenerative diseases of the nervous system such as Fried-

reich's ataxia, other hereditary ataxias, familial spastic paraplegia, adrenoleukodystrophy (ALD), or hereditary motor and sensory neuropathies (Pedersen and Trojaborg, 1981; Pinto et al., 1988; Honan et al., 1993; Kaplan et al., 1993). The prevalence of abnormalities depends upon the condition. Thus in Friedreich's ataxia and ALD the VEP is abnormal in 80 to 90% of subjects, whereas in hereditary motor and sensory neuropathy it is delayed in only 14% (Honan et al., 1993). However, although the VEP findings document the occurrence and frequency of optic nerve dysfunction in these conditions, they are of little practical value in the diagnosis or management of these conditions.

Hemianopic Visual Field Defects

Hemifield visual stimulation produces a VEP that is generally largest over the hemisphere ipsilateral to the field stimulated. This lateralization has been used to detect hemianopic field defects, with good agreement between the field defect predicted by VEP and by perimetry (Maitland et al., 1982; Vallar et al., 1991; Plant et al., 1992). Hemifield VEP studies, however, sometimes fail to detect a field defect that was clinically evident on perimetry (Maitland et al., 1982; Vallar et al., 1991; Plant et al., 1992). As a result, the recording of hemifield VEPs, which is time-consuming and requires patient cooperation, is of limited clinical value.

Cortical Blindness

Both flash and pattern-reversal VEPs are generally abnormal in patients who are cortically blind (Aldrich et al., 1987). However, the fact that these tests are normal in some subjects who are behaviorally blind from a cortical injury (Bodis-Wollner et al., 1977; Celesia et al., 1980, 1982; Aldrich et al., 1987), indicates that a normal VEP cannot be used as evidence that a patient's blindness is nonorganic.

Prognostic Uses of the VEP

The use of the VEP has been explored as an aid in following patients with certain neurological conditions to predict future clinical outcomes. Some preliminary reports suggest that monitoring of the flash VEP during intraorbital surgery may provide early warning to the surgeon of a potentially poor visual outcome. Thus, Harding et al. (1990) found that all of the patients in whom vision was worse after surgery

(5%) had a prolonged absence (>4 min) of the flash VEP during the operation. These results suggest that VEP monitoring may be useful in preventing such visual outcomes, provided that the surgeon can take corrective action to restore the VEP.

In patients with posttraumatic blindness the VEP may be useful in establishing the prognosis for visual recovery. Thus, in a study of 45 such patients, all patients with normal pattern reversal VEPs had partial or complete visual recovery (Mahapatra and Bhatia, 1989). The large majority of patients (13/15) who had abnormal, but preserved, VEPs made a partial or complete recovery, whereas most patients with absent VEPs (20/25) had no recovery and none made a complete recovery.

In a study comparing VEP to computed tomography (CT) in patients with chromophobe adenomas, Holder and Bullock (1989) found that the VEP more accurately predicted the asymmetry of the tumor than did CT, and it provided important preoperative information. This study, however, is inconclusive because the important clinical question using current technology is whether the VEP is superior to MRI rather than CT in this regard.

The VEP has also been used to monitor patients with hepatic encephalopathy in the hope of predicting future decompensation, but the results have been disappointing (Sandford and Saul, 1988; Johansson et al., 1989).

Dementia

There are several reports of a dissociation between the VEP findings elicited by flash and pattern-reversal stimuli in patients with senile dementia of the Alzheimer's type (SDAT) or in normal subjects following the administration of anticholinergic drugs (Bajalan et al., 1986; Ray et al., 1991; Rizzo et al., 1992). These studies have suggested that the flash VEP is characteristically abnormal in SDAT whereas the pattern-reversal VEP is normal. If corroborated, such a finding might assist in distinguishing SDAT from other dementing disorders during life. This would be useful because, with use of current methods, the antemortem accuracy of the diagnosis is only about 80%. Before the VEP is used in this context, however, detailed pathological studies relating VEP changes to pathological findings are necessary, and the specificity of the VEP findings in SDAT relative to other dementing disorders needs to be established.

CONCLUSIONS

Although the clinical role of VEPs has changed over the years since it was introduced, they continue to be important in the diagnosis and management of patients with neurological diseases. They provide an objective and reproducible measure of visual function and are indicated whenever such an assessment of function is needed to help solve a clinical problem. Computer technology has produced machines of even greater speed and capacity and, as a result, the use of more specific visual stimuli in specific visual paradigms may allow even more specific applications of VEP recordings.

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