Principles and Practice of Clinical Electrophysiology of Vision

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4

History of Visual Evoked Cortical Testing

Graham F.A. Harding

Human visual evoked responses (VERs) have been known almost since the origin of human electroencephalography (EEG). In 1934 Adrian and Matthews[1] demonstrated that regularly repeated flashes of light elicited electrical responses from surface electrodes placed over the occipital cortex. By utilizing a sectored disk in front of a car headlight they demonstrated that photic following took place at the same rate as the frequency of the periodically repeated flashes of light. The rates of stimulation that they used varied between 8 and 12 per second, and their classic paper contains clear illustrations of the responses from Adrian's brain. These results were the origin of what is now known as the "steady-state evoked potential."

Early reports of responses to single flashes of light began with Monnier[36] who recorded both the electroretinogram (ERG) and cortical response from the scalp and stated that the most consistent component of the cortical response was a slow surface-positive monophasic potential occurring between 90 and 120 ms. He suggested that earlier components of the cortical response were much more difficult to record but consisted of a diphasic potential, initially positive, with a latency of approximately 40 ms. Cobb[8] following the development of Dawson's superimposition technique, produced averaged responses to 50 flashes of light of high intensity involving the full visual field. The initial components of the evoked potential appeared at times to vary between 35 and 60 ms in different individuals, but in a later study[10] the evoked potential was identified as a small positive deflection with a peak latency around 26 ms followed by a negative one at 45 ms and a larger positive wave around 79 ms. In a further study in 1952 Monnier[38] recorded cortical responses by using bipolar derivations around the occiput. The earliest visual evoked potential (VEP) component consisted of a small occipito-positive deflection with a peak latency of 35 ms. The highest amplitude and most consistent component occurred between 95 and 115 ms, being a positive potential, presumably P2 (see Fig 4–1). Monnier introduced the concept of retinocortical time by simultaneously recording the ERG and determining retinal time by the latency of the b-wave. The latency to the peak of the first component of the cortical response was termed *cortical time*, and the retinocortical time was derived from subtracting the retinal time from the cortical time. In 1956 Calvet et al.[4] demonstrated an initial positive component around this 35-ms peak latency. Monnier in a later paper[37] also reported a positive deflection around 37.5 ms. There is little doubt that these concepts of retinocortical time were a gross oversimplification. There are great difficulties in identifying initial responses as distinct from gross responses by large groups of neurons.

Cobb and Dawson[9] studied the occipital potentials evoked by bright flashes of light in 11 adult subjects. They averaged between 55 and 220 flashes and demonstrated that the earliest component of the VEP had a latency of 20 to 25 ms with an average amplitude of between 1 and 1.5 μV. The following negative deflection at 45 ms was slightly larger, and this component they found to be enhanced when the subject paid attention to the stimulus. It was Ciganek[7] who produced the first morphological description of the human VEP to light flashes and the results obtained on 75 subjects; his classic illustration began the principle of labeling the components, and in addition the components were divided between early or primary components (waves 0 to III)

and late components (waves IV to VII). The first component was positive at 28.6 ms, the second wave negative at 53 ms, the third wave positive at 73 ms, the fourth wave negative at 94 ms, the fifth wave positive at 114 ms, with a later positive wave around 134 ms. Ciganek also described an after-discharge that was sometimes obtained and appeared to be related to the alpha rhythm of the EEG.[6] This concept of labeling was quickly taken up by Gastaut and Regis,[20] but unfortunately the labeling systems were different. They described a typical response that was similar in form to that of Ciganek; in addition, they compared the normal VEP reported by a number of previous investigators.[3, 13, 43, 49, 51] They pointed out that although there was great variation in the presence and shape of many of the components the major positive P2 component was almost invariably present between 100- and 150-ms latency. The components they themselves identified consisted of wave 1, positive at 25 ms; wave 2, negative at 40 ms; wave 3, positive at 60 ms; and wave 4, negative at 80 ms. They found there was a good deal of variation between individuals in both latency and amplitude of these components. Wave 5 was by far the most constant and significant wave of the VEP, the amplitude appeared to vary between 30 and 50 μV, and it was usually monophasic, peaking at around 130 ms. On some occasions they found that

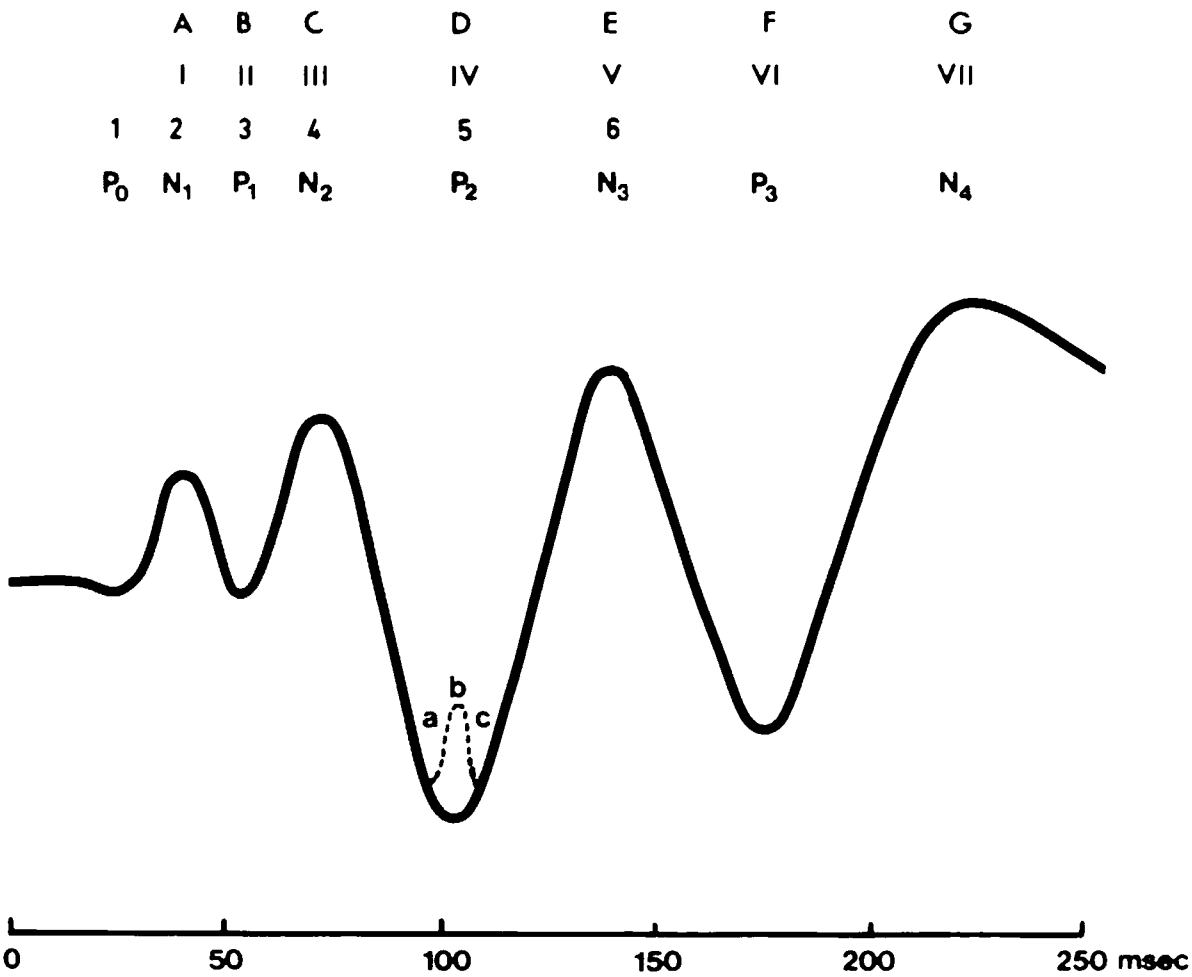

FIG 4–1.
The figure illustrates the stylized VEP to flash stimulation in normal adults. The major positive component, often referred to as P2, can be seen at approximately at 105 ms. In this illustration positive is indicated downward and negative upward. Various systems of nomenclature have been used to identify the components of the VEP. The *top row* of alphabetic nomenclature is that of Dustman and Beck (1969), the *second row* of Roman numerals is that of Ciganek (1961), the *third row* is that of Gastaut and Regis (1967), and the *lowest row* is that of Harding (1974). It is this latter nomenclature that is now quite commonly used in describing the flash VEP. It should be noticed that the P2 component (wave 5 of Gastaut and Regis) can sometimes become a triphasic component showing peaks at both A and C.

this wave was biphasic, with an early peak at 120 ms, and a later positive peak around 180 ms.

Only 20% of the subjects tested demonstrated a complete VEP from wave 1 to wave 4, usually waves 1, 2, or 3 were missing for many of the subjects. For each individual there was little variability in terms of latency from one recording session to the next; indeed, for wave 5 the variation in latency was only ±2.5 ms. Between individuals, however, this wave varied by ±30 ms. They also showed that the separate components of wave 5 could be affected by opening and closing the eyes and by dark adaptation and suggested that the photopic system, that is the fovea, was associated with the early positive peak of wave 5 and the later positive peak associated with the scotopic system.

Over the ensuing years the complexity of labeling systems grew, and it is still not entirely resolved. However, most systems now identify the component as negative or positive and use either a mean latency for the wave as a subscript or alternatively a sequential numbering system. An example of labeling of a flash VEP is given in Figure 4–1.

The early components of the VEP that were frequently mentioned by the pioneer workers have over subsequent years been the subject of much controversy. Some authors, for example, Allison et al., [2] proposed that many of the early components reflect the ERG in view of its high amplitude and its complete domination of the anterior portions of the scalp.[42] However, other authors do not accept this hypothesis;[52] indeed, some authors such as Van Hasselt[50] suggest that even early components around 10-ms latency were arising from the optic nerve. Vaughan and Gross[53] suggested that the early wavelets in the VEP reflected geniculocalcarine input to the striate visual cortex. Corletto et al.,[14] undertaking depth recordings of the VEP before an ablation of the occipital poles in humans, noted persistence of initial components having peak latencies earlier than 45 ms. Spire and Hosobuchi,[47] using depth recordings, located a flash evoked potential of 22-ms peak latency in an area just anterior to the lateral geniculate body.

In a series of studies Harding and coworkers[24–26, 42] identified the components of what they termed the visual evoked subcortical potential (VESP), which consists of a positive around 21 ms, a negative at 28 ms, and a positive at 35-ms latency. In a series of studies[24–26, 42] they demonstrated that the VESP could be elicited by both flash and pattern-reversal stimulation. In patients who had suffered direct optic nerve trauma in whom the ERG was still present, the VESP was absent when that eye was stimulated. This indicated, therefore, that the components were independent of the ERG. Equally, by a combination of binocular and monocular stimulation it could be demonstrated that these potentials were in fact arising postchiasmally. By using luminance-matched red-green color checkerboards it was possible to elicit clear responses that were maximal in response to checkerboards in which each element subtended 2 degrees. When black and white checkerboards were used, the responses were maximal in response to 12 minutes of visual angle checkerboard and showed clear tuning. These findings would be entirely consistent with the potential arising in the parvocellular layers of the lateral geniculate body.

The first study of the flash VEP across the life span was carried out by Dustman and Beck.[15] They found that in the first 6 years of life there was a steady increase in the amplitude of the response followed by a reduction until around the age of 15 years, after which the amplitude of the response was not significantly altered until the 60s or 70s. In older subjects there is an increase in the amplitude of early components and a decrease in the amplitude of later components.

Neonatal flash VEPs were first recorded in full-term infants by Ellingson.[18] However, in 1960[17] he published a comprehensive survey of the VEPs of both full-term and preterm babies and showed that in full-term infants the VEP was of relatively simple morphology consisting of an initial brief positive wave around 180 ms followed by a negative wave of fairly rounded form. However, the preterm infants prior to 35 weeks' gestational age showed only a broad negative deflection that had a longer peak latency than those seen in full-term infants. The initial positive wave appeared to develop in babies around 35 weeks' postmenstrual age (PMA), although the earliest it was seen was around 32 weeks. Flash VEPs have been recorded from human infants of 24 weeks' PMA.[5, 48]

The inherent variability between subjects of the flash VEP and its crudity in representing a response to a gross change in luminance led to the development of pattern stimulation. Early pattern stimulation utilized the flashing of a patterned visual field. This technique has since become known as the flashed-on pattern, and it was by utilizing this technique that the early studies of the response to the commonly used black and white checkerboards or gratings were first investigated.[44] Such responses are of course a mixture of both luminance and con-

tour as well as contrast and show a much closer correlation between the amplitude of the evoked potential and visual acuity.[31] Jeffreys[34] attempted to identify the pattern component of the resulting evoked potential by subtracting the luminance response from the flashed-on pattern response. It has also been shown that such patterns are of great use in studying abnormal evoked potentials such as those found in epilepsy.[33]

The type of reversing checkerboard pattern now commonly used owes its origin to the work of Spekreijse[45] and Cobb et al.[11] By utilizing these techniques it became possible to identify both the average response to a reversing checkerboard pattern as well as the response to the onset and offset of patterns. The reversal response is of relatively simple outline and consists of a negative peak around 75 ms, a positive component at 100 ms, and a later negative peak at 145 ms. These components are usually known by their polarity and their latency, the positive component therefore becoming the P100 component. All studies have shown that these responses have little variability within a subject and remarkably small variability between normal healthy subjects. This lack of variability has encouraged the use of this technique for studies of stimulus variables and subjective parameters in normal individuals and, in addition, in the clinical development of evoked potential testing. Indeed it was the paper of Halliday et al.[22] that provided the spur for many of the evoked potential laboratories that have since developed.

The response to pattern onset-offset is more complex, and certainly there are separate responses to both the onset and offset of patterns.[19] To obtain these separate responses the onset and offset of the stimulus have to be more than 100 ms apart, and under these circumstances it can be seen that the offset response is very similar to the pattern-reversal response. The onset response consists of three components: a positive response around 75 ms (C1), a negative response at 100 ms (C2), and a positive response around 150 ms (C3).[35, 46] These components are only present when the lower half of the field is stimulated. The C2 component appears to be markedly affected by the contour or sharpness of the pattern and is most sensitive to defocusing. The C1 component appears to be related to the contrast present in the pattern.

During the years since their first description all the VEPs have been shown to be dependent to a greater or lesser degree on the integrity of the visual pathway and the normal functioning of the visual cortex. Lesions affecting the optic nerves may affect all forms of evoked potentials, although certainly demyelinating diseases are shown to affect the pattern-reversal response and the pattern onset-offset response far more than the flash response.[28] Gross lesions such as those seen in optic nerve trauma affect all the potentials, and it is under these circumstances and those of major eye injuries that the flash evoked potential comes into its own as an electrodiagnostic tool.[29] With abnormalities affecting the visual cortex the various types of evoked potentials may be differentially affected. Certainly, if the lesion involves the primary visual cortex, there is little doubt that the pattern-reversal P100 response and the C1 component of the pattern-onset response are clearly affected. Surprisingly for extra striate abnormalities, particularly those affecting the association areas, the flash response is often that most affected.[28]

Needless to say, many of the early clinical studies involved the flash technique. Ebe et al.[16] carried out a study utilizing both the ERG and the VEP in a variety of patients including those with retinal disorders, optic atrophy, as well as cataracts. They showed that patients with macular losses had little change in either the ERG or the VEP whereas patients with retinitis pigmentosa showed reductions in both. In patients with optic atrophy the evoked potential was undetectable, and the ERG was normal although the patients were not blind. Vaughan and Katzman[54] confirmed that a normal ERG with an absence of the VER was indicative of optic nerve disease. Gerin et al.[21] showed that in patients with optic nerve lesions the latency of the first peak of the evoked potential was delayed; this was confirmed by Richey et al.[41]

Early attempts to relate the asymmetry of the VEP recorded by at least two channels, one over each cerebral hemisphere, to hemianopic defects began with Cohn.[12] He suggested that there is a prominent amplitude asymmetry in the evoked response, and this was confirmed by Vaughan and Katzman.[54] Many studies followed, including those of Kooi et al.,[36] Jacobson et al.,[32] Harding et al.,[27] and Oosterhuis et al.[40] Such findings of course correlate with subjective sensation in that the patient is complaining of a hemianopic defect. There is little doubt that in other areas the relationship between flash response and sensation is much less clear. The development of pattern reversal and, even more, pattern onset-offset have allowed the precise interrelationship between evoked potentials and sensation to be developed. Particularly with pattern onset-offset there is a freedom that allows nongeometric patterns to be investigated, and therefore patterns that carry

inherent meaning can also be studied, although it must be admitted that such studies are relatively rare.

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