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CLINICAL APPLICATIONS OF THE
HUMAN BRAINSTEM RESPONSES TO AUDITORY STIMULI

Robert Galambos and Kurt Hecox

Department of Neurosciences
University of California, San Diego
La Jolla, CALIFORNIA 92037

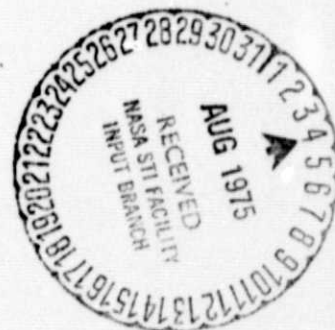
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The auditory evoked potential studies performed on man during the past thirty-five years have mainly examined the activity generated by the rostral portions of his auditory pathway (for reviews see Regan, 1972 and McKay, 1969). Recently, however, two different techniques for recording the human eighth nerve action potential have been described (Sohmer & Feinmesser, 1967; Yoshie, 1968), and Jewett and co-workers (1969, 1970) have demonstrated that activity in the human medulla and midbrain (the brainstem evoked response, or BER) can be visualized. Most recently, Moushegian et al. (1973) reported still another type of human brainstem response, the frequency following response (FFR), which, like the BER, can also be recorded from man via scalp electrodes. Thus, in less than a decade virtually the entire auditory pathway has become accessible for study by electrophysiological methods. This presents opportunities for basic and clinical studies not found elsewhere in human sensory physiology: one can sample and evaluate activity at practically every level of the auditory system from the evoked eighth nerve response in the periphery to the cortically generated vertex potential centrally.

In this chapter we will deal exclusively with the two recently described brainstem responses and focus upon the following questions pertinent to their use in the clinic: (a) can these responses readily be obtained from patients of all ages; (b) how variable are the data, and can one reliably establish clinical norms from them; (c) what recording and stimulating conditions are optimal, and (d) are deviant responses obtained from patients with hearing disorders, and if so, are these sufficiently characteristic to permit differential diagnosis.

While answers to only some of these questions can be given at the present time, this chapter will argue that a sufficient amount of laboratory and clinical data are now available on both the BER and FFR to permit an optimistic estimate of their clinical utility.

We begin by considering the most recently discovered response - the frequency following response (FFR) - and then discuss the BER, the response type with which we ourselves have been principally concerned.

The Frequency Following Response (FFR)

If a short tone burst is repeatedly delivered via earphones to a human observer, a brain wave response at the stimulus frequency can be recorded via electrodes at the vertex and mastoid (or earlobe) after computer averaging (Fig. 1). The response mirrors the signal duration as well as its frequency (between about 100 and 2000 Hz), but only after a delay of some 6 msec (and hence it cannot be due to an electrical artifact or to the physiological hair cell response). The response amplitude covaries with signal intensity, can be reduced or abolished by simultaneously presented noise maskers, and is absent or diminished in persons with impaired hearing (Moushegian, et al, this volume; Marsh et al, 1975).

The human FFR is generated in the brainstem, according to all available evidence. It was first described by Moushegian et al (1973) in a report that is still the only publication on this topic of which we are presently aware. We have, however, been privileged to examine an unpublished manuscript by Marsh, Brown and Smith (1974 in press) which fully confirms and importantly extends the findings of Moushegian et al.

The FFR in animals, by contrast to that in man, has been known and studied for many years, the term itself having been invented by Worden and Marsh in 1968 to describe data obtained from the cat. Somewhat earlier, Tsuchitani and Boudreau (1965) studied the phenomenon in the feline superior olive, describing what they called stimulus "following" in this way: "so faithful was the reproduction of the stimulus that the person speaking could often be identified, a phenomenon rivalling that of the cochlear microphonic". Marsh et al (1974) characterize the cat FFR as "...a microphonic-like wave-form recorded from gross electrodes placed in the lower auditory pathway. It has a fundamental frequency equal to that of the stimulus, a latency appropriate to the level from which it is recorded and is observed to change in amplitude as a function of stimulus intensity...it can be recorded up to and including the central nucleus of the IC (inferior colliculus) but not rostral to that point. FFR has been observed across a frequency range from approximately 0.5-5 kc/sec in the CN (cochlear nucleus)..." In animals with chronically implanted or acutely placed electrodes the evidence convincingly supports the neural origin of this FFR (Marsh et al, 1970), with a given ear activating both the ipsilateral and the contralateral ascending auditory pathways (Marsh et al, 1974).. FFR originates only within the auditory brainstem since it virtually disappears (or appears) with electrode displacements of a few mm when these electrode movements take place at the borders of the auditory tracts or nuclei. The phenomenon in cats, which is also readily recorded via scalp electrodes, seems in all important ways to be identical to that recorded from man (Marsh et al, 1975).

The question of what nucleus or nuclei generate the human FFR has not been settled. The fact that its onset latency approximates 6 msec points to the inferior colliculus as the most probable generator. However, it is known from animal studies that each brainstem nucleus up to the inferior colliculus generates its own FFR, and the theoretical problem of why these various FFR sources fail to cancel each other out at the scalp electrodes has not been resolved. Answers to these questions are essential if the FFR is to be clinically useful in approximating the level of a brainstem lesion in man.

The potential clinical utility of the FFR was heralded by two observations in the cat (Marsh et al, 1970). First, if one auditory nerve is cut no FFR is aroused by stimuli applied on that side, and second, the FFR disappears reversibly when the cochlear nucleus on the side stimulated is cooled and rewarmed. Specific examples of how the FFR can be used as a clinical tool in human disorders is the subject of Chapter [Moushegian] in this volume.

In the clinical studies known to us tone pips of short duration are the stimulus probes by which brainstem responsivity is being assessed. A steady tone of appropriate frequency should also generate the FFR, of course, and that this does happen is shown in Figs. 2 and 3. Three possible advantages in using such a continuous stimulus to generate the FFR in clinical situations can be stated. First, continuous tones are easy to create; producing synchronized tone bursts is technically more difficult than merely turning a tone on and off.

Second, if the sampling of brainstem responsivity is continuous rather than intermittent, larger FFR voltages will be generated in the same amount of time. A tone burst lasting 20 msec applied at 10 per sec drives the brainstem FFR generators for only .2 sec/sec; hence such a stimulus requires, in theory at least, 5 min. to produce the same physiological response voltage which a continuous tone would generate in one. If clinical audiometry using FFR develops into a useful tool it is probable that the actual FFR voltages derived from the patient will be compared with that of appropriate age-dependent norms at various intensities near and well above threshold. If both patient response and norms are to be expressed as volts/time of stimulation, as seems likely, a continuous tone is theoretically the more efficient stimulus to use. A third possible advantage of continuous tones is that they produce transient free, steady state driving of the basilar membrane, whereas short tone bursts do not. Continuous tones are therefore more likely than tone bursts to drive the FFR optimally from the apical region of the basilar membrane.

Among the disadvantages of using continuous tones for FFR generation is the possibility of contaminating the response derived from the brainstem with the signal delivered to the earphone. This source of artifact is excluded when brief tone bursts are applied because competent recordings will always show, as already stated, a delay of some 6 msec between the onset of the physiological response and the onset of the electrical signal. When continuous tones are applied to generate the FFR a frequency-dependent phase difference should appear between the (wanted) physiological and the (unwanted) electrical

signals, as shown in Fig. 2. The frequency-dependency of this phase difference can be estimated from the fact that the FFR onset lags the acoustic signal onset by about 6 msec. This means that the lowest frequency at which the two signals can be in phase approximates the sine wave with a period of 6 msec (167 Hz); furthermore the phase coincidence can occur at integral sub-multiples of that period only. These rules have held, to a first approximation, in the measurements we have made thus far on our subjects.

In summary, our experience as well as that of Moushegian et al (1973) and Marsh et al (1975) suggest that a useful FFR should be obtainable from patients. The FFR is certainly readily recordable from normal adults and children (as young as 9 weeks of age, according to Marsh et al., 1975 and has already been studied in some patient groups. Its threshold, however, appears to be rather high (all workers report approximately 40 dB SL for normal listeners; see, e.g. Fig. 3). Nevertheless the ease with which the FFR can be recorded, and its reliability across and within subjects seems to warrant further studies of its possible clinical utility. Hallowell; Davis in a comprehensive assessment of electrical audiometry appears to be less optimistic on this point than are others (1974). Further discussion of these matters is found elsewhere in this volume (Moushegian chapter).

The Brainstem Evoked Response (BER).

When clicks are repeatedly delivered to a subject via ear-phones, a complex time-locked evoked response is regularly identified in the 10 msec post-stimulus interval. As can be seen in Fig. 4 (and elsewhere in this volume) at least 6 waves appear and these decrease

in amplitude and increase in latency as the stimulus strength weakens. The properties of wave I in this response closely resemble those of the neural deflection seen in the electrocochleogram (electrode on or near the temporal bone) recorded at the same time: wave I amplitude is smaller in such simultaneous recordings, but its threshold latency and its amplitude-latency dependency upon stimulus strength are just like those observed at the more favorable electrode s.ite. These facts are generally taken to mean that the generator of wave I is the auditory nerve. As for the subsequent waves in the sequence, these are taken to reflect the progressive activation of brainstem auditory structures by the acoustic message as it ascends enroute to the cortex. These inferences (for which solid evidence exists, as we shall see) are fundamental to all applications of the brainstem evoked response in clinical situations.

The BER history begins in 1967 with the observation by Sohmer and Feinmesser that the eighth nerve action potential (N₁-N₂) is recordable with scalp electrodes, and that this potential is followed by two additional waves, postulated by them to be either repetitive firings of the auditory nerve, or volume conducted responses from brainstem auditory structures. However, the first convincing demonstration that electrical activity generated in brainstem auditory structures can be recorded via surface electrodes was by Jewett (1969, 1970) in the cat. He and his colleagues (Jewett et al., 1970, and Jewett and Williston, 1971), subsequently described the entire response as it appears in man. A comparison of their recordings with those of the Sohmer group reveals considerable differences which must, in part, be due to differences in recording electrode configurations,

amplifier filter settings, and/or the stimuli used. Records obtained from our laboratory (e.g. Fig. 4) bear a remarkable similarity to those obtained by Jewett and Williston, as do those of many other groups (e.g. Gerull et al., 1972; Shagass and Amadeo, 1973; Moushegian et al., Starr, and Goff et al., this volume).

Several different schemes are presently used to name the various waves in the BER. We (see also Starr, this volume) have adopted the convention proposed by the discoverers of the BER and use Roman numerals to identify its components. Elsewhere in this volume Goff, Allison, et al. arbitrarily offer still another nomenclature which, like ours, is also inconsistent with the one proposed by the Committee on Methods in Evoked Potential Research of this Symposium. In our view no valid reason to change the terminology that has priority in the literature exists. What Jewett and Williston call wave I, by whatever name, normally varies in its latency as a function of signal strength (for our clicks at a rate approximating 40 microsec per dB), and this is the fact that makes it so useful in diagnostic and clinical situations. The Jewett and Williston terminology allows one to emphasize this crucial fact as well as, or better than, any other nomenclature we know.

Following this brief historical introduction we now summarize several studies on the BER which, while not of direct clinical interest, provide the foundation and framework for its clinical application. We will then discuss specific ways in which the properties of the BER defined by these studies vary in the several pathological conditions we have examined.

Response Generators. The BER is distinguished from the more familiar later components of the auditory evoked response (Davis and Zerlin, 1964; Goldstein and Rodman, 1966) by its amplitude (fraction of a μV), latency (within 10 msec post-stimulus), and frequency spectrum (most of its energy lies well above the high frequency cut-off of recording systems traditionally employed). The electrode configuration is identical for recording early, middle and late response components (Picton et al, 1974) but the amplifier gain and filter settings, and the time base required to display the responses are quite different. For two methods commonly employed in BER recording the reader is referred to Jewett and Williston (1971) or Hecox and Galambos (1974).

Considerable effort has been expended on determining the generators of this response. Early work by Jewett's group in the cat and man (1969, 1970, 1971) and subsequent work by Lev and Sohmer (1972) clearly established the response to be neural, not myogenic, in origin. However, the question of how much of a given response component originates within a particular brainstem auditory center is still open. From direct comparisons of intracranial and extracranial recordings in animals (Jewett, 1970; Lev and Sohmer, 1972) and, in man, from extracranial mapping studies (Gerulj et al, 1974; Picton et al, 1974; Plantz et al, 1974), from simultaneous recordings of BER and the electrocochleogram (Sohmer and Feinmesser, 1967; Jewett and Williston, 1971), and from pathological material (Starr and Achor, 1974) it seems to be established that wave I corresponds to the eighth nerve action potential. Such studies also suggest strongly that waves IV and V are

generated from structures lying rostral to the pons. The relative contributions of the successive brainstem auditory centers to each wave beyond Wave I is still uncertain, however.

Stimulus Dependence. Jewett et al (1970) were the first to emphasize the point that decreasing signal strength increases response latency and decreases the amplitude of all response components (Fig. 4). There has been ample confirmation and quantification of this finding (Gerull et al, 1972; Lev and Sohmer, 1972; Lieberman, Szabo and Sohmer, 1973; Terkildsen, Osterhammel and Huisin'veld, 1973; Starr and Achor, 1974; Hecox and Galambos, 1974; Picton et al, 1974). The various reporting laboratories agree to a remarkable extent on these latency-intensity and amplitude-intensity functions, an encouraging fact since the audiometric applications of the BER obviously depends on the universality and limited variability of these relationships (Hecox and Galambos, 1974).

A variety of signals - clicks, noise bursts, tone pips - presented at repetition rates up to at least 70 per sec successfully elicit the BER (Jewett and Williston, 1971; Galambos et al, 1973). Masking studies, as well as measurements of latency and amplitude change produced by varying stimulus rise-fall time and duration, make it clear that the BER is an onset response that depends almost entirely on events originating in the first one or one and one-half turns of the cochlea; the more apical low frequency fibers contribute very little to the response (Hecox, Squires and Galambos, 1974; Hecox, 1974). We use and recommend clicks as stimuli because one cannot distinguish

the BER they produce from those produced by intense tone or noise bursts with abrupt rise-times. However, there is not enough information currently available to define the "optimal" stimulus for clinical purposes, although the fact that the response is an onset response suggests that the slowly rising long duration signals traditionally employed by audiologists are suboptimal for eliciting the BER.

The clinical implications of these observations are that neither low frequency responsivity nor the more complex integrative function of the auditory system can be assessed by this method. Lesions involving only the apical region of the cochlea, or of the complex units mediating temporal integration will be undetected.

Age Dependence. That BER amplitude and latency change with age was first shown by Jewett and Romano (1972) in the developing rat pup and kitten. Their observation that latency decreases as age increases has been confirmed (Lieberman, Sohmer, and Szabo, 1973) and quantified (Hecox and Galambos, 1974) for the human infant. The way in which response amplitude varies with age has received less attention, although Lieberman et al state that the smallest responses are generated by newborns, and that infants produce larger responses than adults; since they treated infants of various ages as a homogeneous group, however, it is not possible to derive from their data quantitative comparisons of amplitude changes as a function of age.

The progressive shortening of wave V latency with increasing age has been attributed to postnatal myelination of brainstem auditory structures (Lieberman et al, 1973). However, since the latency of wave I, the auditory nerve response, is also prolonged in infants,

possible postnatal developments in peripheral structures must be considered as well. Masking studies on infants suggest that a significant part of this developmental latency shift is due to a progressive postnatal increase in responsivity of high frequency units located in the basal portion of the cochlea (Hecox, 1975). To what extent this is due to maturation of middle ear as opposed to cochlear structures however, remains to be resolved. The clinical consequences of these findings are two-fold: (a) the latency and/or amplitude norms upon which clinical diagnoses are based must be age specific and (b) the responsivity of the basal turn or so of the cochlea changes after birth, and so BER measurements made in a newborn cannot predict his high frequency responsivity in adulthood.

Clinical Applications. The BER has already provided a certain amount of information useful in the diagnosis of both audiological and neurological disorders. We will discuss here primarily its application in audiological disorders; for its use as a neurological tool see Sohmer et al, (1974) and Chapter [Starr].

The earliest attempts to utilize BER for the diagnosis of hearing impairment was by the Sohmer group (summarized in Sohmer et al, 1973). They observed that responses obtained from hearing-impaired children generally exhibit prolonged latencies, diminished amplitudes, and elevated thresholds. Evidently their main goal has been to perform identification audiometry in the infant population. Our emphasis has been to develop the BER into a measure which not only identifies the hearing-impaired patient, regardless of age, but which, in addition, permits statements about the nature and location of his disease process. To accomplish this end, we collected data from healthy adults and infants

and described the normal relationships between signal intensity and BER characteristics (Hecox and Galambos, 1974). Fig. 4 shows typical normal BERs and Fig. 5 plots curves derived from three normal-hearing adults on whom the BER was recorded repeatedly over an 8-month period. We have chosen to measure latency, not amplitude, because latency measures always show much less inter-subject and inter-session variability than do amplitude measures. We have selected to measure wave V latency, furthermore, because throughout all age groups wave V stands out as large, stable and easy to identify. (If a given record shows abnormalities in wave V, we separately examine each prior wave to determine the earliest point at which the abnormality appears.)

Having established the norms shown in Fig. 5 (see also Starr, this volume), we next collected BER responses from patients for comparison. Among these patients are numerous infants with suspected hearing losses but because quantitative behavioral information comparable to that obtained by standard audiological procedures in adults is not available for these children we restrict our discussion here to the findings in adults. Generalizing the method to the pediatric population awaits comparable firm correlations between audiological assessment, diagnosis of pathological state, and specific BER patterns which we have been able to obtain in this adult population.

Patients with conductive hearing loss. Conductive losses arise from any impairment in the normal flow of air-borne pressure waves into movements of the inner ear fluids. Examples include wax obstructing the ear canal, tympanic membrane perforation, fluid collections in the middle ear cavity, disarticulations of the ossicular chain, etc. The majority of these lesions result in a hearing loss that is either

"flat" as a function of frequency, or more pronounced in the low frequencies. Cochleograms (eighth nerve action potential recordings) from such patients show the latency-intensity and amplitude-intensity functions to be parallel to, but displaced from, those of the normal adult (Portmann and Ara, 1971; Cullen et al, 1972). The BER from a patient with a conductive loss similarly shows a wave V latency-intensity function which is parallel to but displaced from the norm (Fig. 6A and Table 1). The amount of this displacement of the curve to the right measures the amount of the conductive hearing loss. Thus, in Fig. 6a patient CL required a 65 dB signal to produce a 7.1 msec response, while the normal adult requires only 30 dB to produce the same wave V latency. The difference in these signal strengths, 65 minus 30, or 35 dB is the estimate of the patient's conductive hearing loss. As is evident from the figure this estimate does not depend upon which point is chosen along the latency intensity function since the functions are parallel.

Patients with sensorineural hearing loss. Sensorineural losses follow disease of the cochlear structures involved in transducing inner ear fluid pressure waves into electrical impulses (stria vascularis, hair cells, etc.) and/or damage to the auditory nerve terminals and fibers. Examples of such lesions are salicylate intoxication, noise induced losses, and Meniere's disease. As with conductive losses the audiometric results in sensorineural losses can vary, but typically the loss of hearing in the high frequencies exceeds that in the low. One of the oldest and most reliable signs of sensorineural disease in a given ear is recruitment, the abnormal-

ally rapid growth of loudness as the signal intensity progressively rises above threshold (Fowler, 1928). Where this recruitment is demonstrable the possibility of a simple conductive loss is eliminated.

Fig. 6b shows the latency-intensity function produced by a patient with unilateral Meniere's disease; Table 1 shows his audiometric data. At low intensities a large discrepancy exists between his and the normal BER-wave V latency functions, but his curve converges upon the normal one at higher signal strengths. The number of dB above threshold required to accomplish this convergence has varied from 5 to 20 dB in the Meniere's patients studied thus far. When such patients have unilateral disease, this steep slope in the wave V latency function usually parallels their perceptual phenomenon of recruitment very closely, which means, simply, that the BER could, in them, provide an unequivocal diagnosis of a sensorineural lesion. Only one type of recruiting patient, the one with a steep high frequency loss, has presented a diagnostic problem in this regard; in them the latency-intensity function shows two legs, the first at the lower intensities where wave V latency shortens rapidly, the second at higher intensities, where it changes very little (Fig. 6c and Table 1). Such curves demonstrate a limitation of the BER, namely, that the shortening of latency in recruiting ears, as in normal ones, requires the participation of progressively more basal fibers.

Patients with lesions of the central nervous system. The BER can materially assist in diagnosis of retrocochlear or brainstem lesions if it shows selective abolition of one or more of its response components. Thus an intra-axial pontine mass may yield a record in which waves I, II, and perhaps III are present, while the more rostrally

generated waves IV and V are absent. Sohmer et al (1974) and A. Starr in this volume expand on this idea using data from neurological patients whose brainstem lesions are reasonably well defined.

Still another way the BER can be useful is illustrated by a patient with a diagnosis of mucopolysaccharidoses Type III, who presented clinically as deaf or profoundly hearing impaired. His BER was normal, but his cortical evoked responses were unobtainable (Fig. 7). From these facts we postulate that his disease process did not involve the subcortical auditory centers and that his hearing impairment is due to damage, presumably cortical, at a higher level. BER measurements thus can, as in this case, identify patients whose hearing loss is not due to impaired peripheral processes. Armed with such information, the clinician has a rational guide for his therapeutic intervention; a hearing aid for the patient of Fig. 7, for instance, would undoubtedly prove both costly and useless.

Limitations of the BER. When the BER is used in clinical situations several of its limitations must be kept in mind. From the audiological viewpoint it measures only the performance capabilities of the peripheral auditory apparatus and the brainstem auditory tracts and nuclei; it does not, and cannot, measure "hearing", which requires further processing of the signals at higher neural levels. From the neurological viewpoint the BER is a potentially useful tool only in the patient with functioning cochlea and auditory nerve; it can provide no information of value if the patient being examined is totally deaf due to loss of hair cells in the cochlea.

Finally, the BER seems not to sample activity aroused within the cochlea beyond its basal turn or two; this means that wave V latency

measures will be greatly prolonged - and hence suggest meaningful hearing loss - in a person with excellent hearing up to about 2 kHz but with severe loss at higher frequencies. The FFR by contrast, seems to test the stimulus frequencies which the BER does not, and so the approach of Stillman et al (1974 in press), which is to produce both the BER and the FFR with the same complex signal, may ultimately turn out to be the stimulus of choice in brainstem audiological testing.

Summary

Clinical information potentially available from brainstem audiometry falls into 2 main areas:

1) hearing assessment of patients, especially those unable to cooperate in standard audiological procedures (e.g. young children); and 2) localization of brainstem lesions, both those due acutely to trauma, cerebrovascular accidents etc., and those progressively developing due to tumor and demyelinating disease. This Chapter and those of Starr and of Moushegian et al elsewhere in this volume provide examples of how both the BER and FFR are beginning to aid in diagnosis and treatment of patients with such disorders.

In our laboratory the BER:

1) is recordable almost without exception from adults and infants as young as 33 weeks gestational age; 2) shows such limited inter-trial and inter-subject variability that dependable age-specific BER norms can be established for clinical use; and 3) varies in specific ways in the patient population so that those with pure conductive hearing loss are readily distinguished from those with mixed or with pure sensori-neural loss, and those in turn from still other patients whose lesions lie within the central nervous system.

In our view the BER and the FFR complement one another since each seems to sample a different aspect of cochlear activity and taken together they would seem to sample the whole of it. Similarly, the cortical evoked response complements, without supplanting, the information obtained from the brainstem responses. All have the major advantage of yielding objective data. The brainstem responses may well find their most important application in evaluating pediatric patients, where the BER, at least, is universally elicited, and where one cannot rely on the patient cooperation necessary for standard audiological assessments.

The clinical uses of BER and FFR audiometry are nevertheless still new, unstandardized, and precariously perched upon a limited amount of hard data derived from laboratory experiments. Only time will tell whether our optimistic view of their future potential as diagnostic tools will be realized.

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REFERENCES

- Amadeo, M. and Shagass, C. Brief latency click-evoked potentials during waking and sleep in man. Psychophysiology, 1973, 10:244-250.
- Cullen, J., Ellis, M., Berlin, C. and Loustau, R. Human acoustic nerve action potential recordings from the tympanic membrane without anesthesia. Acta Otolaryng., 1972, 74: 15-22.
- Davis, H. Brainstem and other electrical responses as candidates for electric response audiometry. Actualités Neurophysiologiques, in press, 1974.
- Fowler, E. Marked deafened areas in normal ears. Arch. Otolaryng. (Chicago), 1928, 8: 151-155.
- Calambos, R., Hecox, K., Hillyard, S., Picton, T., Furman, G. and Leigh, M. Human brainstem electrical responses to acoustic signals. J. acoust. Soc. Amer., 1973, 53:362 (A).
- Gerull, G., Giesen, M., Mrowinski, D. and Rudolph, H. Untersuchung eines frühen, von der Kopfhaut ableitbaren Potentials für die objective Audiometrie, H.N.O., 1972, 20: 339-343.
- Goff, W.R., Allison, T., Lyons, W., Fisher, T.C., and Conte, R. Origins of short latency auditory evoked response components in man, this volume, 1974.
- Goldstein, R. and Rodman, L.B. Early components of average evoked responses to rapidly repeated auditory stimuli. J. Speech Hear. Res. 1967, 10:697-705.
- Hecox, K. Frequency specificity of brainstem evoked responses in man. J. acoust. soc. Amer. (A), in press, 1974.

- Hecox, K. Electrophysiological correlates of human auditory development. In: Cohen and Salapatek (Eds.), Infant Perception. Academic Press, New York, in press 1975.
- Hecox, K. and Galambos, R. Brainstem auditory evoked responses in human infants and adults. Arch. Otolaryng., 1974, 99:30-33.
- Hecox, K., Squires, H. and Galambos, R. The dependence of human brainstem evoked potentials on signal duration and rise-fall time. J. acoust. Soc. Amer. (A), in press 1974.
- Jewett, D.L. Averaged volume-conducted potentials to auditory stimuli in the cat. Physiologist, 1969, 12: 262.
- Jewett, D. Volume-conducted potentials in response to auditory stimuli as detected by averaging in the cat. Electroenceph. clin. Neurophysiol., 1970, 28: 609-618.
- Jewett, D. and Romano, M. Neonatal development of auditory system potentials averaged from the scalp of rat and cat. Brain Res., 1972, 36: 101-115.
- Jewett, D., Romano, M. and Williston, J. Human auditory evoked potentials: possible brainstem components detected on the scalp. Science, 1970, 167: 1517-1518.
- Jewett, D. and Williston, J. Auditory-evoked far-fields averaged from the scalp of humans. Brain, 1971, 94: 681-696.
- Lev, A. and Sohmer, H. Sources of averaged neural responses recorded in animal and human subjects during cochlear audiometry (electrocochleography). Arch. Ohr.Nas.-KehlkHeilk., 1971, 201: 79-90.

- Lieberman, A., Sohmer, H. and Szabo, G. Cochlear audiometry (electrocochleography) during the neonatal period. Develop. Med. Child. Neurol., 1973, 15: 8-13.
- McKay, D. Evoked brain potentials as indicators of sensory information processing. Neurosci. Res. Prog. Bull., 1969, 7: 181-276.
- Marsh, J., Brown, W. and Smith, J. Differential brainstem pathways for conduction of auditory frequency-following responses. Electroenceph. clin. Neurophysiol., 1974, 36: 415-424.
- Marsh, J., Brown, W. and Smith, J. Far-field recorded frequency-following responses: correlates of low pitch auditory perception in humans. Electroenceph. clin. Neurophysiol., in press, 1975.
- Marsh, J., Worden, F. and Smith, J. Auditory frequency-following response: neural or artifact? Science, 1970, 169: 1222-1223.
- Moushegian, G., Rupert, A.L. and Stillman, R.D. Scalp recorded early responses in man to frequencies in the speech range. Electroenceph. clin. Neurophysiol., 1973, 35: 665-667.
- Picton, T., Hillyard, S., Krausz, H. and Galambos, R. Human auditory evoked potentials. I: Evaluation of components. Electroenceph. clin. Neurophysiol., 1974, 36: 179-190.
- Plantz, R., Williston, J. and Jewett, D. Spatio-temporal distribution of auditory-evoked far field potentials in rat and cat. Brain Res. 1974, 68: 55-71.
- Portmann, M. and Aran, J. Electrocochleography. Laryngoscope (St. Louis), 1971, 81: 899-910.
- Regan, D. Evoked potentials in psychology, sensory physiology and clinical medicine. London: Chapman and Hall, 1972.

- Sohmer, H. and Feinmesser, M. Cochlear action potentials recorded from the external ear in man. Ann. Otol., 1967, 76: 427-435.
- Sohmer, H., Feinmesser, M. and Szabo, G. Sources of electrocochleographic responses as studied in patients with brain damage. Electroenceph. clin. Neurophysiol., 1974, 37: 663-669.
- Starr, A. and Achor, J. Auditory brainstem responses in neurological disease. Neurology, in press 1974.
- Stillman, R.D., Moushegian, G. and Rupert, A.L. Early tone-evoked responses in normal and hearing-impaired subjects. Audiology, in press 1974.
- Terkildsen, K., Osterhammel, P. and Huis in't Veld, F. Electrocochleography with a far-field technique. Scand. Audiol., 1973, 2: 141-148.
- Tsuchitani, C. and Boudreau, J. Wave activity in the superior olivary complex of the cat. J. Neurophysiol., 1964, 27: 814-827.
- Worden, F. and Marsh, J. Frequency-following (microphonic-like) neural responses evoked by sound. Electroenceph. clin. Neurophysiol., 1968, 25: 42-52.
- Yoshie, N. Auditory nerve action potential responses to clicks in man. Laryngoscope, 1968, 78: 198-215.

Table I. Audiometric data on patients of Fig. 6

<u>Patient</u>	(Frequency (Hz))					
	<u>250</u>	<u>500</u>	<u>1000</u>	<u>2000</u>	<u>4000</u>	<u>8000</u>
CL	35	40	30	35	30	40
	5	15	0	10	0	10
TR	25	35	40	35	45	40
	10	0	7	15	5	5
LF	15	30	20	25	65	65
	5	15	10	15	10	10

FIGURE LEGENDS

FIG. 1 The human FFR. Vertex to earlobe recording. Tone: microphone response to the 500 Hz toneburst emitted by earphone applied to subject's ear.

A: averaged FFR (N=2000) to that tone burst with EEG amplifier bandpass 8-10,000 Hz. B: Same, with amplifier bandpass 200-1000 Hz. From Marsh et al, 1975.

FIG. 2 The human FFR to continuous tones of 400 Hz (above) and 300 Hz (below). Response: 3 superimposed replications of the vertexmastoid activity (vertex positive up) recorded during 2 mins. of continuous monaural stimulation at 60 dBSL. Signal: The sine wave delivered to the earphone, recorded during stimulation, and used to trigger all sweeps at the same phase angle. Note phase shift relative to response that accompanies change in signal frequency.

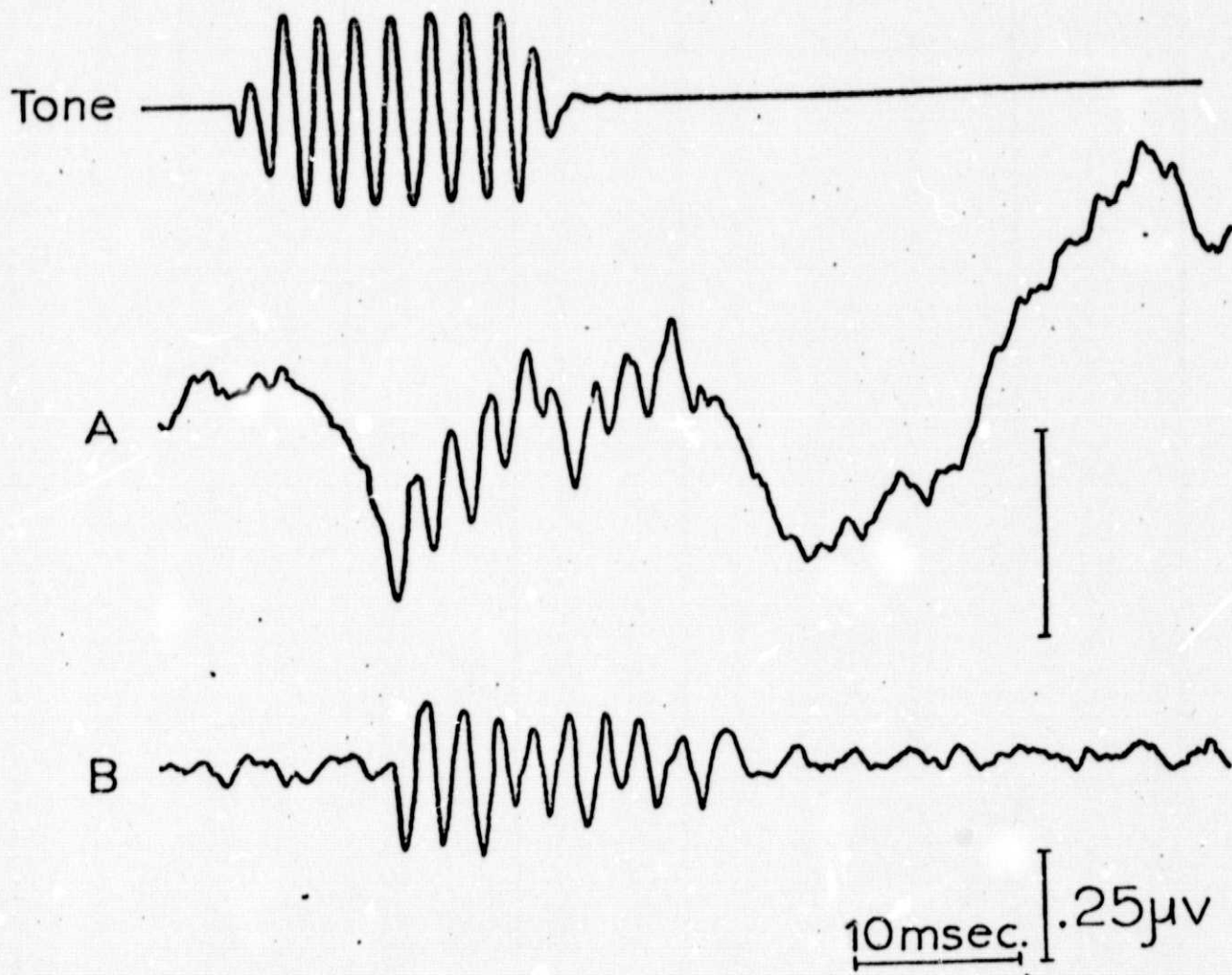
FIG. 3 The human FFR to 350 Hz tone at different intensities. Details as in Fig. 2, except tones lasted 90 sec.

FIG. 4 The human BER to monaural clicks (30 per sec) at various intensities. Same subject and recording configuration as in Figs. 2,3. Each trace sums 2000 responses; superimposed traces are replications obtained during the same recording session. Note that wave V latency increases and its amplitude decreases as signal strength weakens.

FIG. 5 The BER wave V latency-intensity function for 3 young adults. Dashed lines: each shows the mean values for one subject on whom at least 10 measurements were made over an 8 month period. Solid line: mean and standard deviations for all subjects. From Hecox and Galambos 1974.

FIG. 6 BER wave V latency-intensity functions for three patients with predominantly unilateral hearing loss. Hatched areas: the normal relationship shown in Fig. 5; open circles: wave V latencies from the "normal" ear of each patient. CL: girl with monaural (solid dots) conductive loss. TR: adult with flat sensorineural loss due to Meniere's disease. LF: adult with sensorineural loss from Meniere's disease, severe above 2000 Hz. See Table 1 for audiograms of each patient.

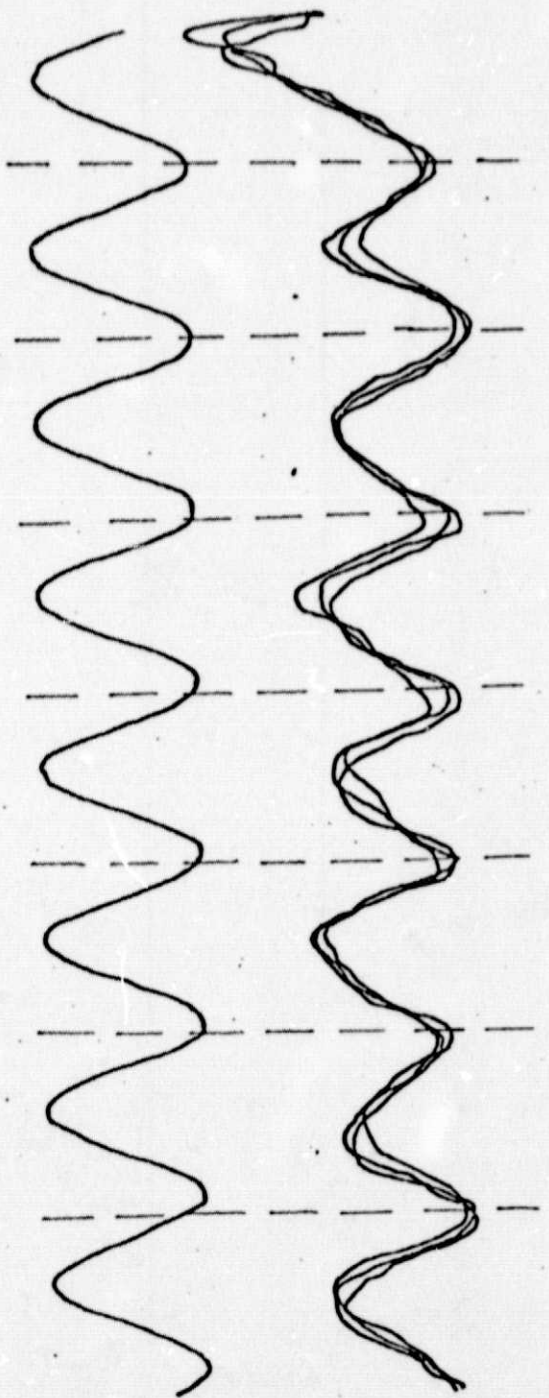
FIG. 7 Normal BER (above) and absent cortical response (below) in a patient suffering from San Filippo's Disease. Clinically, the patient appeared to have a profound hearing loss. Each superimposed tracing was obtained in response to a 60 dBSL monaural click, with positivity to the vertex upwards in all recordings.



400 hz

Response

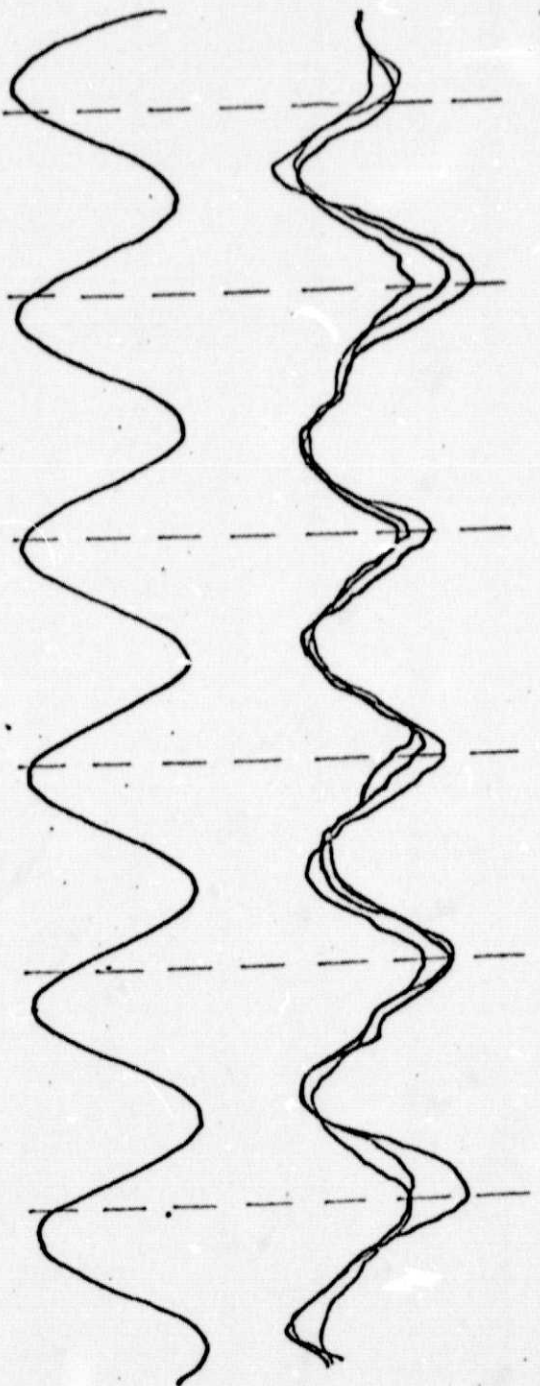
Signal



300 hz

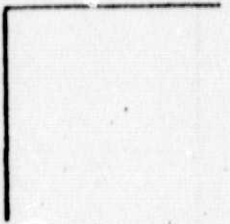
Response

Signal



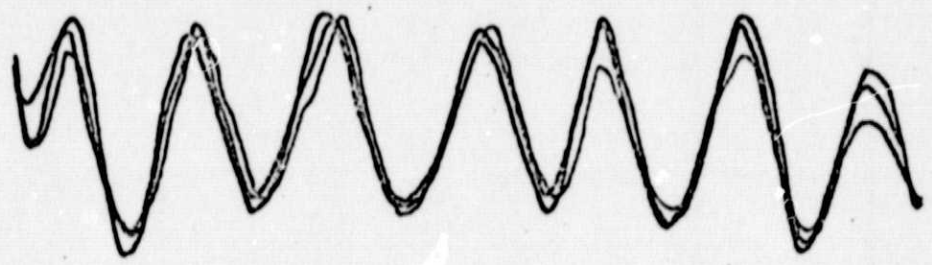
.3 μ V

3 msec



350 hz

dbSL



70



60



50



45



35

