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SENSORY EVOKED POTENTIALS IN CLINICAL DISORDERS OF THE NERVOUS SYSTEM

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A. Starr
Department of Neurology, University of California Irvine Medical Center, Orange, California 92668

INTRODUCTION

The diagnostic tools presently used by clinicians in the field of neuroscience provide useful information about the structure of the nervous system, but fall short with respect to providing insights into function. For this, the clinician must still rely on history, physical examination, and the patient's own description of the experience of his disorder. The search for relatively noninvasive, simple tests of brain function has stimulated the recent development of sensory evoked potentials recorded from the scalp as low-risk, clinically applicable procedures capable of providing new and objective information about a variety of nervous system functions. In this review I summarize the various applications of auditory, visual, and somatosensory evoked potentials to the study of clinical neurological disorders in man, beginning with a brief description of the stimuli employed, normal patterns of evoked potentials, stimulus and subject variables that influence these potentials, and their probable neural generators.

Clinical applications are analyzed with reference to each sensory system rather than according to disease states. Table 1 contains a listing of the various types of auditory, visual, and somatosensory evoked potentials based on their presumed sites of origin from along the sensory pathway. The evoked potential wave forms are included in the figures and the technical details of their recording are in Table 2.

Sensory evoked potentials were among the earliest measures used to study the functions of the brain (Lindsley 1969, Davis 1976, Bergamini & Bergamasco 1967). While techniques for quantifying intracellular and single neuronal activity now predominate in the study of other animals, interest in evoked potentials persists particularly for the analysis of human brain functions. Moreover, the development

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Table 1 Sensory evoked potentials in man: analysis of evoked potential tests and their probable generators in relation to the afferent pathway

Sensory pathway components	Auditory		Visual		Somatosensory	
	Test	Generator	Test	Generator	Test	Generator
Receptor	Electrocochleogram auditory far field potentials	Hair cells	Electroretinogram	Mostly rod function	Not available	—
Primary afferent neuron	Electrocochleogram	VIII nerve	Not available	—	Whole nerve action action potentials	Peripheral nerve–large myelinated fibers
	Auditory nerve and brainstem potentials					
Ascending path	Auditory brainstem potentials	VIII nerve through inferior colliculus	Not available	—	Spinal evoked potentials	Dorsal column
					Far-field potentials	Medial lemniscus Diencephalon Cerebellum
Primary sensory cortex	Middle latency potentials	Unknown	Visual evoked potentials	Primary visual cortex	Somatosensory evoked potentials	Specific sensory-motor cortex
Nonspecific cortex	Long-latency auditory potentials Sustained potentials	Unknown	Visual evoked potentials	Unknown	Long-latency somatosensory potential	Unknown

of "averaging" techniques for extracting low-level stimulus-related signals from the background electroencephalogram and other biological potentials now provides a reliable basis for the quantitative study of evoked potentials. Some of the clinical reasons for investigating sensory evoked potentials in humans are:

1. Evoked potentials can provide quantitative and objective measures of sensory function (Sokol 1976, Picton et al 1977). The establishment of reliable correlations in normal subjects between attributes of the physical stimulus (i.e. intensity, frequency, wavelength), sensory perception, (i.e. loudness, pitch, hue, etc), and the latency or amplitude of the various components of evoked brain potentials permits the application of these measures to individuals who are unable to accurately describe their sensory experiences, such as infants, retarded individuals, some patients with neurological disorders, or even normal but anxious subjects. The information obtained about such an individual's sensory function may provide important clinical information ("Does the child hear?" "Is there a problem of visual acuity?"), public health data (the sensory effect of exposure to toxins), or it may be of medicolegal value when an objective definition of disordered function is essential.

2. Sensory evoked potentials are relevant in clinical neurology as an objective test of brain function (Regan 1972). Changes in these potentials may localize the lesion to a particular site along the afferent pathway from receptor to cortex. The analysis depends on the presence of a precise relationship between particular anatomical structures and components of the evoked potential wave form. This is an expanding area of research interest in which information from both clinical-pathological correlations in humans and experimental studies in animals provides the framework for accurate clinical application of evoked potential measures. Knowledge of the generators of the various sensory evoked potentials would be of immense help in defining the locus of lesions producing sensory deficits (i.e. numbness), coma (Greenberg et al 1977), or dementia (Visser et al 1976).

3. Sensory evoked potentials can provide insight into normal physiological processes related to maturation (Hecox 1975) and aging (Dustman & Beck 1969). The finding that psychological factors such as "attention," "habituation," and "significance" can influence sensory evoked potentials (Picton et al 1976), has been utilized by several investigators to gain insight into affective and thought disorders in man (Shagass 1972, Callaway 1977) and, more recently, as an objective measure of general brain functions (John et al 1977).

TECHNICAL CONSIDERATIONS

There are many sources of interference that can obscure the detection of low-amplitude sensory evoked potentials. These include electrical impulses from other monitoring devices on the patient or patient-generated events such as muscle potentials, electrocardiogram, or eye movements. Special computer circuits that reject samples containing the artifact from the averaging process or filter circuits that attenuate unwanted potentials have been utilized to reduce this problem.

Once an average evoked potential is obtained, several strategies are employed to assess both its reliability and relation to the sensory stimulus. These include (*a*)

Table 2 Sensory evoked potentials in man: recording parameters

	Electrode placement[a]	Band pass (kHz) (3 dB down points)	Stimulus	Time base (msec)	Trials (*n*)	Amplitude (μV)	Test name
Auditory							
Receptor	I Mastoid-reference	Variable	Tones	Up to 10	2,000	<1.0	Cochlear microphonic
Afferent	I Mastoid-reference	0.1–10.0	Clicks	3	2,000	<1.0	Auditory nerve and brainstem potentials
Ascending	Vertex-I mastoid	0.1–3.0	Click	10	2,000	<1.0	Auditory brainstem potentials
	Vertex-C mastoid	0.1–3.0	Tone	20	2,000	<1.0	Frequency-following potentials
Specific cortex	Vertex-mastoid	0.01–0.3	Tone/Click	60	100	<2.0	Middle latency potentials
Nonspecific cortex	Vertex-mastoid	0.001–0.1	Tone	500	50	<10.0	Long latency potentials
Visual							
Receptor	Cornea-reference or lower canthus–reference	0.001–1.0	Light flash	100	1	<500.0	Electroretinogram
		0.001–1.0	Light flash	100	25	<50.0	Electroretinogram
Afferent	—	—	Not available	—	—	—	—

Table 2 *(Continued)*

Ascending	—	—	Not available	—	—	—	—
Specific cortex	O_z–vertex	0.001–0.1	Light flash or pattern reversal	200	50	<20.0	Visual evoked potentials
Nonspecific cortex	O_z–vertex	0.001–0.1	Light flash or pattern reversal	500	50	<20.0	Visual evoked potentials
Somatosensory							
Receptor	—	—	Not available	—	—	—	—
Afferent	Over peripheral nerve	0.1–1.0	Shock	20	100	<5.0	Nerve action potential
Ascending	Over spinal column	0.1–3.0	Shock	20	8,000	<1.0	Spinal cord potentials
	Vertex-reference	0.1–3.0	Shock	20	2,000	<1.0	Far-field potentials
Specific cortex	Sensory cortex contralateral to stimulus (C3 or C4)-reference	0.01–1.0	Shock	75	100	<10.0	Somatosensory evoked potentials
Nonspecific cortex	Vertex-reference	0.001–0.1	Shock	500	100	<10.0	Somatosensory evoked potential

[a] I = Ipsilateral to acoustic stimulus; C = contralateral to acoustic stimulus.

reproducibility of the potential wave forms in duplicate averages, (*b*) determining the absence of the potential wave forms by alternating the sign of the averaging process between addition and subtraction, and (*c*) the loss of evoked potential wave form when averages are performed in the absence of the sensory stimulus.

The sensory signals must be carefully calibrated, and the patient's level of arousal and clinical neurological deficit defined. Finally, if sensory evoked potentials are to be useful in a clinical environment, the procedures should be (*a*) rapid, (*b*) simple to perform, and (*c*) relatively inexpensive.

Somatosensory Evoked Potentials

STIMULUS Somatosensory evoked potentials are typically elicited by electrical stimulation of peripheral nerve trunks. This technique provides a precise onset for averaging purposes, but the number and types of nerve fibers activated are difficult to quantify. A major drawback of electrical stimulation of peripheral nerves is that it can be extremely uncomfortable. There is need for the development of precisely controlled natural forms of stimulation for the clinical evaluation of somatosensory functions.

NORMAL EVOKED POTENTIALS

Afferent: peripheral nerve The potentials ascending in the peripheral nerve can be recorded from skin electrodes overlying the nerve or from needle electrodes inserted close to the nerve trunk (Figure 1, *primary afferent, neuron*). Their latency can be used to calculate the conduction velocity of the ascending somatosensory impulses. The presence of abnormally slow conduction velocities is evidence of a peripheral nerve disorder and can by itself be associated with alterations in somatosensory evoked potentials from central structures (Desmedt & Noel 1973). The measurement of peripheral-nerve conduction velocity is a prerequisite for evaluating abnormalities of somatosensory evoked potentials in the clinical setting.

Ascending pathway: spinal cord and brainstem The shortest latency somatosensory evoked potentials originating in the central nervous system can be detected from the skin surface overlying the spinal cord (Cracco 1973). Their amplitudes are less than 1 μV, so that as many as 8000 stimulus trials are needed to insure a satisfactory average. The ascent of the evoked potential up the spinal cord can be monitored at several points to provide a measure of spinal cord conduction velocity. An indirect method of estimating spinal cord conduction has been suggested by Dorfman (1977), using the difference in latency of scalp-derived potentials from stimulating peripheral nerves in the arm and leg. More recently, far-field recordings of activity in somatosensory pathways of the spinal cord and brainstem have been made with electrodes located on both the scalp and a distant reference site such as the hand or knee (Cracco & Cracco 1976). The potentials recorded in this manner from stimulation of the median nerve at the wrist consist of a sequence of components of less than 1.0 μV in amplitude with peak latencies of 9, 11, 14, and 19 msec (Figure 1, *ascending path*). The neural origins of the components are still uncertain, but there is evidence that they derive from activity in peripheral nerve fibers and

ascending brainstem, diencephalic, and cerebellar somatosensory pathways, respectively (Wiederholt & Iragui-Madoz 1977).

Thalamus and specific cortex The somatosensory evoked potentials recorded from the scalp that occur between 15 and 65 msec after stimulation of a peripheral nerve in the upper extremity appear to derive from activation of specific sensory areas within the cerebral hemispheres (Figure 1, *sensory cortex*). Their amplitudes are maximal from scalp regions overlying the primary sensory-motor cortex *contralateral* to the limb stimulated (Goff et al 1977). Moreover, the potentials evoked by stimulating the peripheral nerves of the legs are maximal medial to those sites where potentials evoked by upper-limb stimulation occur (Desmedt 1971). These somatosensory evoked potentials can be up to 10 μV in amplitude and require only 60–120 stimulus repetitions to elicit clear averages. The potentials consist of a sequence of positive and negative components that have been variously designated. A nomencla-

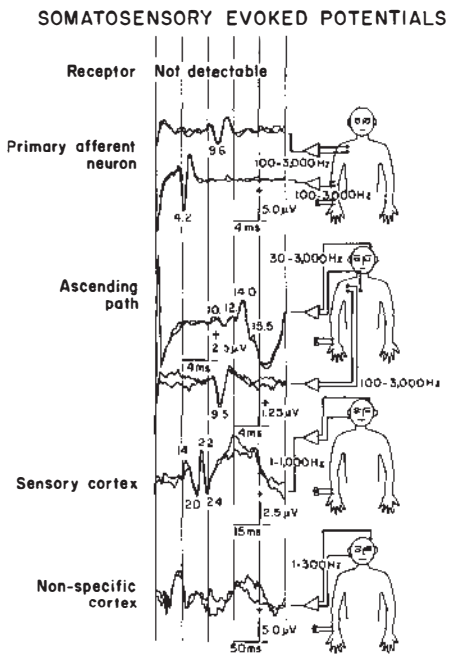

Figure 1 Somatosensory potentials evoked by electrical stimulation of the median nerve at the wrist. The intensity of the stimulus was adjusted to be just below that necessary to elicit a contraction of the thenar muscles. The evoked potentials are designated by their presumed generators listed on the left, i.e. "receptor, primary afferent neuron, ascending path, sensory cortex, and nonspecific cortex." The recording sites for these potentials are depicted on the figures to the right with the particular amplifier bandpass settings in Hz. The numbers inscribed above the component peaks of the evoked potential wave forms refer to their latency in msec. Note that the time base and amplitude calibrations vary.

ture has recently been proposed that signifies a component's polarity (positive, P, and negative, N) and latency in msec (i.e. P15, N100, etc). Stimulation of the median nerve at the wrist elicits a P15, N20, P28, or a dual positive complex P25 and P30, N35 and P45 (Giblin 1964, Liberson 1966, Desmedt 1971). Stimulation of the posterior tibial nerve at the ankle will elicit a similar set of potentials, though they are somewhat delayed because of the additional length of the ascending pathway. The initial positive component is often difficult to detect with stimulation of the lower extremity (Dorfman 1977). The new nomenclature may prove inadequate, since latency is affected by the location of the stimulating electrodes along the length of a peripheral nerve.

Nonspecific cortex Somatosensory evoked potentials occurring after 60 msec are distributed over both hemispheres (Figure 1, *nonspecific cortex*). The components from 65 to 100 msec appear to be a mixture of both muscular and neural activities, whereas the components from 140 to 500 msec appear to be of neural origin (Goff et al 1977).

EVOKED POTENTIALS, STIMULUS AND SUBJECT VARIABLES Stimulus strength has minimal influence on the latency of somatosensory evoked potentials. Moreover, maximal response amplitudes are achieved with current strengths only slightly above threshold (Uttal & Cook 1964). Thus, the precise quantification of suprathreshold electrical stimulation of peripheral nerves may not be a significant issue in clinical testing. Recovery functions of somatosensory potentials from stimulation of the median nerve require 100–200 msec for full return of the amplitude of the specific cortical components (latency $<$ 65 msec), whereas the longer-latency components may require up to 3000 msec for recovery (Namerow 1970, Allison 1962).

Prolonged stimulation may produce a decrement in amplitude of the N40 component (Giblin 1964) that could be pertinent in situations requiring prolonged testing, such as evoked-potential monitoring during surgical procedures.

Aspects of the subject's waking state can also influence the evoked potential. Thus sleep can affect the amplitude of the long-latency components ($>$ 100 msec), whereas the shortest-latency N14 response is little influenced by sleep or even deep anesthesia (Goff et al 1966, Desmedt & Manil 1970). Muscle potentials from the scalp contribute to some of the components, particularly between 65 and 100 msec following the stimulus. Their amplitude is largest over the forehead, neck, and temporalis muscles (Goff et al 1977). Perceptual factors such as attention to the stimulus can produce enhancement of the N120, P190, and P300 components (Desmedt 1971). The latency of the initial negative component to median nerve stimulation is slightly less in the newborn than in adults. However, considering the reduced length of the somatosensory pathways in infants, conduction velocity during childhood is actually quite slow, and adult values are achieved only at about 8 years of age (Desmedt, et al 1976). Senescence has little effect on the latency of the potentials (Luders 1970). Among other variables, movement of the stimulated limb has been reported to be associated with a decrease in evoked-potential amplitudes. A similar attenuation of evoked potentials can occur during the simultaneous appli-

cation of natural cutaneous stimulation to the skin surface innervated by the stimulated nerve. The mechanism of attenuation probably involves the "masking" of one sensory stimulus by another (Giblin 1964).

NEURAL GENERATORS OF THE EVOKED-POTENTIAL COMPONENTS The fiber pathways that are essential for detecting somatosensory potentials from the scalp are in the dorsal column and medial lemniscus. Individuals with anterolateral spinal-cord tract lesions that produce isolated loss of pain and temperature functions have normal somatosensory evoked potentials, whereas individuals with dorsal-column spinal-cord lesions that produce loss of vibration and position sense have altered somatosensory evoked potentials (Halliday & Wakefield 1963, Namerow 1969, Giblin 1964). There are some clear correlations between somatosensory evoked potentials recorded from the scalp and the cortical surface. Broughton (1969) and, more recently, Allison et al (1977) showed that the P20 and N30 components recorded anterior to the central sulcus become of opposite polarity posterior to the sulcus. These results are compatible with a cortical dipole source in the precentral sulcus oriented in a rostral-caudal direction. The P25 component that can be recorded from the scalp in some subjects appears to be generated at the central sulcus by a dipole oriented in an orthogonal direction, which may account for the variability of detecting this component in different individuals. The earlier positive component at 15 msec (P15), detected in scalp recording, is not present in recording from the cortical surface, which suggests its origin in subcortical structures (Broughton 1969).

CLINICAL UTILITY OF SOMATOSENSORY EVOKED POTENTIALS

Peripheral nerve function Measurement of the change in latency of the initial scalp-derived negative component from stimulation at various points along a peripheral nerve can provide a measure of the nerve's conduction velocity (Desmedt 1971). This technique is particularly applicable to individuals with advanced peripheral neuropathies in whom compound nerve-action potentials may be difficult to detect.

Spinal cord function The techniques of recording ascending activity in the spinal cord from surface electrodes located over the spinal column has been used by Cracco (1975) to localize the level of spinal cord pathology in infants. The technique may also be used to define somatosensory functions in infants.

The presence of potentials that can be recorded from the scalp following stimulation of the nerves in the legs has been utilized by Perot (1972) as a rapid and objective clinical measure of spinal cord function in individuals rendered unconscious or uncooperative from trauma. Normal somatosensory evoked potentials indicate integrity of dorsal column function, whereas their absence, prolonged latency, or diminished amplitude alerts the clinician to the presence of a spinal cord lesion. This technique has also been utilized to monitor spinal cord function in the operating room in individuals undergoing laminectomy for removal of spinal cord tumors or in individuals undergoing correction of spinal column curvature (Allen & Starr 1977). An awareness of changes in spinal cord function may assist the surgeon in preventing some of the undesirable side effects of operative manipulation

of the spinal cord. The effects of anesthesia, fluctuations in blood pressure, and manipulation of the spinal cord, dura, and roots on the evoked potentials need to be defined in greater detail before the utility of this technique can be fully realized.

Slowed conduction in the somatosensory pathways of the spinal cord and the brainstem Partial lesions of the somatosensory pathway, such as those occurring in demyelinating disease, can be associated with a prolongation of latency and decrease in amplitude of the potentials recorded at the scalp. The evoked potentials recorded from patients with the clinical diagnosis of multiple sclerosis may even be delayed when sensation is normal (Namerow 1968, Desmedt & Noel 1973). Thus, as is the case for visual and auditory brainstem evoked potentials (see the appropriate sections in this article), somatosensory evoked potentials can be used to define clinically inapparent lesions of the somatosensory pathways in individuals suspected of having multiple sclerosis. Variations in the methods of somatosensory testing, including recovery to paired stimuli or the effects of differing rates of stimulation on the amplitude of the potentials, may enhance the detection of lesions of the ascending somatosensory pathways (Sclabassi et al 1974). Knowledge of the state of peripheral nerve function must be known, since prolonged latency of evoked potentials also occurs with peripheral nerve disorders. Furthermore, a prolonged latency of evoked potential in the absence of peripheral nerve lesions cannot be equated with a specific disease such as multiple sclerosis, since other pathological processes such as vascular lesions of the brainstem (Noel & Desmedt 1975) and infiltrating tumors of the ascending pathway will also have the same effect.

Disorders in the somatosensory pathways of the cerebral hemispheres The effects of cerebral lesions on evoked potentials depend on (*a*) the extent and type of sensory loss, (*b*) the time interval between the lesion and evoked potential testing, and (*c*) the locus of the lesion (Giblin 1964, Halliday 1967b). Lesions of the cerebral hemisphere that result in a loss of sensation (touch, pin, position sense) are associated with a loss of evoked potentials from both the affected and normal hemispheres if the stimulus is applied to the limbs with decreased sensibility (Williamson et al 1970, Liberson 1966, Green & Hamilton 1976). In contrast, stimulation of the unaffected limbs results in the bilateral appearance of normal evoked potentials (Tsumoto et al 1973). Thus, the primary somatosensory pathway within the cerebral hemisphere must be intact for the bilateral representation of evoked potentials. Giblin (1964) described a group of patients in whom sensory loss was particularly evident during simultaneous bilateral sensory testing (a phenomenon called "extinction"). These patients also failed to detect light touch during unilateral stimulation of the affected limb, though somatosensory evoked potentials were normal. Finally, there are patients with normal sensation in whom the amplitude of the evoked potentials is significantly altered. They may be increased (Halliday 1967a, Giblin 1964, Tsumoto et al 1973), decreased (Giblin 1964), or even have additional components not usually encountered (Giblin 1964).

Disorders of evoked potentials in epilepsy The amplitude of somatosensory evoked potentials may be up to tenfold larger in myoclonic epilepsy. Even the earliest

latency components are thus enhanced (N20, P30), whereas their latencies are unaffected (Dawson 1947, Halliday 1967a). Halliday noted that the evoked potentials were particularly enhanced if the patients were actively experiencing myoclonic jerks at the time of the tests.

Functional sensory loss Normal somatosensory evoked potentials have been recorded in patients with a sensory defect due to hypnosis (Halliday & Mason 1964) and in patients suspected of having hysterical hemianesthesia.

Visual Evoked Potentials

STIMULUS A wide variety of stimuli have been employed to study human visual evoked potentials, including diffuse, patterned, and colored lights. Factors such as the rate of presentation, the portion of the visual field stimulated, and monocular vs binocular presentation are significant variables (Regan 1975). The various types of stimuli and methods of analysis have particular applications. For instance, the onset of an infrequently presented signal evokes a "transient" set of potentials in which one can measure the latency and amplitudes of the various components as indices of visual function. In contrast, "steady-state" evoked potentials can be detected by analyzing only those components that have spectral energies at the fundamental or a harmonic of the stimulus rate. If Fourier analysis is used, these potentials can be detected at extremely low levels ($<1.0\ \mu V$) and both the phase and amplitude of the components can be precisely specified. A significant advantage of "steady-state" potentials for clinical testing is that they can be defined after a brief period of stimulation.

NORMAL EVOKED POTENTIALS

Receptor: the retina Retinal potentials or the electroretinogram (ERG) evoked by diffuse light flash can be detected, without averaging, by electrodes placed directly on the cornea or sclera. These same retinal potentials can also be recorded by electrodes placed on the skin surface close to the eye, using a computer to average the low-amplitude potentials from background activity (Figure 2, *receptor*). The reader is referred to standard texts for details of the ERG. The assessment of retinal function by the ERG has been suggested as a necessary prerequisite for evaluating abnormalities of visual evoked potentials in clinical disorders. However, the relationship between the two types of potentials is complex since the ERG primarily reflects
visual evoked potentials seem to reflect
central connections.

Ascending pathway, optic nerve, and lateral geniculate Efforts at recording the activity of optic nerve and lateral geniculate nucleus by far-field recording techniques analogous to those used in recording activity of ascending pathways in the somatosensory and auditory systems have not been successful. The high amplitude and prolonged time course of the retinal potentials are probably the major factors contributing to this failure.

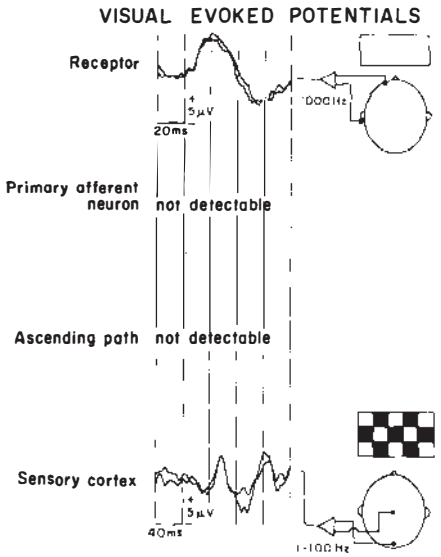

Figure 2 Visual potentials evoked by light flash (upper trace) or pattern reversal stimulation (lower trace). The format for this figure is the same as in Figure 1.

Specific cortex Scalp-derived visual evoked potentials (Allison et al 1977) to brief diffuse light flashes that can be distinguished from retinal potentials occur between 40 and 145 msec following stimulus onset and are best recorded over the occipital area. The latency, amplitude, and even occurrence of the components have not been consistently described in the literature. Factors such as stimulus luminance (DeVoe et al 1968), level of arousal (Oosterhuis et al 1969), and electrode location (Biersdorf & Nakamora 1971) influence the form and latency of the flash
are probably responsible for the variations reported in the literature.

In contrast, pattern evoked potentials are reliable both in form and latency between subjects (Harter & White 1968). A checkerboard stimulus in which the black and white squares reverse position at a rate of 2 sec^{-1} evokes a prominent positive potential over the occipital region with a latency of about 100 msec. The location of the recording electrode and stimulus luminance (over two log units) have only minimal effects on the latency of the potential evoked by the full-field reversing checkerboard signal (Halliday et al 1970). However, changes in the location of the pattern within the visual field do affect the distribution of potentials (Shagass et al 1976, Halliday & Michael 1970, Jeffreys & Axford 1972a,b, Michael & Halliday 1971). Stimulation of the right visual field with patterned or even diffuse light will elicit a positive potential between 80 and 100 msec of maximal amplitude over the left occiput that reverses polarity near the midline. The opposite distribution of potentials occurs upon stimulation of the left visual field. Furthermore, stimulation of the upper and lower halves of the visual fields by patterns evokes differing

amplitude and polarity distributions of potentials over the occipital region. The prominent positive component at 100 msec seen with full field is also present on activating just the lower half of the visual field, whereas stimulation of only the upper half visual field evokes a small negative component at this latency.

Steady-state visual evoked potentials to repetitive diffuse or patterned stimulation have three distinct amplitude maxima (10 Hz, 16–18 Hz, and 45–60 Hz) that Regan (1972) suggests correspond to separate neural channels of visual processing.

Nonspecific cortex Transient visual evoked potentials to diffuse or patterned light flash that occur between 90 and 500 msec after stimulus onset are distributed widely over the scalp (Allison et al 1977). One of these components (P130) appears to be a mixture of neural and myogenic components. A positive component at 300 msec (the P300) appears in stimulus situations in which the subject must "attend" to the signal.

EVOKED POTENTIALS AND STIMULUS VARIABLES Luminance has significant influence on both the latency and amplitude of diffuse flash-evoked potentials but has little effect on potentials evoked by patterned stimuli. Factors such as the visual angle of the components of the pattern and their location within the visual field affect the amplitude of the potentials (Harter 1971). Visual spacings of 10–20 min are the most effective in evoking potentials if the stimulus falls on the central 3° of the visual field, whereas spacings of 50–60 min are most effective in the parafoveal regions. The clarity of focus of the patterned stimuli on the retina affects the amplitude but not the latency of evoked potentials. Insertion of lens to distort the patterns leads to decreased amplitudes, whereas a lens that corrects refractive errors will increase the amplitude of pattern evoked potentials (Harter & White 1968).

EVOKED POTENTIALS AND SUBJECT VARIABLES The effect of sleep on visual evoked potentials has not been as thoroughly investigated as other sensory evoked potentials, but changes in amplitude and form do occur (Kooi et al 1964). Muscle potentials from the scalp contribute to visual evoked potentials and have similar latency and distribution to the muscle potentials generated by auditory and somatosensory stimulation (Allison et al 1977). Perceptual factors, such as attention, can produce enhancement of certain components of flash- or pattern evoked potentials. In particular, the positive components occurring at a latency of 300–400 msec distributed over the central parietal or frontal regions are enhanced during perceptual tasks (Courchesne et al 1975). Both flash- and pattern evoked potentials change with maturation and senility. Diffuse light flash
form in young infants that is delayed in latency and of lower amplitude than the evoked potentials recorded from adults (Ellingson 1966). Evoked potentials can define the changes in visual acuity that occur during maturation (Marg et al 1976). With senescence the latency of pattern reversal evoked potential lengthens without any change in amplitude (Celesia & Daly 1977).

NEURAL GENERATORS OF THE EVOKED POTENTIAL There are excellent studies reviewed by Creutzfield & Kuhnt (1973) on the neuronal basis for visual evoked

cortical responses in experimental animals. In contrast, details of cortical and subcortical visual evoked potentials in humans and their relation to the scalp-derived components are lacking.

CLINICAL UTILITY OF VISUAL EVOKED POTENTIALS

Ocular function The excellent correlation between amplitude of pattern evoked visual potentials and the clarity of focus of the image on the retina provides a precise means for the objective definition of visual acuity. This technique may be of value in selecting corrective lenses for young children with refractive errors. Astigmatic errors can also be detected by using evoked potential to patterns of various orientation (Regan 1977). The correction of such defects may prevent "meridional amblyopia," that is, amblyopia restricted to a particular plane of orientation (Freeman & Thibos 1975). Evoked potential studies in "amblyopia ex anopsia" have, in general, been unrewarding in defining the underlying mechanisms of this disorder. Diffuse flash-evoked potentials are normal, whereas pattern evoked potentials are larger than normal if the stimulus acts on the parafoveal region (Spekreijse et al 1972). This finding raises the possibility that visual pathways from parafoveal regions are more extensively developed in amblyopic than in normal eyes. Finally, the definition of color blindness can be objectively specified by use of evoked potentials to pattern reversal stimuli of appropriate spectral composition. Regan & Spekreijse (1974) have shown that red-green color-blind individuals do not generate evoked potentials when checkerboard patterns reverse between these two hues but have quite normal potentials when presented with only the red or green checkerboard.

Optic nerve function Abnormalities of evoked potentials to diffuse light flash found in patients with visual loss due to optic nerve involvement from tumors or acute demyelination (Richey et al 1971, Vaughan & Katzman 1964). Moreover, these potentials were also abnormal in some individuals with multiple sclerosis, even when their vision was not impaired, which raises the possibility of using visual evoked potentials as a diagnostic test for multiple sclerosis. Several groups of investigators found that between 50 and 100% of patients with multiple sclerosis without visual loss had abnormalities of the flash-evoked potentials (Richey et al 1971, Feinsod et al 1973, Feinsod & Hoyt 1975, Namerow & Enns 1972). However, the marked variability of diffuse flash-evoked
accounted for its lack of acceptance as a clinical test for defining optic nerve disorders in multiple sclerosis. Recently, the consistency and reliability of the pattern-reversal evoked potentials led Halliday and his associates (1972, 1973a,b) to reassess this technique in patients with multiple sclerosis. They first noted that pattern-reversal evoked potentials were delayed in latency in $>90\%$ of patients with an acute retrobulbar neuritis and that the delay persisted even after the patients' visual acuity and fields returned to normal (Halliday et al 1973a). Moreover, in patients suspected of having multiple sclerosis but without visual complaints, pattern-reversal evoked potentials have been reported to be delayed in latency in between 59 and 96% by three separate groups of investigators (Asselman et al 1975, Halliday et al 1973b, Celesia & Daly 1977). The sensitivity of the technique is

enhanced if the criteria of abnormality for unilateral optic nerve involvement are expanded to include differences in latency between the two eyes (Celesia & Daly 1977). Steady-state evoked potentials to repetitive diffuse or patterned light stimuli are also abnormal in patients with multiple sclerosis independent of clinical evidence of optic nerve involvement (Regan et al 1976, Milner et al 1974). The abnormality was restricted to the steady-state potentials evoked by repetitions at 18–20 Hz, whereas the potentials to more rapid repetitions at 45–60 Hz were normal. There are no studies in patients with multiple sclerosis to compare the ability of transient pattern reversal and steady-state stimulation to detect optic nerve disorders. Steady-state potentials are apparently remarkably sensitive since they can define small quadrantic defects of glaucomatous eyes (Cappin & Nissim 1975).

The enthusiasm for using pattern evoked potentials as a diagnostic aid in multiple sclerosis must be tempered by the awareness that *any* lesion of the optic nerve can alter these potentials (Halliday et al 1976, Feinsod et al 1976). Halliday's suggestion that the type of abnormality of the evoked potentials (i.e. latency, form, or amplitude) may distinguish between demyelination and compression of the optic nerve needs further study.

Disorders of the central visual pathway Vaughan and his collaborators (1963) explored the use of visual evoked potentials as an objective measure of central lesions of the visual pathway. They utilized an amplitude difference between the two occipital poles of >50% to full-field diffuse light stimulation as an indicator of homonymous visual pathway alteration. Visual evoked potentials have also been described as normal in individuals with hemianopsia (Asselman et al 1975). The characterization that there are definite hemispheric asymmetries in normal subjects of potentials evoked by stimulation of the half visual fields will allow a reassessment of central lesions on visual evoked potentials and visual field defects (Shagass et al 1976). Certainly an abnormal hemispheric distribution of steady-state potentials has been clearly demonstrated in patients with central lesions producing visual field defects (Regan & Heron 1969, Wildberger et al 1976, Bodis-Wollner 1977).

Epilepsy Visual evoked potentials have been recorded in individuals with photosensitive epilepsy (Hishikawa et al 1970, Harden & Pampiglione 1971). In neuronal storage disease the amplitude of diffuse flash-evoked potentials was markedly enhanced even though the ERG was either absent or depressed in amplitude. In other forms of photosensitive epilepsy the amplitude of flash-evoked potentials will vary, depending, in part, on whether the stimulus can precipitate an epileptic discharge (Hishikawa et al 1970).

Operating room Flash-evoked visual potentials have been used to monitor optic nerve function during operation on individuals with orbital (Wright et al 1973) or chiasmatic lesions. Feinsod and his associates (1976) showed that visual evoked potentials increase in amplitude following removal of tumors compressing the optic nerve. Allen & Starr (1977) describe the sudden appearance of visual evoked potentials in the course of surgery in individuals with pituitary tumors who had been

without vision or evoked potentials prior to the operation. The effects of anesthesia and blood pressure on these potentials need to be defined in detail before their full utility can be appreciated.

Miscellaneous Visual evoked potentials have been used to define possible alterations of central connections of the visual pathways in albinos (Creel et al 1974). Moreover, these procedures have been utilized to help explore such diverse neurological problems as dyslexia (Symann-Louett et al 1977) and classic migraine (Regan 1972).

Auditory Evoked Potentials

STIMULUS Auditory evoked potentials are elicited by clicks or brief tone bursts that can be varied in intensity, frequency, repetition rate, "rise" and "fall" times of the tones, duration, or monaural and binaural presentations.

NORMAL EVOKED POTENTIALS

Receptor and afferent input Both cochlear microphonic and VIII nerve activity can be detected from an electrode located in the middle ear on the bony promontory of the cochlea in a procedure called electrocochleography (Eggermont et al 1974). Requirements for accurate and safe placement of the electrodes demand the skills of an otorhinolaryngologist. Recently it has become possible to detect both cochlear microphonic and VIII nerve activity from scalp electrodes located in the ear canal or on the mastoid of the stimulated ear (Sohmer & Pratt 1976) by averaging responses to a great number of acoustic signals (Figure 3, *receptor* and *primary afferent neuron*).

Ascending activity The electrical events generated in the central auditory pathway can be recorded in the far field from scalp electrodes if many stimulus presentations are averaged (Jewett 1970). The resultant potentials have been variously designated as auditory brain responses (ABR) or brainstem evoked responses (BER). Click signals evoke seven low-amplitude ($<1.0\ \mu V$) potentials in the initial 10 msec following stimulus presentation with the positive components at the vertex designated in sequence by Roman numerals (Figure 3, *ascending path*). Approximately 2000 clicks are required to obtain a reliable average, but since the clicks are presented at rates between 5 and 30 sec the recording time is not excessive. The concept of "active" and "reference" electrodes in the far-field detection of electrical events is not useful since all electrode sites, even those remote from the scalp, are "active." The designation of the electrodes as "active" and "less active" would be more accurate. While a variety of electrode locations have been employed, the practice in our laboratory is to record between the vertex and mastoid ipsilateral to the stimulus site.

Low-frequency tone bursts evoke another form of activity from the ascending auditory pathway that is termed the frequency following response or FFR (Moushegian et al 1973). These potentials occur at the same frequency as the stimulus tone in the range below 1 kHz (Figure 3, *frequency following potential*). Care must be taken to insure that the recorded potentials are not contaminated by the stimulus voltages applied to the earphones.

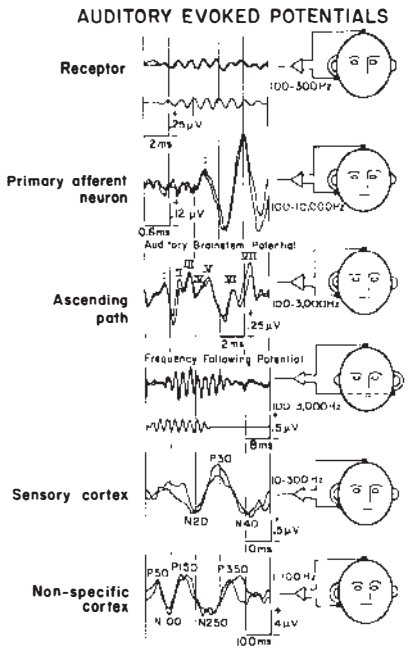

Figure 3 Auditory potentials evoked by clicks and tones. The format is the same as Figure 1. The voltage wave form applied to the earphone for tone stimulation is depicted just below the tracings of the "receptor" potentials (cochlear microphonic) and "ascending path" potentials (frequency following potential). Tone bursts were also used to elicit sensory cortex and nonspecific cortex potentials. Clicks were used to evoke primary afferent neuron and auditory brainstem potentials. The components of these latter two potentials are designated by Roman numerals. The letters and numbers above the potential wave forms in the lower two traces refer to the polarity (positive, P, or negative, N) and latency in msec of the components.

Thalamus and specific cortex A set of potentials occurring between 10 and 50 msec after stimulus presentation can be detected from scalp electrodes and have been termed "middle-latency components" (Davis 1976). These components are candidates for thalamic and primary auditory cortical activity (Figure 3, *sensory cortex*). They are best elicited by filtered clicks or brief tones, and their detection is enhanced by appropriate filters (10–100 Hz). The study of these middle-latency components is complicated by the existence of scalp-derived sound-evoked muscle potentials [i.e. "the inion response" or the "micro reflex" (Bickford 1972)] at this same latency. However, the two types of potentials can be distinguished by the differential effects of signal intensity and level of arousal.

Nonspecific cortex Long-latency sound-evoked potentials can be detected by an electrode located at the vertex and consist of P50, N100, P150, and N200 components (Figure 3, *nonspecific cortex*). These potentials are of maximal amplitude at

the vertex and are best elicited by tone-burst stimuli that are at least 30 msec in duration (David 1976, Picton et al 1977).

Sustained potentials A steady potential shift to sustained tone signals can be detected from scalp electrodes at the vertex (Keidel 1971). Their detection requires either DC recording or relatively long time constants. The potential can be distinguished from the contingent negative variation (CNV) of Walter by the differential effects of sleep and perceptual task (Picton et al 1977).

EVOKED POTENTIALS AND STIMULUS VARIABLES An increase in signal intensity is associated with both a decrease in latency and a growth in amplitude of cochlear microphonic and VIII nerve responses, auditory brainstem potentials, middle latency, and certain components of the long latency potentials. The orderly relation between signal intensity and evoked potential latency provides a means for the objective definition of auditory function.

Stimulus frequency may have significant influence on the evoked potentials. Auditory brainstem responses are most easily elicited by click signals containing energy above 2 kHz. In contrast, the FFR can only be elicited by tones below 1 kHz (Marsh et al 1975). The middle- and long-latency potentials are relatively independent of stimulus frequency.

Stimulus repetition rate will affect all of the evoked potentials. The amplitude of the early components of the brainstem potentials (Waves I–III) are significantly attenuated at click repetitions greater than 20 sec^{-1}, whereas Wave V is little affected (Don et al 1977). Long-latency cortical evoked potentials are attenuated in amplitude if stimulus presentation is more rapid than 1 per 10 sec (Davis et al 1966).

EVOKED POTENTIALS AND SUBJECT VARIABLES Sleep affects the amplitude of long-latency evoked potentials but has no effect on cochlear microphonic, VIII nerve, brainstem or middle-latency responses (Mendel et al 1975, Amadeo & Shagass 1973). Muscle potentials from the scalp can be a major contaminant of both the middle- and long-latency evoked potentials but do not influence brainstem potentials other than increasing the background recording "noise" (Goff et al 1977). Behavioral tasks requiring "attention" to the stimulus will enhance the amplitude of the P300 component of long-latency cortical responses but is without effect on middle-latency, brainstem, VIII nerve, or cochlear microphonic potentials (Picton & Hillyard 1974). There is a systematic decrease in latency of the auditory brainstem potentials with maturation (Starr et al 1977, Schulman-Galambos & Galambos 1975), and adult values are achieved between 1 and 2 years of age (Hecox & Galambos 1974, Salamy & McKean 1976). Slow cortical evoked potentials change in a more complex manner both in form and latency during this same developmental period (Barnet et al 1975, Davis & Onishi 1969).

NEURAL GENERATORS OF AUDITORY EVOKED POTENTIALS There is evidence that the potentials recorded by electrocochleography represent activity of the hair cells and VIII nerve since they correspond in many respects to these same potentials recorded from the cochlea in animal experiments. Short-latency auditory

evoked potentials (>10 msec) appear to originate from the brainstem portions of the auditory pathway. Studies in animals show that activity recorded from particular brainstem nuclear regions occurs at the same times as do the components of the far-field potentials (Jewett 1970, Lev & Sohmer 1972). Moreover, the effects of focal brainstem lesions in both animals and man (Starr & Hamilton 1976, Buchwald & Huang 1975) suggest that Wave I originates from the VIII nerve, Wave II from the region of the cochlear nucleus, Wave III from the region of the superior olive and trapezoid body, and Waves IV and V from the midbrain. The generators of Waves VI and VII are unknown. The neural generators for middle-latency (10–50 msec) and long-latency (50–500 msec) auditory evoked potentials are uncertain. Celesia & Puletti (1971) recorded sound-evoked potentials from the exposed auditory cortex in man and described components occurring between 12 and 22 msec following stimulation restricted to primary auditory cortex and long-latency potentials from more widespread cortical regions. The correlation between evoked potentials recorded from the scalp and those recorded from exposed cortex has been poor (Celesia 1968).

CLINICAL APPLICATION AND AUDITORY EVOKED POTENTIALS

Cochlear function Auditory evoked potentials can serve as an objective measure of hearing (Davis 1976, Picton et al 1977). Electrocochleography, while providing reliable and accurate measures of cochlear function, requires that the patient be sedated or even anesthetized. In contrast, auditory brainstem potentials are relatively simple to record and provide information as to both threshold and type of hearing loss (sensorineural, conductive). There is no need to employ any special sedation, and the potentials are present independent of level of arousal. However, auditory brainstem potentials seem to reflect the functions of the basal end of the cochlea and thus do not provide an accurate reflection of low-frequency hearing. The use of the FFR (frequency following response) may correct this deficiency. Middle-latency evoked potentials are also suitable for defining auditory sensitivity to a wide range of tonal frequencies, but the detection of the potentials may be contaminated by muscle activity. Finally, long-latency cortical evoked potentials are affected by the subject's level of arousal, which may interfere with the determination of hearing threshold (Zerlin & Davis 1967).

The availability of a wide variety of evoked potential methods for reliable and objective hearing evaluation is a major clinical advance. The problem as to which is the most suitable test has not yet been resolved.

Central auditory pathway disorders Evidence that the various components of auditory brainstem potentials depend upon the functional integrity of particular portions of the auditory pathway in its course from the cochlea to the cortex has obvious application for the localization of brainstem disorders in clinical situations. The latency separation between component peaks is relatively independent of signal intensity or cochlear function (Starr 1977). This measure of "central conduction time" in the auditory pathway has been used to localize and define abnormalities of the brainstem (Stockard & Rossiter 1977). Furthermore, changes in the amplitude

of the various components have also been associated with lesions of appropriate portions of the auditory pathway (Starr & Achor 1975). The characterization of absolute amplitude in far-field recordings is complicated by the poor signal size relative to background noise (Thornton 1975) and relative amplitudes between the various peaks have been used instead to detect abnormalities in brainstem potentials. Measurement of auditory brainstem potentials in clinical neurological disorders is relatively new, but there is evidence of clinical relevance in the definition of acoustic neuromas (Thornton & Hawkes 1976, Brackman & Selters 1977, Terkildsen et al 1977), brainstem tumors, infarcts, and demyelinating diseases (Starr & Achor 1975, Stockard & Rossiter 1977, Sohmer et al 1974, Robinson & Rudge 1975). Auditory brainstem potentials can help assess brainstem function in patients in coma and in the evaluation of "brain death" (Greenberg et al 1977, Starr 1976). The low amplitude of the far-field potentials requires careful recording techniques, since the potentials can be obscured by a wide variety of artifacts. An advantage of auditory brainstem potentials is that they can be measured rapidly at the bedside to provide quantitative information about brainstem function for the clinician.

Thalamic and cortical disorders Middle-latency and slow cortical evoked potentials have had little application to neurological disorders (Rapin & Graziani 1967) other than as an objective method of hearing function. The paucity of study may reflect the uncertainties as to the neural generators of these potentials.

PERSPECTIVES

The relative simplicity of recording sensory evoked potentials and the present optimism as to their clinical utility will certainly lead to increasing clinical use. Several areas are particularly well suited for investigation.

First, the *establishment* of a reliable relation between the site of neurological lesion and alterations in evoked potentials will provide important clues as to the generators of the evoked-potential components.

Second, assessing the development of sensory and neurological functions in the infant, and their subsequent change with senescence, is likely to replace behavioral testing which has serious limitations.

Third, the measurement of long-latency evoked-potential components related to "attention" (P300) or "expectancy" (CNV) will be used to analyze dementia and memory impairment.

Fourth, while event-related potentials that precede motor behavior were not discussed in this review, their investigation could provide a means of quantifying the wide variety of movement disorders that occur in clinical neurology.

There is a need, however, for improvements in technology. The computers should become small, easy to use, and provide automatic stimulus control and analysis of the evoked-potential wave forms.

It is difficult to predict whether the present enthusiasm for clinical application of evoked-potential measures in man will persist. There is general agreement, however, that evoked potentials are one of the best techniques for objective and noninvasive study of the human brain.

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