THE 40 HERTZ AUDITORY EVENT-RELATED POTENTIAL: SCALP TOPOGRAPHY AND EFFECTS OF AGING

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The 40 Hz Auditory Event-Related Potential: Scalp Topography and

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ABSTRACT

Event-related potentials (ERP's) provide a noninvasive measure of the electrical activity associated with cerebral processing activities. Recently, the 40 Hertz steady-state auditory ERP has received considerable interest with respect to its intracerebral generators and as a potentially useful tool in the assessment of drug effects on brain systems and in clinical audiometric testing. Several basic questions need to be addressed before the 40 Hz response can be developed as such a tool. First, additional normative data are required. The majority of 40 Hz studies to date have used subjects from a restricted age group of young adults. Since there are numerous reports of age-related changes in transient auditory ERP's, similar variations in the 40 Hz steady-state ERP may be anticipated. Second, the scalp distribution of the 40 Hz response needs to be more fully characterized in order to throw light on the generators of the response. Most of the 40 Hz literature is based on data from only one or a few electrode positions. The present study was designed to address these two issues. ERP's were recorded from a group of normal elderly subjects and a group of normal younger subjects, using auditory stimulation rates of 30 to 50 Hz. A 21 channel recording system was used, representing a substantially more complete scalp distribution than has been used in previous 40 Hz electrical studies. Amplitude and phase angle maps were constructed from these data. These maps reveal that the 40 Hz response is considerably more stable at fronto-central recording sites than at other sites on the head. Elderly subjects exhibit a response which is similar in phase and amplitude to the younger subjects. However, an index consisting of the difference in amplitude between Cz and Fz was found to discriminate 4 of the 5 aged subjects from the younger group. These data are discussed with respect to models of the physiological sources underlying the

generation of the 40 Hz ERP.

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Introduction

The scalp-recording of event-related potentials (ERP's) provides a noninvasive technique for studying the functioning of the human brain. The potentials measured at the scalp are related in a time-dependent fashion to sensory, cognitive or motor "events" and are therefore considered to be indices of cerebral processing activities. If an ERP can additionally be attributed to a specific brain source, it is a valuable tool for the study of the relationship between structure and function in the brain. As such, there is considerable interest in the effort to relate potentials recorded at the scalp to their intracerebral generators. Convergent evidence for the source of scalp-recorded potentials is obtained from brain lesion studies, by comparison with intracranial recordings and from appropriate animal models, scalp distribution studies of electrical and magnetic fields, and analysis of equivalent dipole sources.

The 40 Hz auditory event-related potential (AERP) is a steady state, middle latency auditory response which shows an increase in amplitude with steady-state stimulus rates between 30 and 50 Hz, with a maximal amplitude and sinusoidal waveform at a stimulus rate of about 40 Hz (Galambos, Makeig and Talmachoff, 1981). The 40 Hz ERP has several properties of theoretical and practical interest. First, it resembles similar phenomena in the visual, somatosensory and olfactory systems, facts which suggest that the adequate processing of sensory information may require cyclical brain events in the 30-50 Hz range. Second, latency and amplitude measurements on the 40 Hz ERP indicate that it may provide useful information on the number and basilar membrane location of the auditory nerve fibers that a given tone excites. Third, the response is present at sound intensities very close to normal adult thresholds for the audiometric frequencies, a fact that could have application in clinical audiometric testing.

Before these potentials can be used clinically, however, additional normative studies are required. In particular, the majority of 40 Hz studies have used subjects from a restricted age group of young adults. Most patients requiring audiometric assessment, however, belong to a substantially older adult population. Since there are numerous reports of age-related changes in early, middle and late transient AERP's (Psatta and Matei, 1988; Woods and Clayworth, 1986; Pfefferbaum et al., 1984), similar variations in the 40 Hz steady state AERP may be anticipated.

Aging has recieved relatively little attention in the 40 Hz literature. Two studies which have included age as a variable in the 40 Hz response (Stapells et al., 1984) have reported negative results. The data of Stapells et al. (1984), however, were limited to young and middle aged adults. Borda (1984) concluded that the responses of younger and elderly subjects were quite similar, but did not perform any in-depth analyses. Since aging has been shown to be a significant variable affecting early, middle and late transient AERP's, it is apparent that aging as a variable in the steady-state 40 Hz response has been neglected in the studies reported to date.

In addition to the question about the effects of aging on the 40 Hz AERP, another basic question that has recieved inadequate attention is the scalp distribution of the response. The majority of 40 Hz studies to date have collected data from only one (usually vertex) electrode. Judd (1987) used four electrode sites at Fz, Cz, Oz and either C5 or C6 and reported a clear dissociation between the scalp distributions of the auditory and visual 40 Hz responses. Clearly, information about the scalp distribution of the 40 Hz response will provide important data concerning the generators of the response.

The intention of this study was to record the distribution of electrical potentials associated with 40 Hz auditory stimulation in order to further characterize the scalp distribution of the 40 Hz response, and compare the response in younger and aged adults in order to assess the effects of aging on the response. A 21 channel recording system was used, representing a substantially more complete scalp distribution than has been used in previous 40 Hz studies.

Review of the Literature

Transient and Steady-State Evoked Potentials

Evoked potentials (EP's) are defined as electrical responses of the nervous system to sensory stimulation (Spehlmann, 1985). They consist of a sequence of deflections, or waves, characterized by latency from stimulus onset and amplitude of positive or negative deflection from a reference potential. In clinical and research settings, EPs are elicited by auditory or visual stimulation, the parameters of which are carefully specified; or by stimulation of sensory nerves. These EPs are recorded from the surface of the body with electrodes on the scalp or on the skin over the spinal cord or peripheral nerves.

Scalp electrode placement is standardized with systems for determining electrode positions using identifiable skull landmarks as reference points. One of the most common systems is the International 10-20 System of Electrode Placement which is based on the established relationship between a measured electrode site and uderlying cortical structures and areas (Jasper, 1958). The system is termed "10-20" because electrodes are spaced either 10% or 20% of the total distance between a given pair of skull landmarks.

A single response to a stimulus typically has low amplitude and will be obscured by ongoing spontaneous EEG activity. To extract EPs from the EEG, stimuli are presented repeatedly and the responses time-locked to the stimulus are averaged by computer. EEG components that are not related to the stimulus are thus averaged out, while the stimulus-related features of the response are enhanced.

The term *event-related potential* (ERP) is now commonly used to denote both EPs and other potentials resulting from cognitive processes invoked by the task demand characteristics of a stimulus situation. ERP is thus the more general term for brain activity related to cerebral processing events, while EP is typically used to describe brain events related to the processing of sensory information.

"Transient" ERPs are obtained when stimuli are presented at a sufficiently slow rate that the response to one stimulus has ended prior to the presentation of the next. "Steady-state" responses are elicited when stimuli are presented at a sufficiently high rate that there is an overlapping of the responses with those elicited by subsequent stimuli In coining the term "steady-state evoked potential", Regan (1972) defined the idealized response as a repetitive EP whose constituent harmonic components remain constant in amplitude and phase over an infinitely long period. Steady-state responses may have simple or complex waveforms, but in any case the response is most simply characterized in terms of its constituent frequency components. Transient waveforms, in contrast, are most simply characterized in terms of their time or latency components.

In making the distinction between transient and steady-state ERPs, Regan (1972) pointed out that any waveform may be completely described in either the time or the frequency domain, but that in any given case, one may be more convenient than the other. In the case of the steady-state ERP, the power of such a signal must necessarily be concentrated into a few narrow frequency bands, namely the fundamental component at the frequency of stimulation and the harmonics of this frequency. These components occupy only a small fraction of the total EEG bandwidth, whereas biological noise is continuously distributed throughout the frequency band. The signal-to-noise ratio of a steady-state ERP will thus be much greater within these narrow frequency bands than at frequencies between these concentrations of signal power.

The concentration of steady-state ERP signal power into a few narrow bandwidths makes this type of ERP amenable to a frequency-based analysis; namely, the Fourier Transform. The transformation of the time-domain description of an ERP waveform into a frequency-domain description makes the job of quantifying the waveform considerably easier. Describing and quantifying an averaged transient waveform can be difficult when peaks overlap or when the baseline is uncertain, and especially when the waveform is unusual. In contrast, the Fourier Transform of the steady-state ERP provides a straightforward means of quantification of a component. The frequency of a component, together with its amplitude and phase, unequivocally describe the particular component, with one qualification. The phase description of the component is more ambiguous than a latency description because of the nature of angular values. For example, 6.26 radians is fairly close in phase to 0.02 radians, but they are quite far apart in numeric value. This introduces certain problems in the analysis and comparison of waveforms which is not encountered when they are described in terms of latency from stimulus onset.

From the above description of steady-state ERPs, it is apparent that they have two principal advantages in terms of data analysis: they are more easily described than the transient waveform, and the process of signal-to-noise enhancement can be much speedier with the use of the Fourier Transform. In practical terms, perhaps the most important feature of the steady-state response is that it can often be more easily recorded than the transient response. This can be an important consideration in clinical situations, considering the stress imposed on the patient by long recording sessions.

The 40 Hertz Auditory Steady-State ERP

Until recently, the human steady-state potentials were mainly studied in the visual modality, with only occasional reports of auditory steady-state responses (Picton, 1984). Interest in auditory steady-state potentials was reawakened by the description by Galambos et al. (1981) of the "40 Hz ERP". They demonstrated that as the rate of auditory stimulation (clicks or tones) is increased, the response is maximal in amplitude and sinusoidal in form at rates of about 40/sec. Response amplitude and form of the waveform degenerate at rates above and below about 40 Hz.

The 40 Hz ERP has several properties of theoretical and practical interest. First, it resembles similar evoked and spontaneous phenomena in the visual, somatosensory and olfactory systems, facts which suggest that the adequate processing of sensory information may require cyclical brain events in the 30-50 Hz range (Sheer, 1987). Second, Galambos et al. proposed that latency and amplitude measurements on the 40 Hz ERP would provide useful information on the number and basilar membrane location of the auditory nerve fibers that a given tone excites. Third, the response was shown to be present at sound intensities very close to normal adult thresholds for the audiometric frequencies, a fact that could have application in clinical audiometric testing.

Description

A. Effect of Stimulation Rate

The basic paradigm of the Galambos et al. (1981) study was to record ERPs from individuals using auditory stimulation in the form of clicks or tones at presentation rates of 10 to 55/sec. A plot of the amplitude of response shows a peak at rates of about 40/sec and minima at 25 and 55/sec. Galambos and his group summarized the characteristics of the 40 Hz response as follows:

1. Its form resembles one or more cycles of a 40 Hz sinusoid;
2. Although individuals vary in the number of such cycles they produce at low stimulus rates, at the 40 Hz rate their responses are similar (ie. the number of cycles follows the number of stimuli in the recording epoch).
3. The 40 Hz ERP is easy to record from normal subjects.
4. The 40 Hz ERP usually peaks in the 35–45 Hz range, but the actual optimal rate probably varies from one person to the next.

B. Effect of Stimulus Intensity

Galambos et al. (1981) found that stimulus intensity has several interesting effects on the 40 Hz ERP. First, response amplitude rises with intensity increase, and the rate of amplitude rise is very steep near threshold, such that the response is readily apparent at near-threshold stimulus intensities. Galambos et al. found that the 40 Hz ERP was a very reliable index of hearing thresholds in young adults, and proposed its use in audiometric testing of clinical patient populations. Second, the response increases in latency with increase in stimulus intensity in a a manner similar to that of the transient middle-latency response, a finding that may reflect a similarity of physiological generators.

C. Effect of Stimulus Frequency

Galambos et al. (1981) also manipulated the frequency of tones presented at a rate of 40/sec. They found that as the frequency of the carrier tone increases, the 40 Hz ERP decreases in amplitude and latency. They attributed this effect to mechanical properties of the basilar membrane, such that as stimulus frequency drops, the mechanical wave initiated by the low-frequency stimulus activates more of the basilar membrane but at a slower rate of activation. Thus, larger numbers of sensory neurons are excited by the low-frequency tones, but it takes more time to initiate and complete their activation.

D. Subsequent Studies

After the initial description of the 40 Hz ERP by Galambos' group, a series of studies were initiated to further investigate the parameters of the response and to test the hypotheses generated in the 1981 study. Stapells et al. (1984) replicated the findings of the Galambos group and demonstrated the utility of Fourier analysis in defining the properties of the 40 Hz ERP. Stapells et al. (1984) found that signal averaging and (on-line) Fourier analysis provide nearly identical amplitude/rate, amplitude/intensity and latency/intensity functions. Both methods of analysis may be used, therefore, to record the 40 Hz ERP, but on-line Fourier analysis was advocated as the fastest and least expensive method.

With the Fourier analysis method, Stapells et al. (1984) found that while amplitude to a 500 Hz toneburst was maximal in all their subjects at rates of 30-45 Hz, there was considerable variability in the absolute amplitude across subjects. Phase, on the other hand, proved to be quite stable both with a given subject and across a group of 6 subjects.

Spydell et al. (1985) confirmed the finding of relative stability of phase across subjects, and in addition, demonstrated that phase was approximately normally distributed across control subjects. Stapells et al. (1987) used "phase coherence", a statistical measure of phase variance, and found that this index is less variable than response amplitude both within and between subjects. They concluded that phase coherence is better than amplitude for determining the optimal presentation rate for the 40 Hz response and that, within the rate range of 19–54 Hz, that rate is near 40/sec. Interestingly, Stapells et al. (1987) also found a significant linear correlation between signal-to-noise ratio and phase coherence. Thus, phase coherence provides an index of response amplitude at the stimulus rate to EEG background amplitude at that frequency, regardless of the absolute size of the response.

The description of the 40 Hz ERP in the frequency domain has thus provided a complementary view of the original time domain description. Data from frequency-based studies indicates that what is "special" about the 40/sec stimulus presentation rate is that it provides the highest phase coherence, amplitude, and signal-to-noise ratio in most adult subjects (Stapells et al., 1987).

Picton et al. (1987) found that at near-threshold stimulus intensities, most of the signal information is carried by the phase rather than the amplitude of the signal. Picton et al. compared several methods for assessing the signal-to-noise ratio of the 40 Hz response in order to measure the threshold for reliably detecting the response. This threshold is the intensity at which the stimulus evokes a clearly recognizable response (that is, one that is significantly different from what would be expected if there were only residual noise in the recording and no evoked potential). Hotelling's T^2 statistic and phase coherence were found to provide equally accurate assessments of the signal-to-noise ratio at threshold intensities. Since phase coherence is essentially an amplitude-free version of the T^2 statistic, phase seems to be of predominant importance for establishing the presence of a signal at near-threshold intensities.

Generators of the 40 Hz Auditory ERP

The anatomic origins of the 40 Hz ERP is a matter of some dispute at this time. There are those who contend that the response is generated primarily or entirely in midbrain/thalamic structures (Firsching et al., 1987; Galambos et al., 1981; Galambos, 1982; Spydell, 1985). Alternately, there are those whose data strongly supports the involvement of auditory cortex in the generation of the response (Makela and Hari, 1987; Romani et al., 1982; Sheer, 1987; Weinberg et al., 1987).

In the original description of the 40 Hz ERP (Galambos et al., 1981), the authors argued against an exclusively cortical origin on the basis of evidence that scalp recorded cortical auditory EP's attenuate quickly at stimulus rates above 10/sec (Picton et al., 1974), whereas the 40 Hz ERP is maximal in amplitude at a rate of 40/sec. Lee et al. (1984) have confirmed this finding using chronic subdural electrodes in the area of Heschl's gyrus in man. Lee et al. (1984) also report that the auditory ERPs recorded from the area of Heschl's gyrus exhibit a very steep potential field gradient and that response amplitude falls off quickly at short distances from the site of maximum response amplitude. Thus, it would appear unlikely that an electrode located at the vertex, the usual location in 40 Hz studies, would be able to record activity originating from the area of Heschl's gyrus.

Galambos (1982) speculated that the 40 Hz ERP may originate within polysensory areas of the thalamus, on the basis of evidence that similar ERPs are obtained with both auditory and somatosensory stimulation at rates between 30 and 50 per sec. Support for a midbrain/thalamic site of origin was provided Spydell et al. (1985), who found that the 40 Hz response was not affected by temporal lobe lesions that included primary auditory cortex. Spydell et al. (1985) also found that the phase of the 40 Hz ERP varied independently with that of the brainstem auditory evoked potential (BAER), indicating that the response is generated in structures rostral to brainstem auditory structures.

Firsching et al. (1987) reported that in comatose patients, the 40 Hz ERP was not found in cases where the BAER was also missing, while a normal 40 Hz ERP was found in a patient with massive destruction of the right temporal lobe. These findings are consistent with the hypothesis of Spydell et al. (1985) and Galambos (1982) that midbrain/thalamic structures play the major role in the generation of the 40 Hz ERP. However, while these studies have failed to find an alteration of the 40 Hz ERP with lesions of the temporal lobe, the possible involvement of other cortical areas is not ruled out.

Contradictory evidence has come from several investigators (Makela and Hari, 1987; Romani et al., 1982; Weinberg et al., 1987) regarding the role of the temporal cortex in the generation of the 40 Hz ERP. Weinberg et al. (1987) obtained sequential magnetic recordings (using a 3rd order SQUID gradiometer) from a wide distribution over the head in order to produce maps of the magnetic field over the head and to calculate estimates of dipole locations. Their results indicated that the source-system active during 40 Hz auditory stimulation includes bilateral temporal cortex.

Makela and Hari (1987) similarly obtained sources in temporal cortex with magnetoencephalographic data. To estimate to what extent the source in temporal cortex could explain the measured electric potential. Makela and Hari (1987) used a spherical volume conductor with concentric inhomogeneities simulating the brain, CSF, skull and scalp. When a current dipole corresponding to the strength of the equivalent source of the 40 Hz response was placed in bilateral superior temporal planes, a potential difference of about 2 *u*V was found in the vertex-mastoid derivation. Since these simulations agreed well with measured values, the authors suggested that the source in temporal cortex is the dominant, if not necessarily the only, source of the electric 40 Hz response recorded at the vertex.

Romani et al. (1982) recorded magnetoencephalographic responses to auditory stimulation at frequencies of 200, 600, 2000 and 5000 Hz, presented at rates of 32/sec. They estimated sources in primary auditory cortex which increased in depth below the scalp as the frequency of the tone was increased, and interpreted their data with respect to the tonotopic organization of the auditory cortex.

The evidence for the generators of the 40 Hz ERP is therefore contradictory. Lesion studies indicate that while the response is likely generated in structures rostral to the brainstem auditory pathways, primary auditory cortex is apparently not necessary for generating the response. While temporal cortex is not necessary to produce the response, the MEG data cited above strongly indicates that temporal cortex is strongly activated in normal individuals with auditory stimulation at 40 Hz.

In order to account for the contradictory evidence cited above, it may be necessary to invoke a more complicated model of the response than one which involves a simple linear activation of structures in the auditory pathway. The model proposed by Galambos et al. (1981) to account for the amplitude augmentation of the ERP amplitude at stimulation rates of 40/sec was straightforward. They suggested that the augmentation was due simply to superimposition in the signal-averaging process of several sinusoidal components in the transient response which happen to exhibit interpeak intervals approximating 25 msec. Similarly, the minimal amplitudes seen at stimulus rates around 25 and 55 Hz are accounted for by this model because at these rates the successive transient components should appear out of phase and thus cancel in the computer memory during the averaging process.

The simple superimposition model proposed by Galambos et al. (1981) does not, however, account for certain aspects of the 40 Hz response which were reported by later investigators. Borda (1984) presented subjects with 40/sec click stimuli for train durations of 120 msec, but used an averaging window of 500 msec. He found that the recorded 40 Hz oscillations reach a maximum amplitude after the fourth to fifth click, but interestingly, continue for some oscillations beyond the end of the stimulus train. Borda (1984) suggested that while superimposition probably accounts for some of the 40 Hz augmentation effect, the persistence of the ERP beyond the cessation of auditory stimulation indicates a "resonance" in some portion of the neuronal pathway underlying the generation of the middle latency response.

According to Borda's (1984) model, then, the specificity of response to stimulus rates of 40/sec is a reflection of the organization of the neural circuitry underlying the generation of the response, circuitry which has an optimal inherent rhythmicity near this frequency. In physical models this phenomenon is known as "tuned resonance" (Sheer, 1987). Such resonance has been shown to be present in other neural circuits, such as those in the visual cortex (Singer, 1979), lateral geniculate (Fertziger and Purpura, 1971), hippocampus (Anderson et al., 1963), thalamo-cortical pathways (Andersen and Andersson, 1968), and the olfactory bulb (Freeman, 1979).

Borda (1984) proposed that with the introduction of the concept of resonance within a limited portion of the auditory pathways to account for some of the amplitude enhancement at 40/sec stimulus rates, one need not postulate a long, linear pathway, similar to that of the BAER, as the substrate for the generation of the response. Since similar responses can obtained from somatosensory (Galambos, 1982) and visual (Sheer, 1987) stimulation it is likely that such responses represent activation of nonspecific sensory nuclei as well as some structures which are modality specific. Borda (1984) proposed that the amplitude enhancement in the 40 Hz ERP is due to input from primary auditory pathways activating nonspecific thalamic nuclei, nuclei which are responsible for modulatory gating processes and which possess inherent resonance at a frequency of about 40/sec.

Ryugo and Weinberger (1976) argue that corticofugal mechanisms ordinarily support rhythmic discharges which may involve thalamus. Weinberg et al (1987) have proposed a model to account for resonance effects within the auditory system which is composed of a thalamocorticothalamic loop with projections to auditory cortex from thalamic relay nuclei and reciprocally organized corticofugal projections from auditory cortex to thalamus. They propose that convergence of primary auditory input and cyclic activity in the thalamocortical system results in an increased activity in primary auditory cortex, so that enhancement of the response to 40 Hz stimulation is seen at auditory cortex as well as at other parts of the system.

Weinberg et al (1987) thus elaborate on Borda's model, proposing that the enhancement of the steady-state potential at rates of about 40/sec is due to inherent resonance of thalamo-cortical-thalamic systems at that frequency. They point out that, in a model of this type, the generator of the response must be viewed as a "source-system". When the brain is in a steady-state, responding to repetitive stimulation with fixed interstimulus intervals, feedback loops are established between midbrain nuclei and cortex in which no part of the loop can be construed as "the" source. In this case, a source can be estimated whereever the system is sampled.

While the Weinberg et al (1987) model accounts for augmentation of the auditory 40 Hz response, there is also evidence that similar responses can be recorded with visual and somatosensory input. Judd (1987) found a consistent distribution of amplitudes across the scalp with both auditory and visual inputs. He found a clear dissociation, with visual input amplitudes highest at Oz, over the visual cortex, and auditory amplitudes highest at Cz and Fz, though also high at C5 and C6, over auditory cortex. Somesthetic input amplitudes are also higher over somatosensory cortex (Galambos, 1982).

The dissociation between auditory, visual and somatosensory stimulation with respect to site of maximal response provides additional evidence for a cortical source for the response, and indicates that the sensory cortex activated is specific to the modality of stimulation. However, amplitudes are generally higher at vertex electrode sites from subcortical sources (Sheer, 1987), and for auditory inputs, the auditory amplitudes are are significantly higher at Cz and Fz than at sites over auditory cortex (Judd, 1987). This raises the question of an additional subcortical source along with the cortical source, volume conducted to the surface electrode sites. The model proposed by Sheer (1987) is that the (polysensory) 40 Hz ERP reflects coherent resonance of specific thalamic relay nuclei and sensory cortex, volume conducted to the active electrode site.

The subcortical source of Sheer's model is clearly consistent with the "source-system" model proposed by Weinberg et al (1987). It does not, however, rule out the possibility that nonspecific systems, as well as specific systems, are activated as proposed in the Borda (1984) model. If this is the case, then it may be that auditory, visual and somatosensory cortex is activated by stimulation in any modality, although additional specific systems are recruited in the specific sensory system being stimulated. This would account for the persistence of the auditory 40 Hz ERP in patients with temporal lobe lesions.

The Borda (1984), Weinberg et al (1987), and Sheer (1987) models described above differ in some of their specifics (for example, whether the resonance occurs in the auditory system or is multimodal) but all three describe resonating neural systems. They can therefore be described as "non-linear" models, in contrast to the linear superimposition model of Galambos et al, 1981).

Age-Related Changes in the 40 Hz ERP

Galambos et al (1981) have suggested that one of the major applications of the 40 Hz ERP may be in clinical audiometric testing. The majority of 40 Hz studies to date have used subjects from a restricted age group of young adults. However, patients requiring audiometric assessment are typically from a substantially older or substantially younger age group. Several studies have been carried out to collect age-normative data from infants and young children, but as yet, no systematic study has been carried out on aged subjects.

A. The 40 Hz ERP in Young Children and Infants

Suzuki and Kobayashi (1984) evaluated the effect of stimulus rate on steady-state responses in young children aged 3 months to 6 years. No significant increase in the amplitude of the responses was obtained for children, and although a following response could be discerned in the recorded waveforms, they were considerably degraded in form compared to the sinusoidal waveforms of adult subjects.

Stapells et al (1988) examined the 40 Hz ERP in young infants aged 3 weeks to 28 months. They confirmed the results of the Suzuki and Kobayashi (1984) study that infants do not show highest response amplitudes at rates between 35 and 40 Hz. In fact, infants' responses rarely attained adult size, and their amplitudes remained essentially unchanged over a wide range of stimulus rates.

Stapells et al (1988) used an ingenious method of testing their hypothesis (Galambos et al, 1981) that the 40 Hz ERP is created by overlapping the several EP components visible in the transient middle latency response. They created a "synthesized" 40 Hz ERP from the middle latency response and compared it to the obtained 40 Hz ERP for each subject. They found that the response synthesized from the middle latency response predicted the 40 Hz ERP fairly well in adult subjects, but not in infants.

The linear overlap hypothesis clearly fails to predict the steady-state ERP in infants. The responses synthesized from the transient middle-latency response were much larger than the steady-state responses actually obtained. It is not clear from the results of the Stapells et al (1988) whether (a) the relationship between the transient middle latency response changes between infancy and adulthood or (b) the 40 Hz ERP is a non-linear phenomenon in both cases, as is suggested by the resonating systems hypotheses discussed above.

Certainly it is attractive to speculate the 40 Hz response requires an adult level of myelination and synaptic development in brain systems in which there is a convergence of excitation and inhibition initiated by steady-state stimulation of sensory systems. It is not clear why the steady-state response should be non-linear only in infants, unless the infant brain becomes refractory at stimulus rates that the adult brain can readily follow. However, this refractory argument is undermined by the finding of Stapells et al (1988) of large individual differences in infants: there is no clear relationship between developmental age and the ability to follow steady-state stimulation.

B. The 40 Hz ERP in Old Age

A diminished sense of hearing is one of the most common functional deteriorations experienced with aging. A substantial proportion of patients encountered in audiometric assessment are from an aged population. If the 40 Hz ERP is to be developed as a tool in clinical audiometric assessment, normative data are clearly needed from aged populations. However, to date little systematic attention has been paid to aged populations by 40 Hz investigators.

Stapells et al (1984) found no effect of aging in subjects 20–61 years of age. This indicates that the 40 Hz ERP does not appreciably change during the age range of normal adult activity. Borda (1984) found that Alzheimer's patients, Parkinson's patients, normal elderly controls (aged 59–61), and normal middle aged controls had similar 40 Hz ERP's in terms of amplitude and latency of the waveform. He did not however, systematically study the effects of aging in the control subjects. Borda (1984) obtained large individual differences in amplitude of the 40 Hz ERP, as have the other investigators discussed in the sections above. Amplitude therefore cannot be considered a very subtle index of population differences. Borda's study does show that the 40 Hz response is readily obtainable in elderly subjects, as they are not in infants. It remains to be shown whether aging has any systematic effect on the 40 Hz response in terms of the more stable measures provided by Fourier analysis of the ERP.

The Effects of Aging on the Transient Auditory ERP

Transient auditory ERP's have been investigated extensively across the lifespan in order to evaluate the effects of aging on sensory and cognitive brain events. Significant effects of aging have been found in early, middle and late components of the transient response. If the linear superposition model is correct, an effect of aging is expected on the 40 Hz ERP, due to changes in the early and middle components of the transient ERP. If the relationship between transient and steady-state responses is non-linear, it is not as clear what effect of aging is expected in the 40 Hz ERP. It may well be, however, that the changes in brain sensory systems will be reflected in changes in the tuned resonance characteristics of these systems.

Of all the evoked potentials studied, the BAEP shows the least variability, being less affected by various factors that significantly influence later components of auditory EPs (Rosenhall, 1985). From the beginning, the small variability of these potentials was an essential argument in favor of their widespread clinical use. Nevertheless, the BAEP is influenced by several variables, the most significant being gender and age (Chu, 1985). A progressive prolongation of latency of waves I–V with age has been demonstrated by various investigators (for example, Allison et al, 1983; Rosenhall et al, 1985; Chu, 1985).

While some of the increase in latency can be attributed to age-related mechanical and neuronal changes in the peripheral auditory system, an increase in central conduction time (the I–V interval) is likely related to aging effects on central auditory structures (Chu, 1985). In addition, reduction in amplitude of the BAEP with aging accounts for a significant proportion of the variability of the BAEP in the population (Psatta and Matei, 1988). Age-related amplitude and latency changes in the late components of the auditory ERP are well established by an extensive literature (see Picton et al, 1984).

Age-related latency increases are also found in the auditory middle latency ERPs (Woods and Clayworth, 1986). However, age seems to have the effect of *enhancing* the amplitude of middle latency component, in contrast to the effect on earlier and later components. Kelly-Ballweber and Dobie (1984) examined a group of audiometrically matched young and elderly subjects and found a dramatic enhancement of Na-Pa and Pa-Nb amplitudes in the elderly subjects. Woods and Clayworth (1986) confirmed that this effect is quite specific - enlarging Pa amplitudes but not other components - and the effect is very consistent in elderly subjects. Since groups were audiometrically matched these data indicate that the Pa component is due to changes in the CNS and not in peripheral auditory structures. Age-related enhancement of middle latency EPs has also been reported in visual and somatosensory modalities (see Woods and Clayworth, 1986).

The enhancement of middle-latency responses with aging has several implications for the study of the 40 Hz ERP. First, it implies that aging differences should be carefully examined in 40 Hz studies. Second, it provides additional evidence for nonlinearities at the level of the system indexed by middle latency responses. Woods and Clayworth (1986) discuss their data with respect to the effects of aging on inhibitory systems within the thalamus, specifically on GABAergic projections from the thalamic reticular nucleus to the medial geniculate nucleus, which has been implicated as a relay to a cortical Pa generator or as a possible Pa generator itself.

To summarize, it is apparent that the scalp distribution of the 40 Hz response and the effects of aging on the response have recieved little systematic attention in the studies reported to date. The present study was undertaken to examine these two questions. A 21 channel recording system was used, representing a substantially more complete scalp distribution than has been used in previous studies.

Method

Subjects

Twelve female subjects participated in the study, constituting two age groups. The five subjects in the "young" group were between the ages of 36 and 40 years (mean age, 38.0 years). The seven subjects in the "old" group were between the ages of 65 and 77 years (mean age, 69.6 years). All subjects were healthy, functioning individuals with no history of neurological or psychiatric dysfunction. Young subjects were mature university students. Older subjects were recruited from a campus seniors group. Care was taken to select for the healthiest subjects among the volunteers. Among a pool of 22 volunteers in the older group, it was found upon interview that the majority of individuals in this age range were taking some form of prescription drug for a variety of ailments. Subjects were asked to refrain from caffeine, nicotine and alcohol for at least two hours before the study. In addition, in the elderly group it was important to screen for individuals with normal hearing in both ears. Given the above criteria, seven subjects were finally selected, of whom five were used in the final data analysis (one subject was found on testing to have a significant hearing loss in one ear; the other subject was dropped from analysis because of faulty electrodes).

Recording

Subjects were seated in a chair in a quiet but not soundproof laboratory. An electrode cap fitted with 21 electrodes was positioned on the head to correspond to the International 10-20 system of electrode placement (Jasper, 1958), and referenced to linked earlobes. Figure 1 shows diagrammatically positions of electrodes placed according to the 10-20 system. A midline

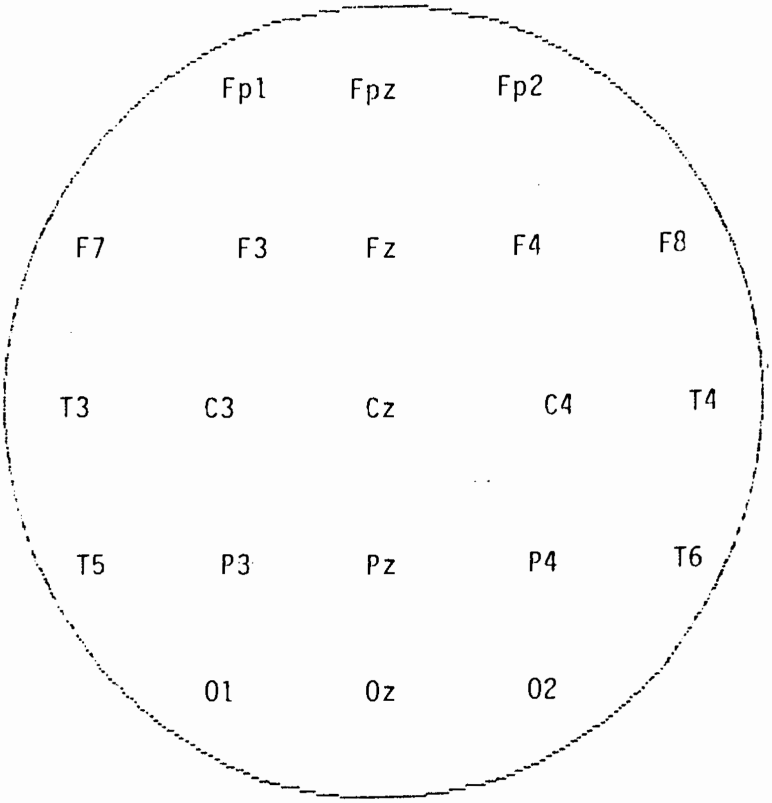


Fig. 1 Standard International (10-20)
Electrode Placement

forehead electrode at the hairline served as ground. Interelectrode impedances were maintained below 2 kOhms. Standard headphones, with cushions, were placed over the ears. Subjects were instructed to relax with eyes closed while listening to stimuli.

Stimuli consisted of 1000 Hz ramped tone bursts with rise and fall times of 2 msec and a plateau of 10 msec, delivered at rates of 30, 35, 40, 45 and 50 per second. One trial was recorded at each stimulation rate, binaural stimulation, except at 40 Hz, in which case there were two binaural trials and one each of right ear only and left ear only.

Thresholds were obtained for each subject by the method of limits. This procedure provided only a crude estimate of hearing threshold, since the ambient noise level in the recording room was about 30 dB. This rough procedure did however detect a loss of hearing in one ear of an older subject who was eliminated from the experiment.

Data were recorded and averaged with a Bio-logic Systems Corp. Brain Atlas III computer. Averages of 500 reponses were recorded using a 128 msec sweep time. These averages were stored on floppy disks for further analysis.

Data Analysis

The Bio-logic mapping system was utilized for the following types of analysis:

1. Display of the averaged waveforms;
2. to produce color contour maps of the scalp distribution of response amplitude at any of 256 points along the 128 msec recording epoch;
3. to provide color contour maps of the scalp distribution of response

amplitude at specific frequencies via a Fast Fourier Transform of the averaged data.

Additional off-line analysis was performed after subjecting the averaged waveforms to Fourier analysis at the frequency of stimulation. The results of the Fourier Analysis are the phase (in radians) and amplitude (in microvolts) of the fundamental frequency of the waveforms. These data were analysed in several ways:

1. Amplitude and phase were graphically plotted against recording position for each subject and an estimate of variability across subjects was obtained;
2. pure sine waves were generated from the phase and amplitude output of the Fourier analysis to provide "Fourier filtered" waves to be reanalysed using the Bio-logic system.
3. contour maps of the scalp distribution of the amplitude of response at the frequency of stimulation were produced;
4. phase angle maps, using vectors to represent phase and amplitude at the frequency of stimulation were produced to represent activity at each of the 21 recording postitions.

Results

The scalp distribution of ERP's for subject A.R. (age 40) is shown in Figure 2. The steady-state following response can be seen clearly at all stimulation rates and at most scalp sites with the exceptions of the very frontal sites (Fp1, Fpz, Fp2, F7 and F8). Steady-state responses clearly have a wide scalp distribution. Looking at the response across stimulation rates (Figure 2-A), amplitude is maximal and the waveform is clearly sinusoidal at 40 Hz. The response degenerates in form and amplitude at rates above and below 40 Hz. Figure 2-B shows two seperate 40 Hz trials in subject A.R. These waveforms are nearly identical in scalp distribution and in form and amplitude. Consistent 40 Hz replications were obtained in all subjects. Poor responses were obtained from the monaural stimulation trials (Figure 2-c). In all subjects the following responses from monaural stimulation were decreased in amplitude from the binaural responses and were much "noisier" in form, although a following response could usually be discerned at fronto-central sites.

Similar responses were obtained in the rest of the younger subjects, with variations in maximal electrical response with respect to electrode site and rate of stimulation. Figure 3 shows one younger subject (D.E.) whose response at 35 Hz is nearly twice the amplitude of the response at 40 Hz. Similarly, subjects varied in aspects of the scalp distribution of the response. Responses were low in amplitude at frontal sites in all subjects, while responses at fronto-central sites (around Fz and Cz) were good in nearly all subjects. Temporal and occipital sites were more variable, with some subjects showing very good responses at these sites, but more showing poor responses at these sites.

The phase angle maps of Figure 4 indicate the scalp distribution, amplitude of response, and phase of response with respect to stimulus onset for each subject at each stimulation rate. Vectors on the maps show amplitude and phase of the Fourier component of the waveform at the frequency of stimulation. The phase angle maps for subject A.R. can be compared to the scalp distribution of her ERP waveforms in Figure 2.

Clearly, considerable between-subject variance exists in the response to steady-state stimulation. For comparison with the 40 Hz literature, Figure 5 shows the response at Cz at the different stimulation rates for each subject. Between subject variance in amplitude of response at Cz is consistent with that reported in previous studies (Borda, 1984; Stapells et al., 1987).

When Cz waveforms are averaged across subjects (Figure 6), a "classic" 40 Hz response is seen in the younger subjects, with an increase in amplitude and sinusoidal waveform at 40 Hz. However, given the between-subject variability of the response, differences in amplitude between stimulation rates and between groups are not significant.

Figure 7-A shows the amplitude of the 40 Hz component for the 40 Hz stimulation rate for each of the young subjects for all electrode sites. Note the spread in amplitude at each site between subjects and that the midline sites form "clusters" within each subject. Similar responses were thus recorded at sites adjacent to each other along the midline (for example, C3, Cz and C4).

Figure 7-B plots the phase of the 40 Hz component of the 40 Hz following response for the younger subjects. Note that the midline "clusters" are also apparent in this plot, and that the inter-subject spread is much less at fronto-central sites than is the spread in amplitude. These data agree with the

finding of Stapells et al. (1987) that phase is a better index of the 40 Hz response than is amplitude. Similar plots were obtained at each stimulation frequency and in both age groups.

Variance of amplitude and phase of the 40 Hz component of the 40 Hz ERP is plotted in Figure 8. Figure 8–A shows that the amplitude variance in the two age groups is very similar at all sites on the head. The divergence in variance between the two age groups at the back of the head is due entirely to the contribution of one old subject (N.M) who showed a very large response in parieto–occipital regions but a small response at fronto–central regions. Discounting the contribution of this subject, variance in amplitude is very similar between the two groups. Thus, amplitude variance is approximately equal at all recording sites in the two groups. A different situation is portrayed in the phase variance plot of Figure 8–B. Frontal and central sites form distinct clusters of low variability compared to other sites. The differences between young and old plots is difficult to interpret because of the large contribution to the variance of one or two subjects. It is clear that the plots for the two age groups follow a similar trend, however.

Phase variance for all ten subjects is plotted in Figure 9. Figure 9–A shows that the phase variability across electrode sites shows a very similar pattern for binaural and monaural stimulation. Fronto–central sites show very distinct clusters, with the other locations being considerably more variable. Figure 9–B plots phase variance against electrode location for the five stimulation rates. A pattern of phase variability and stimulation rate is not clearly discernable in this plot, but it is clear that at all stimulation rates, phase is most stable the frontal (F3, Fz, F4) sites. More variability is present at Cz at stimulation rates of 30 and 35 Hz.

The absolute value of the difference between Cz amplitude and Oz amplitude ((Cz–Oz)) and the absolute value of the difference between Cz amplitude and Pz amplitude ((Cz–Pz)) was calculated for each subject at each stimulation frequency , and mean differences for each group were tested for significance with a *t*–test. The difference between age groups was significant (*t*=2.29; *df*=8; p<.05) only for (Cz–Pz) at the stimulus rate of 40/sec. Four of the five old subjects had a (Cz–Pz) value of >0.2 uV. All of the young subjects had a (Cz–Pz) value of <0.2 uV, and four of the five had a value of <0.1 uV.

Differences in phase and amplitude of response at Cz and Oz in the two age groups are manifested in the average amplitude contour maps in Figure 10. These maps plot the amplitude of the Fourier component of the average waveforms for each group, at the exact stimulation frequency. A "hole" in the map at parietal sites is seen in the map for the older subjects which is not seen in the map for the young subjects, reflecting the difference in activity between Cz and Pz in the old subjects. The difference in amplitude between Cz and Pz in the younger subjects is not significant, nor are contour steps at other sites on the average map. This "hole" is also seen in the average waveforms for each group shown in Figure 10. These group average maps must be interpreted with the between–subject variability in mind, such that the only between–group difference that can be considered significant is the (absolute) difference in activity between Cz and Pz. However, the between–subject consistencies in phase demonstrated in Figures 7 and 8 are manifest in the sinusoidal waveforms at fronto–central sites in the average maps, especially at stimulation rates of 35 and 40 per second.

Fig. 2 Scalp Distribution For Subject A.R. (Age 40)

Calibration bars indicate a recording epoch of 128 msec and an increment of 0.5 uV. Waveforms are displayed in the International 10-20 positions.

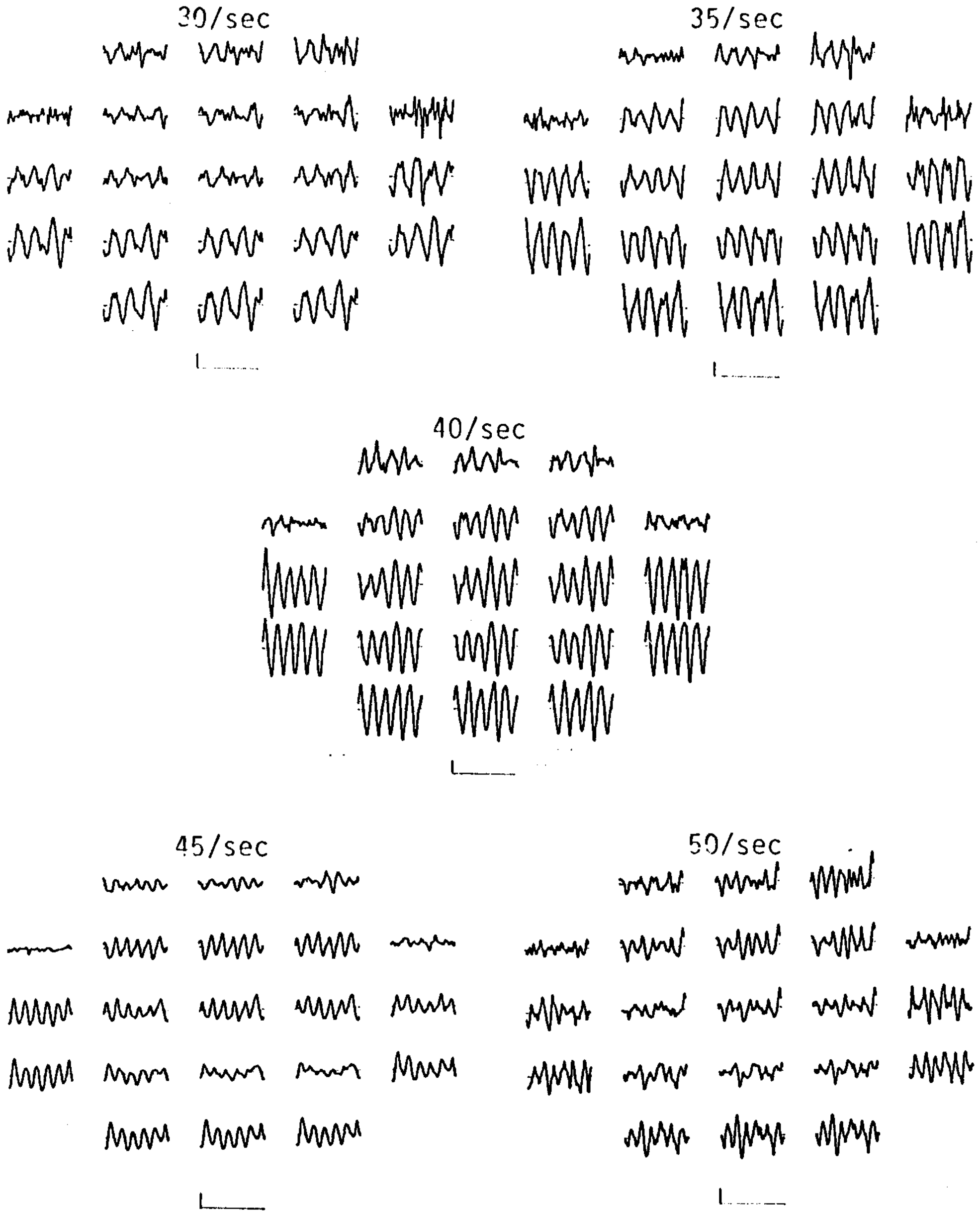
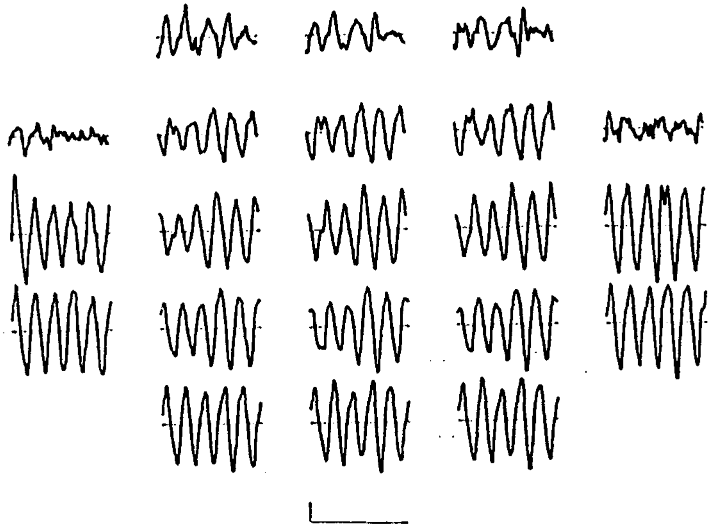


Fig. 2-A Scalp Distribtion of Subject A.R. (Age 40)

Effect of Stimulation Rate

Calibration bars indicate a recording epoch of 128 msec and an increment of 0.5 uV. Waveforms are displayed in the International 10-20 positions.

40/sec Trial 1



40/sec Trial 2

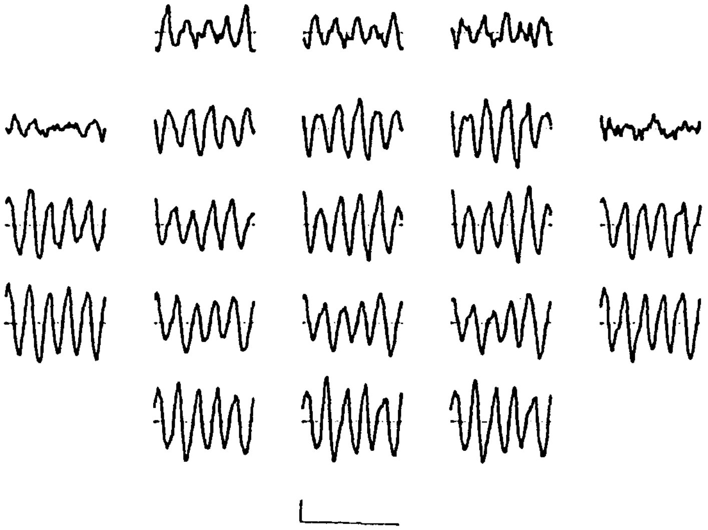
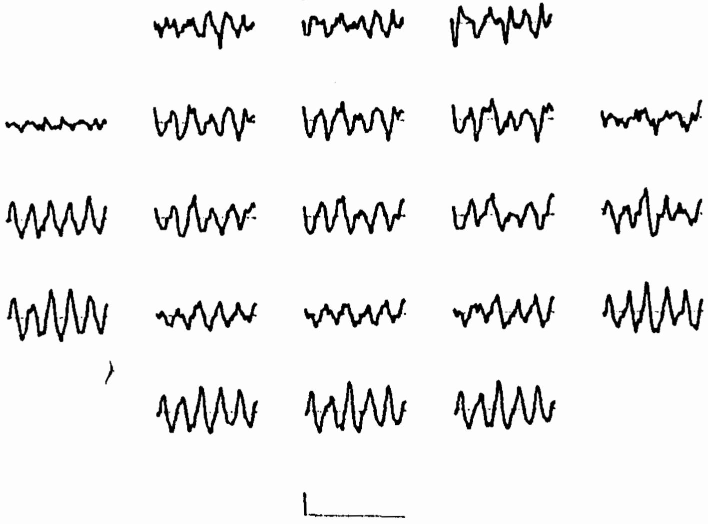


Fig. 2-B 40 Hz Replications

Right Ear



Left Ear

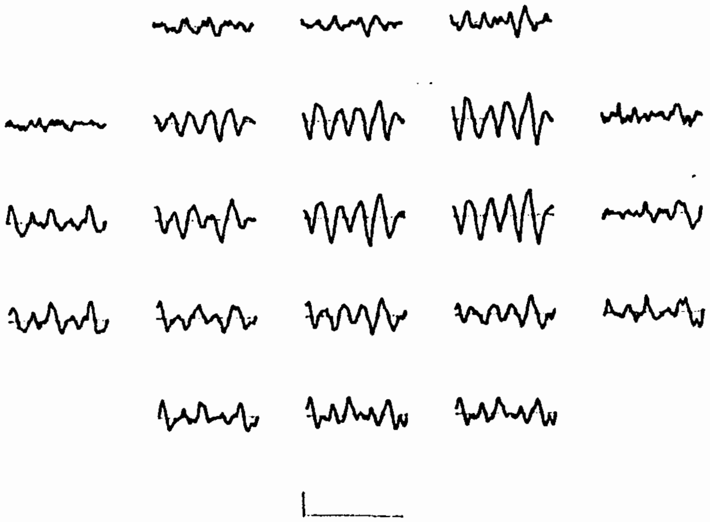
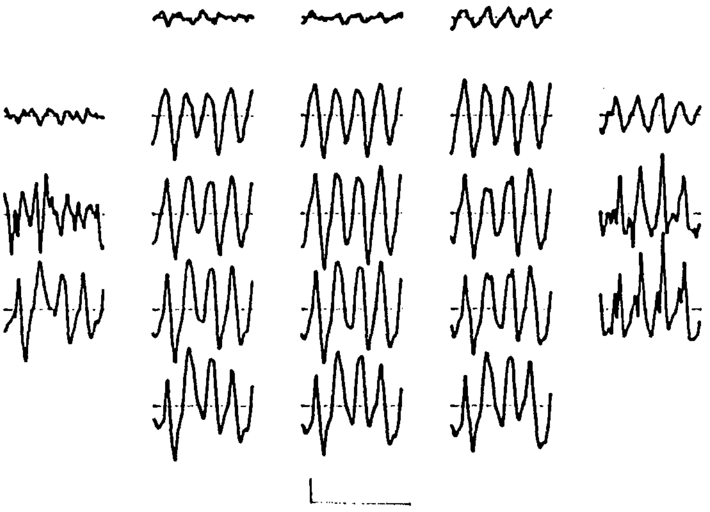


Fig. 2-C Monaural Stimulation Trials at 40 Hz

35/sec



40/sec

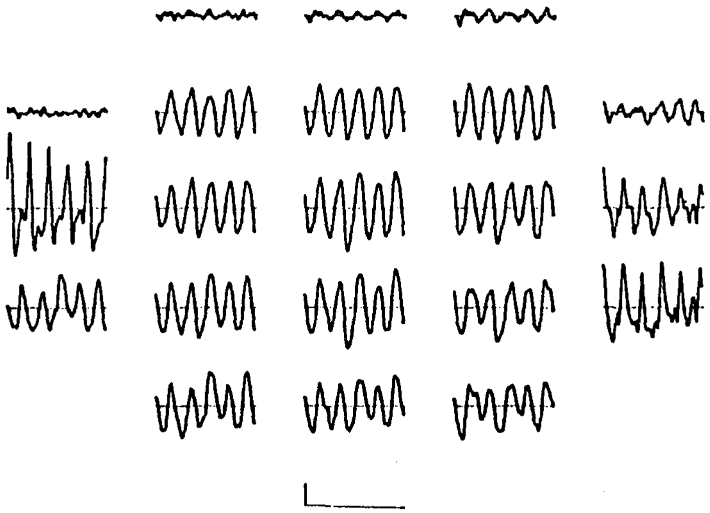


Fig. 3 Scalp Distribution of Subject D.E. (Age 37)

Maximal response is at 35 Hz

Calibration bars indicate a recording epoch of 128 msec and an increment of 0.5 uV.

Fig. 4 Phase-Angle Maps

Vectors show phase and amplitude of Fourier component at the rate of stimulation. International 10-20 recording positions are shown. Numbers above each map indicate the rate of auditory stimulation. Subject initials identify each map.

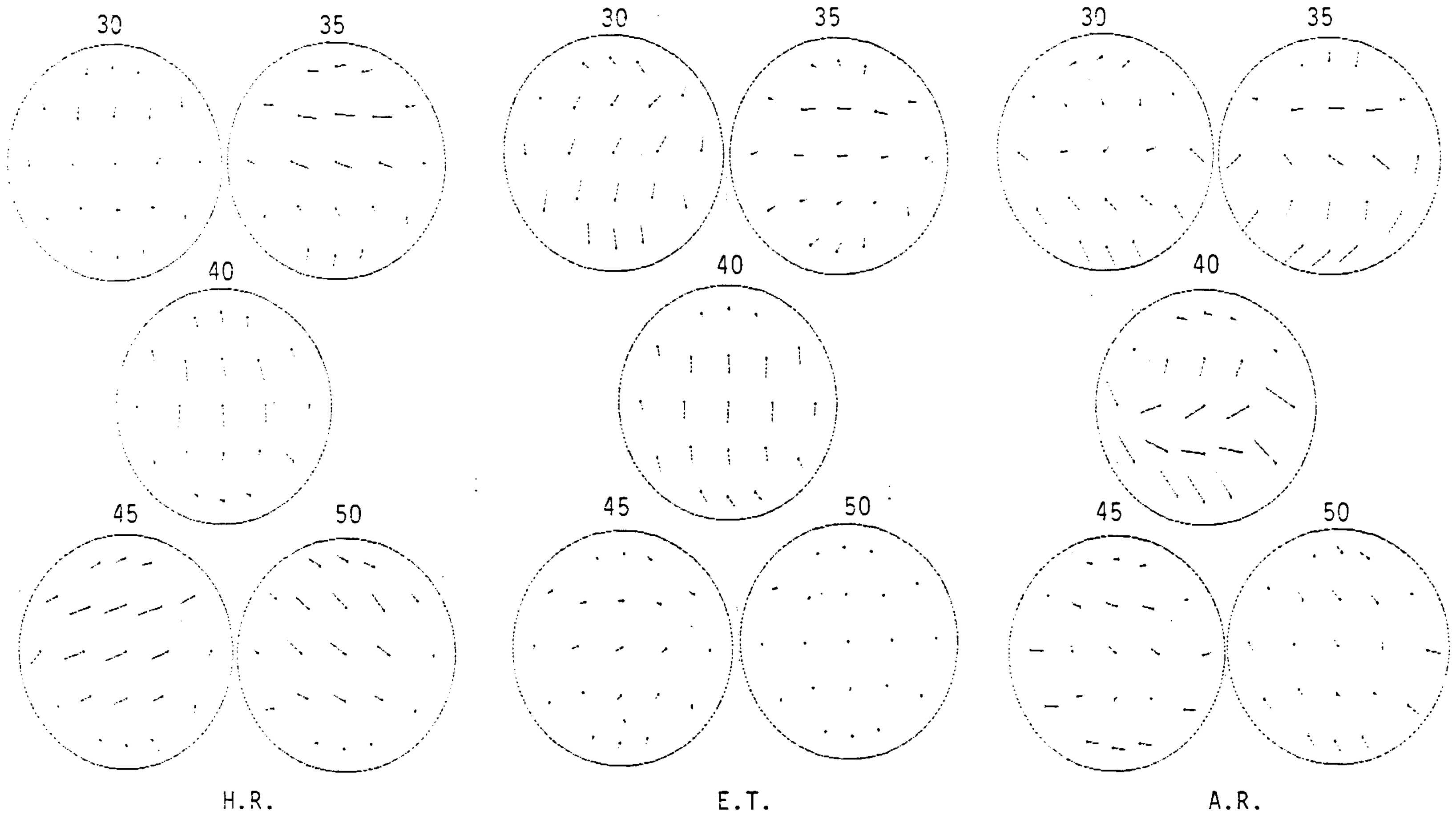
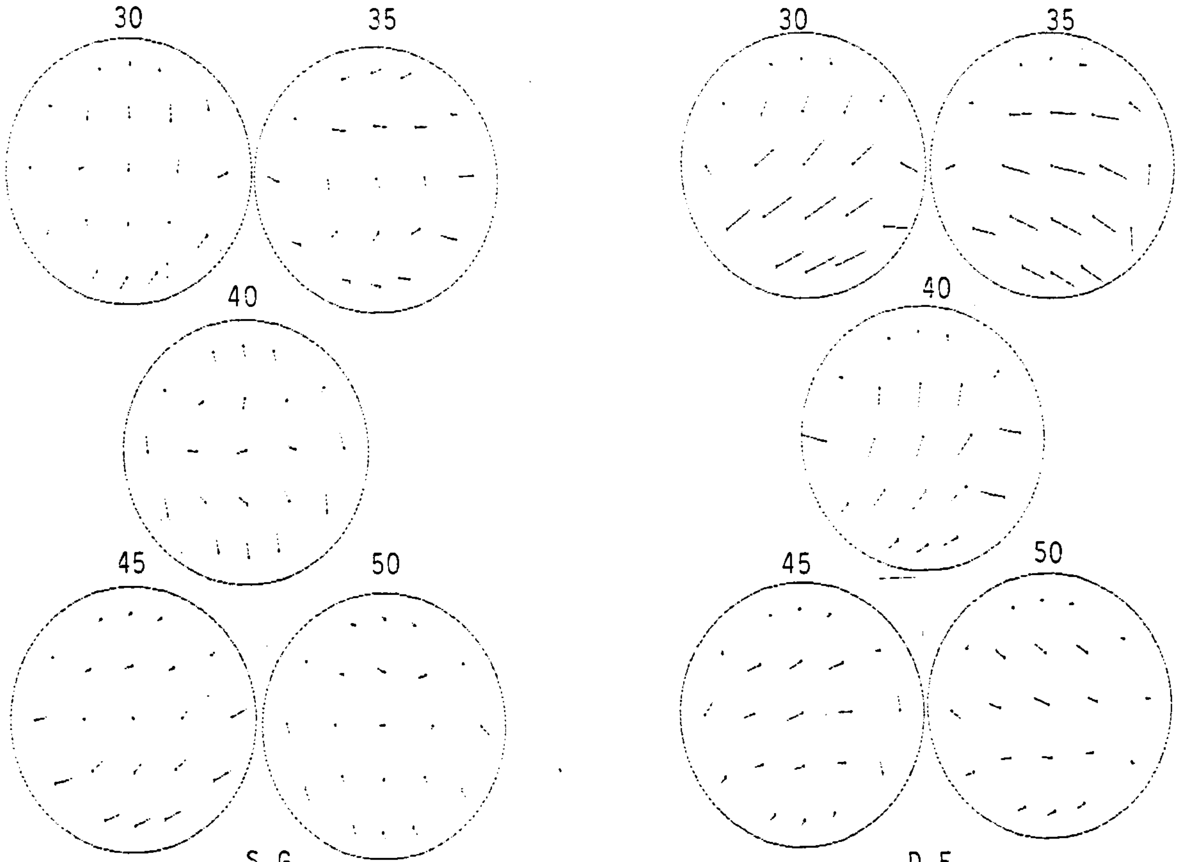


Fig. 4-A Young Subjects



S.G.

D.E.

Fig. 4-A Young Subjects

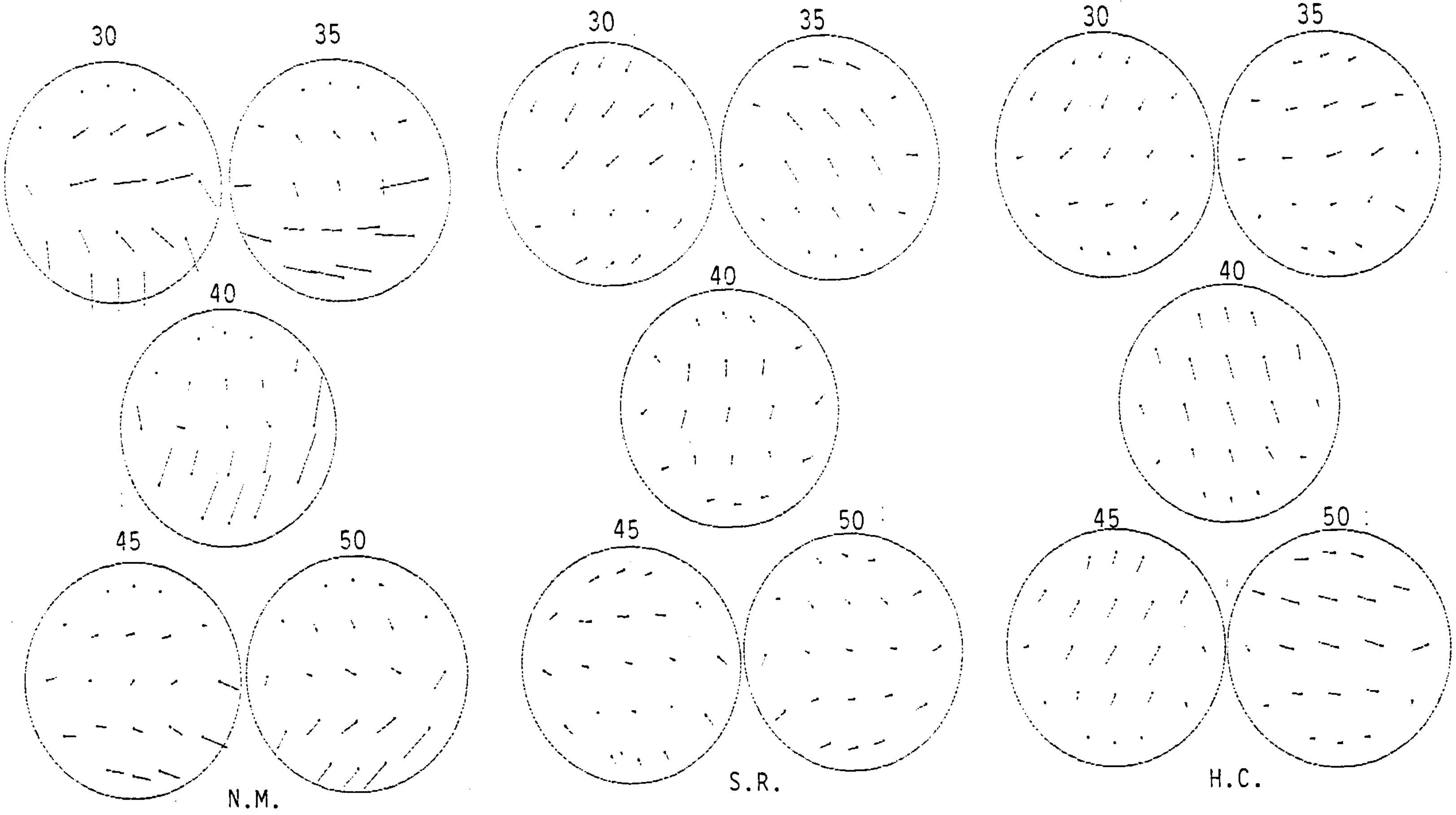


Fig. 4-B Old Subjects

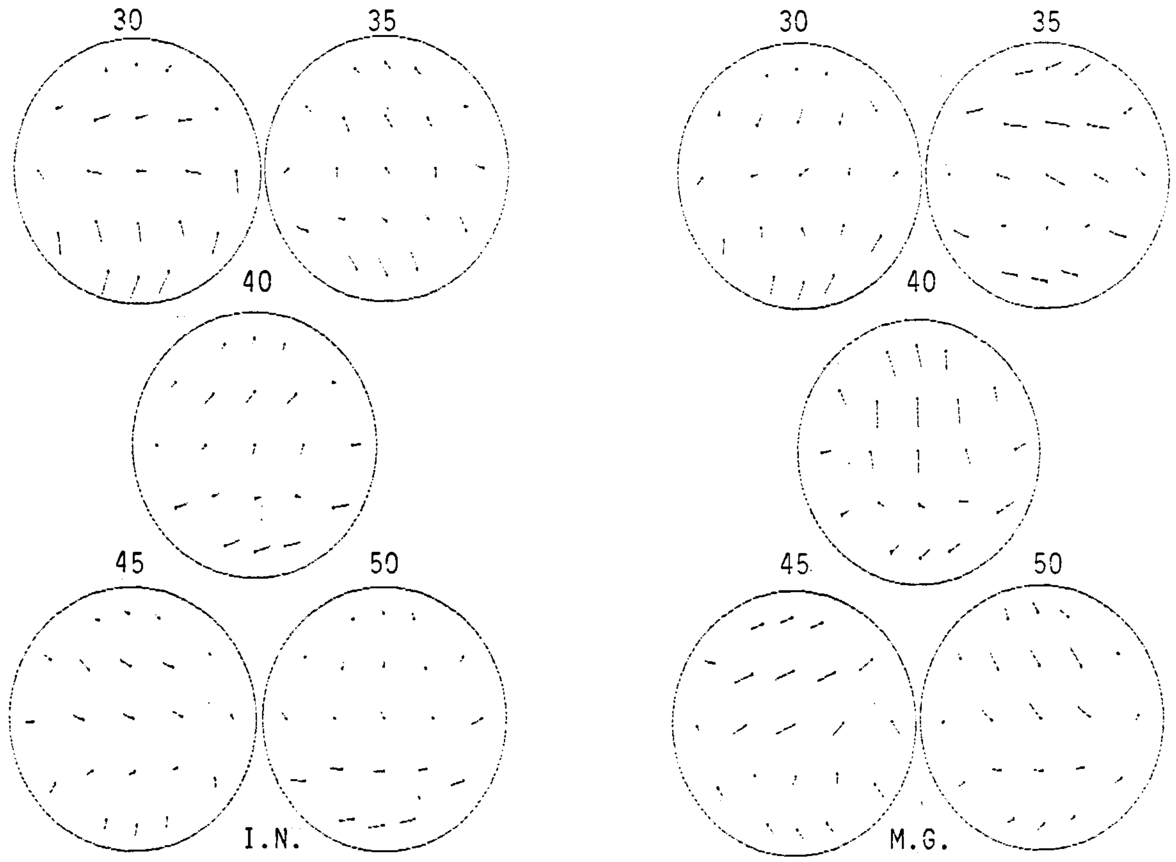
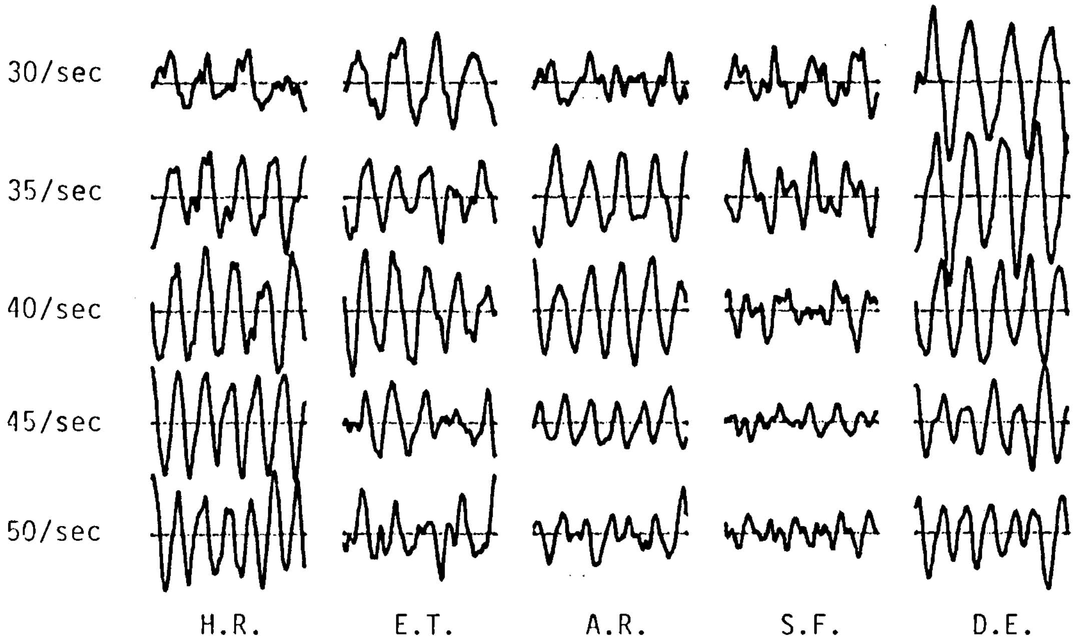


Fig. 4-B Old Subjects

A. Young Subjects



B. Old Subjects

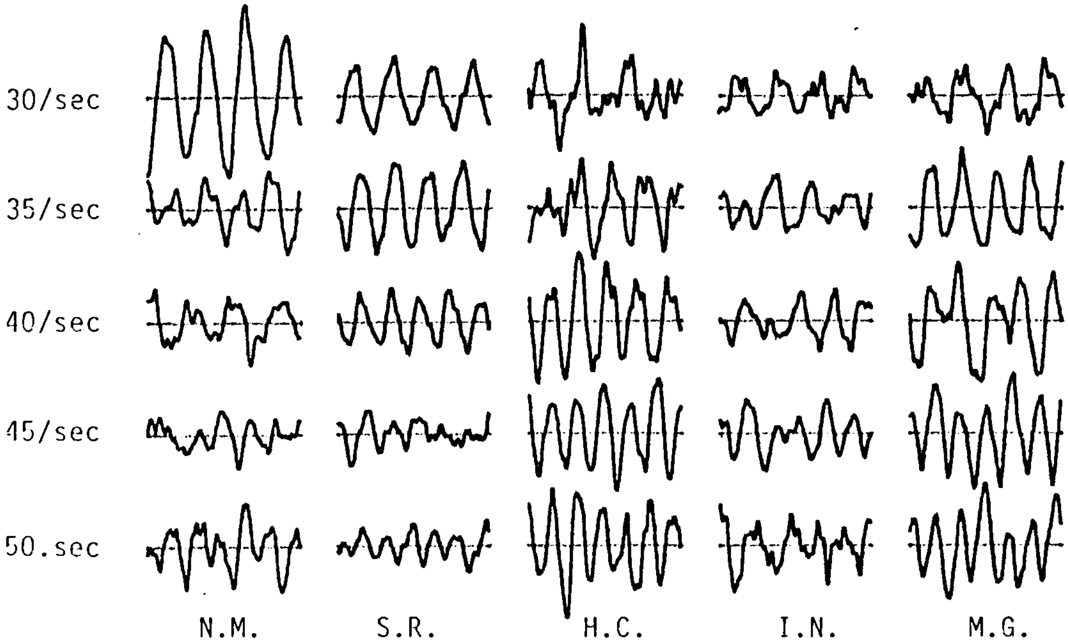


Fig. 5 Response at Cz Over the Range of Stimulation Rates Subjects initials identify each rate series. Calibration bar indicates a recording epoch of 128 msec and an increment of 0.5 uV.

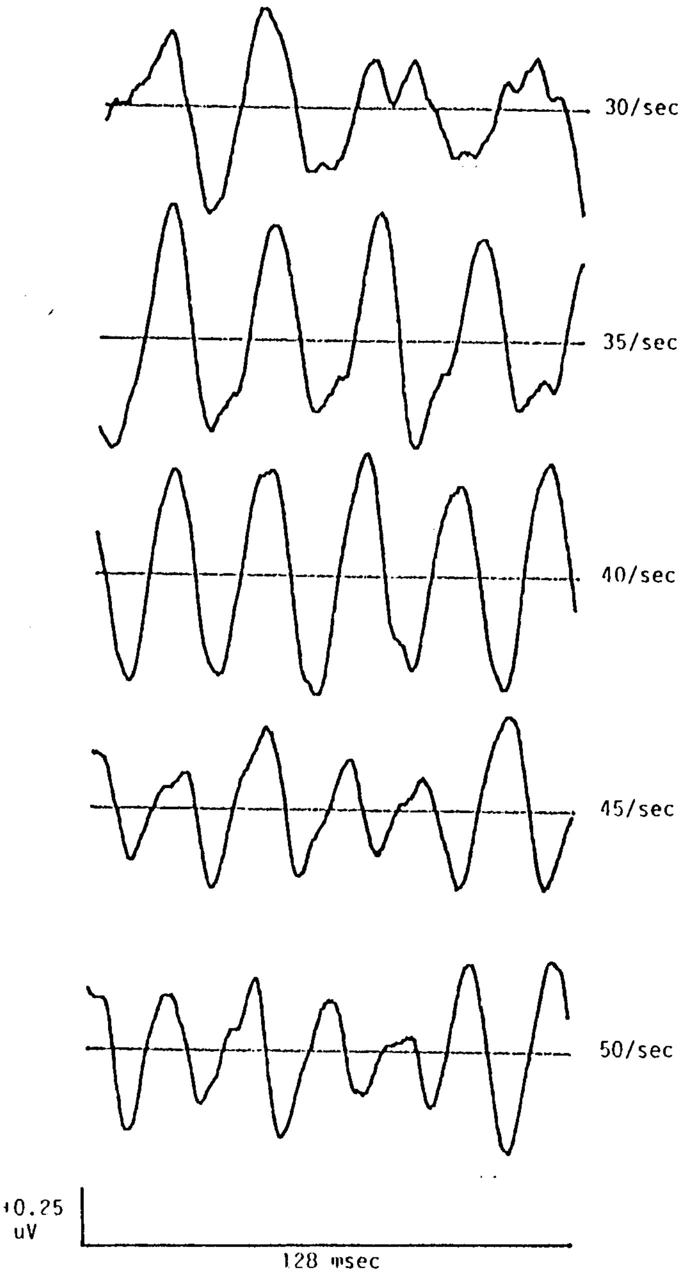


Fig. 6 A

Effect of Stimulation Rate On Response at Cz

Average of Young Subjects (N=5)

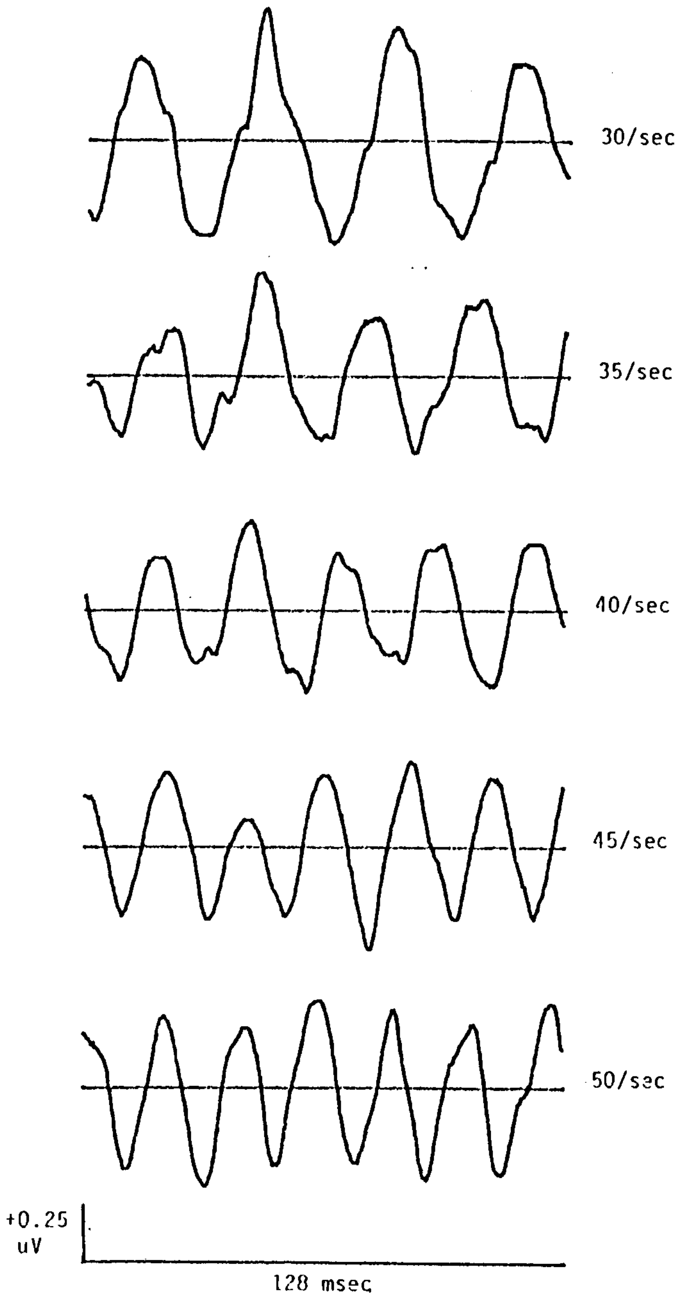


Fig. 6-B

Effect of Stimulation Rate On Response at Cz

Average of Aged Subjects (N=5)

Fig. 7-A

Amplitude of the 40 Hz Component For Five Young Subjects

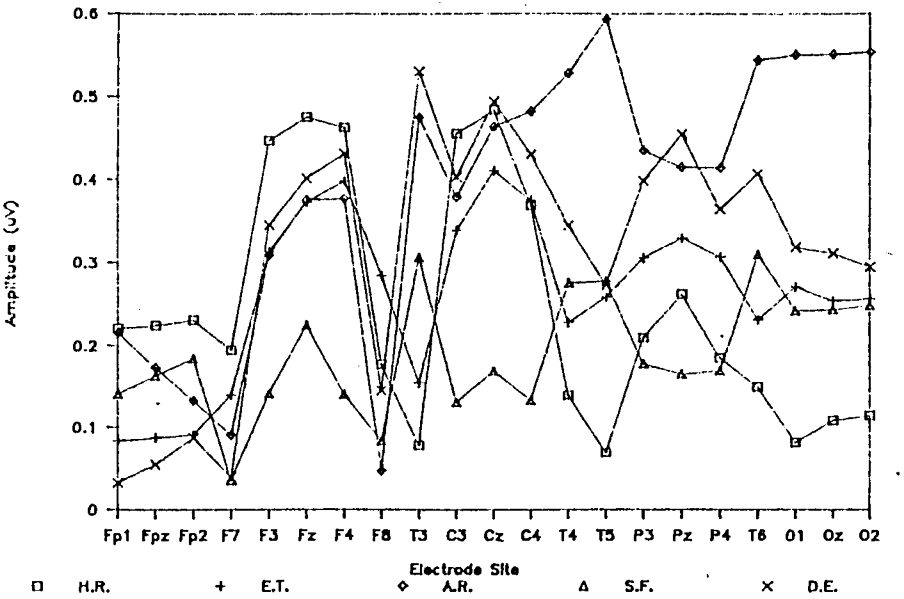


Fig. 7-B

Phase of the 40 Hz Component For Five Young Subjects

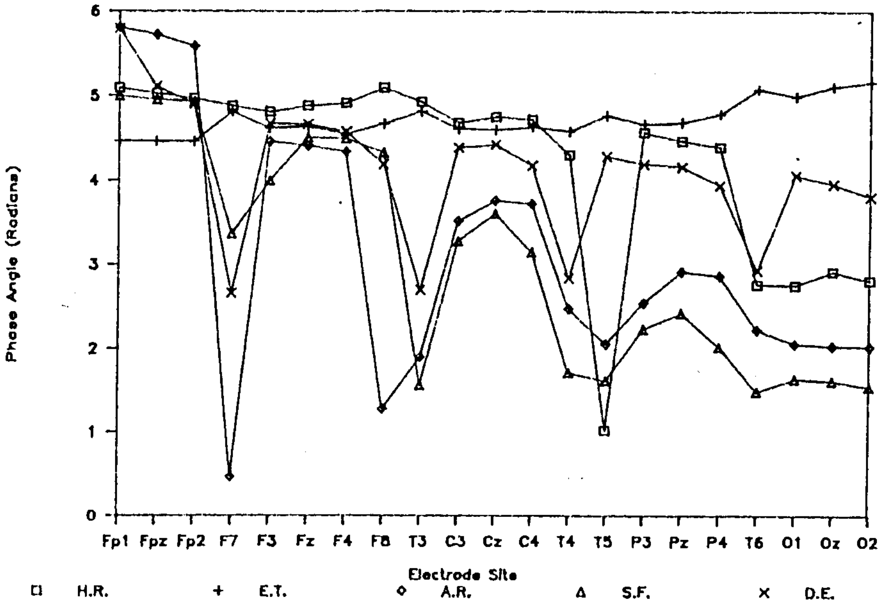


Fig. 8-A

Variance of Amplitude of the 40 Hz Component For Both Age Groups

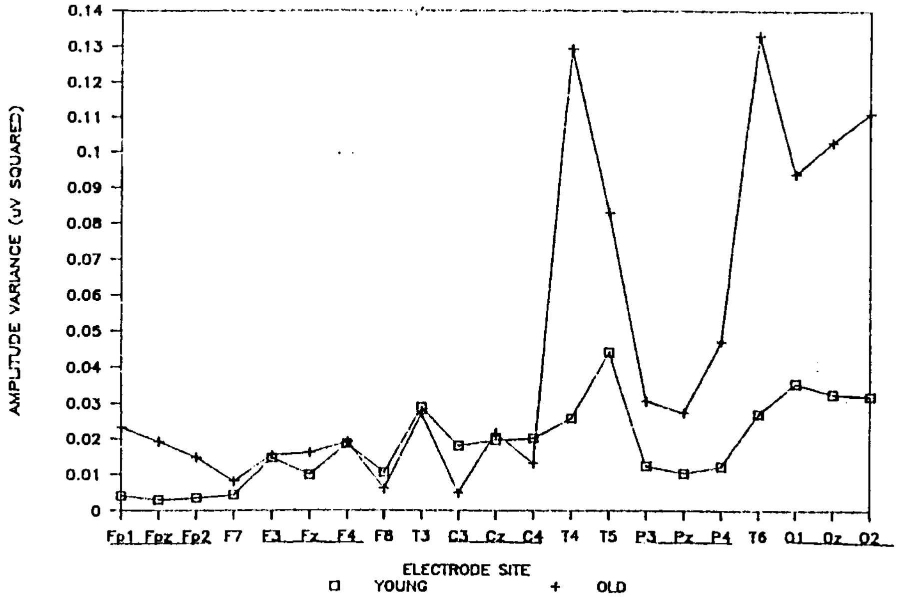


Fig. 8-B

Variance of Phase of the 40 Hz Component For Both Age Groups

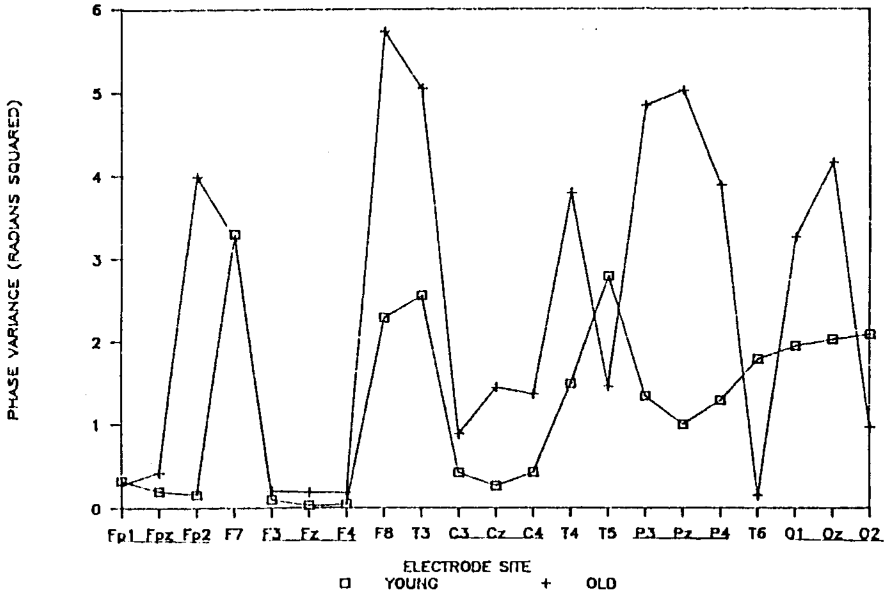


Fig 9-A

Phase Variance of the 40 Hz Component For Binaural and Monaural Stimulation at 40 Hz. Combined Groups (N=10).

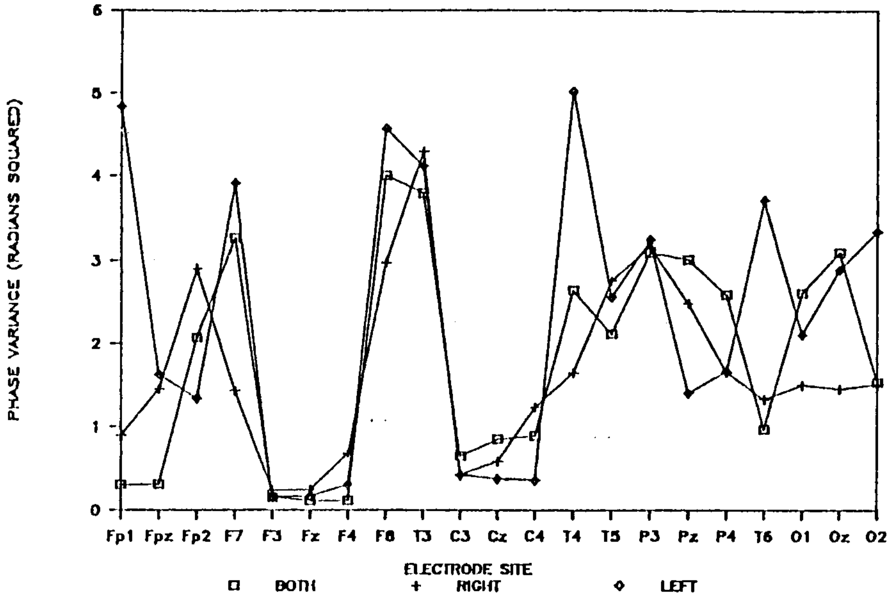
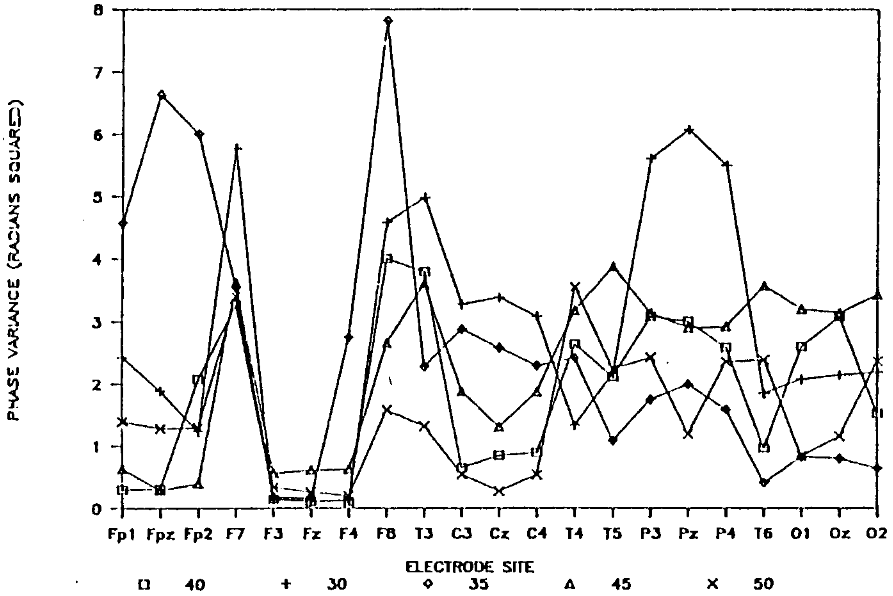


Fig. 9-B

Phase Variance of the Fourier Component at the Frequency of Stimulation. Combined Groups (N=10).



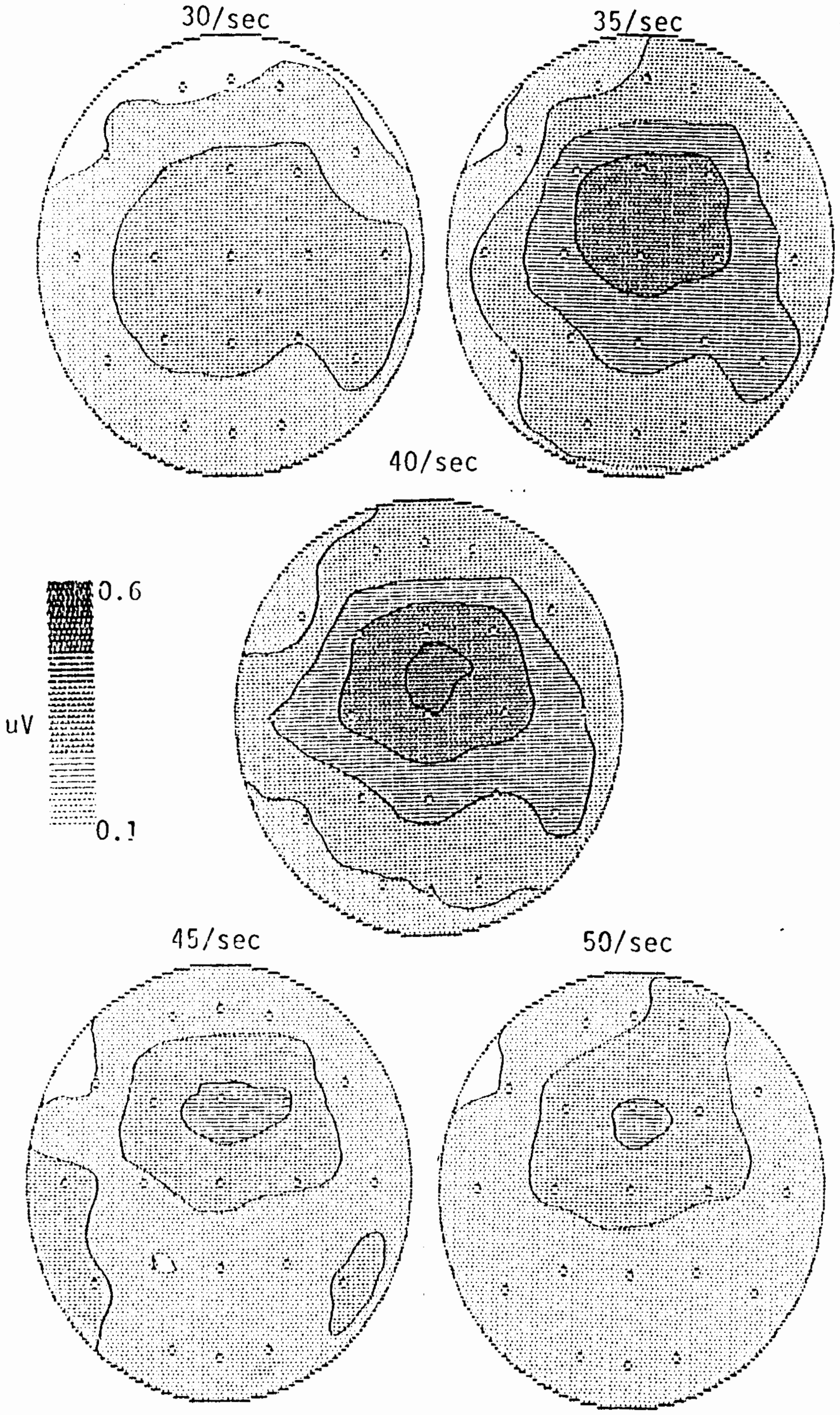


Fig. 10-A

Contour Maps of the Fourier Component at the Frequency of Stimulation. From the Average Waveforms for the Younger Subjects (N=5).

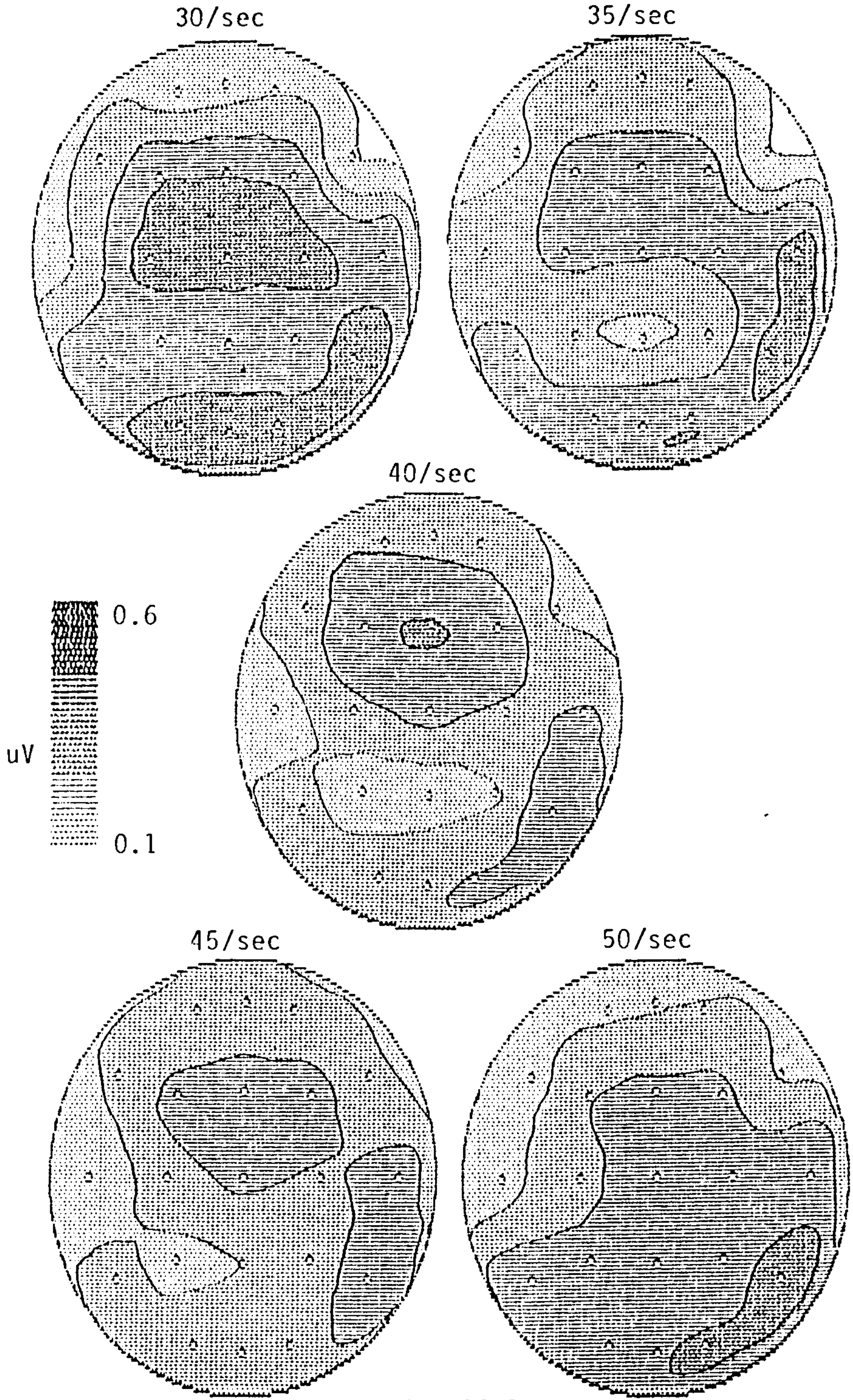


Fig. 10-B

Amplitude Maps of the Amplitude of the Fourier
Component at the Frequency of Stimulation
From the Average Waveforms for the Older Subjects (N=5).

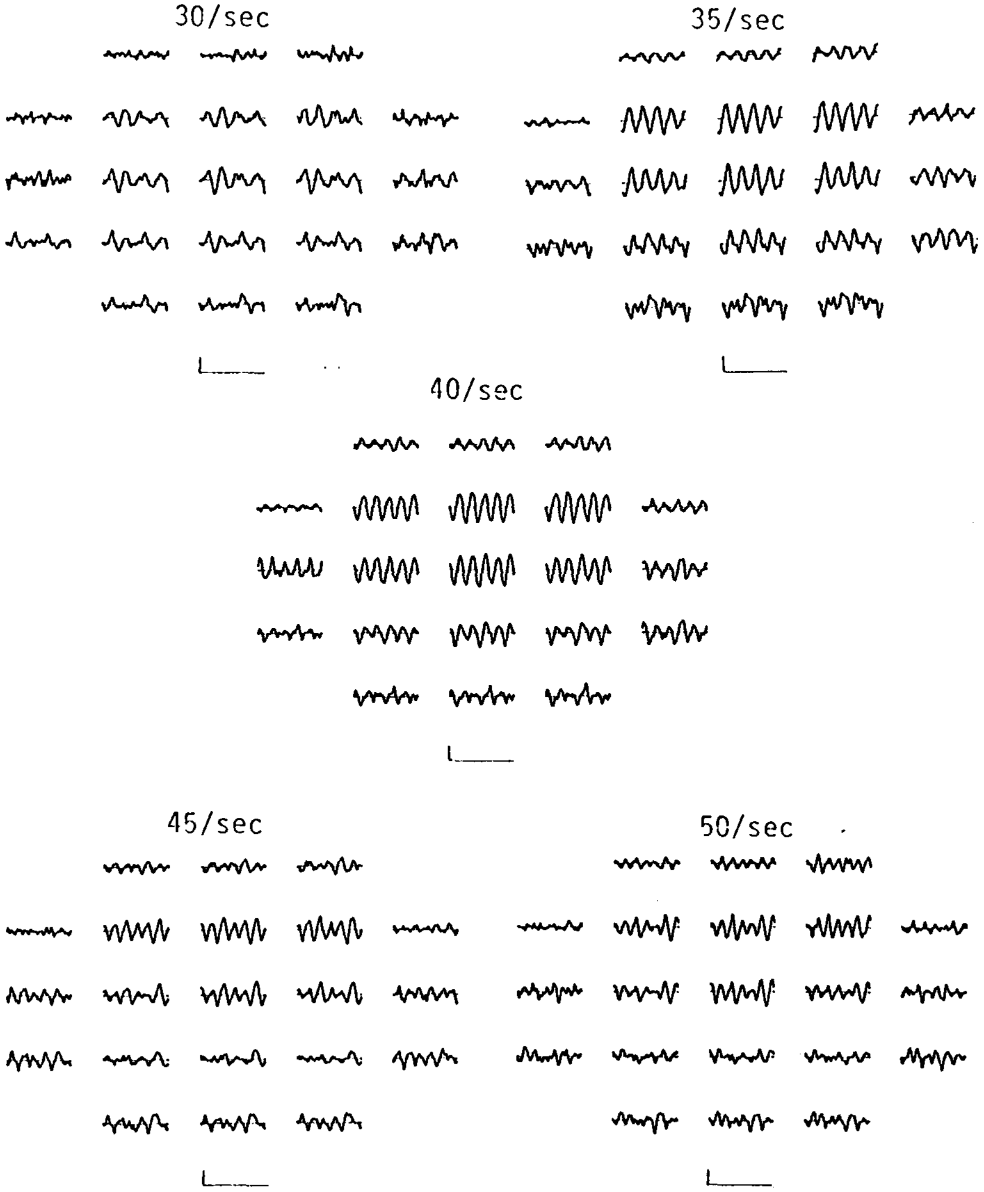


Fig. 11-A

Average waveforms for the younger subjects (N=5) at the various stimulation rates. Calibration bars indicate a recording epoch of 128 msec and an increment of 0.5 uV.

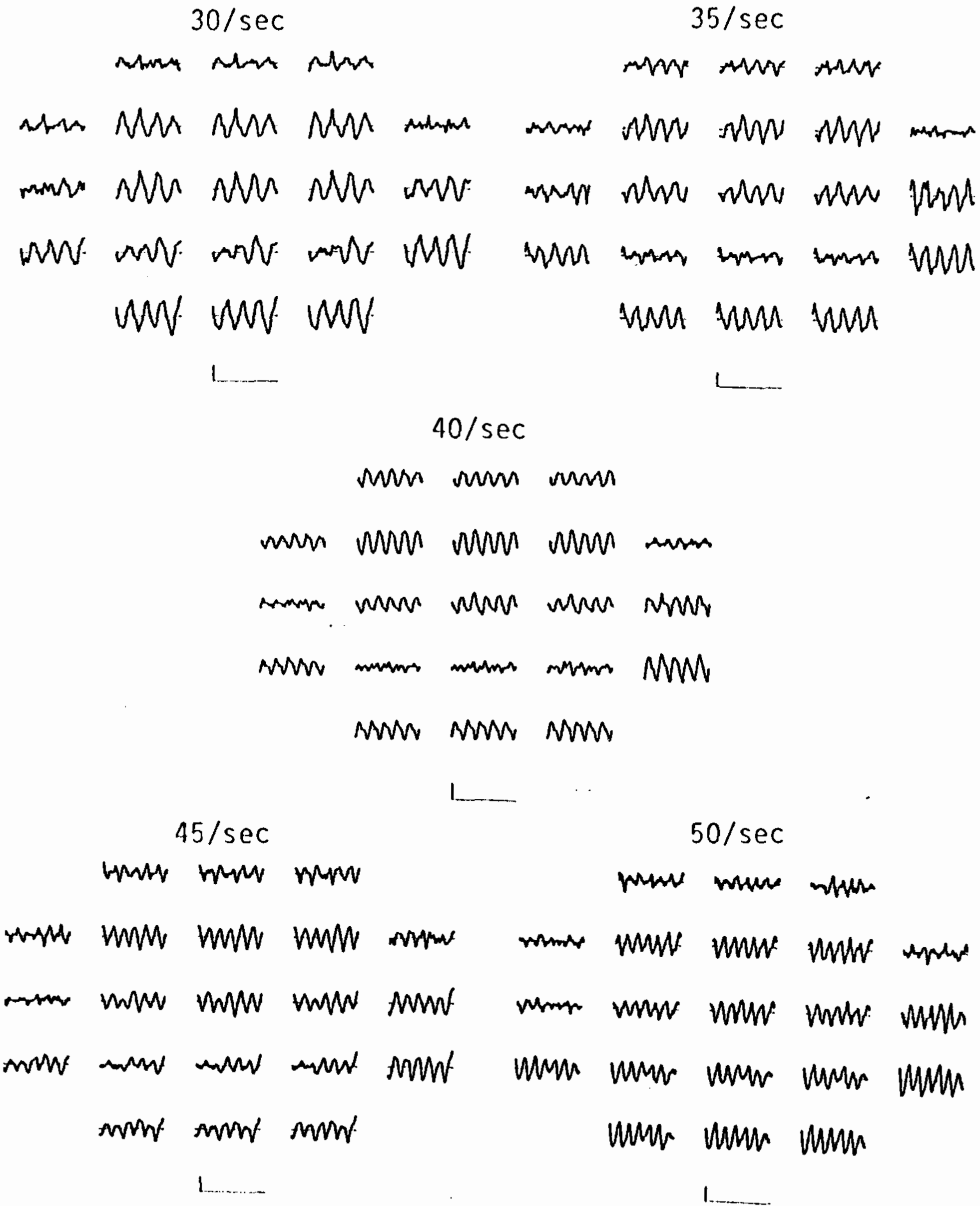


Fig. 11-B

Average waveforms for the older subjects (N=5) at the various stimulation rates. Calibration bars indicate a recording epoch of 128 msec and an increment of 0.5 uV.

Discussion

The results of this study are of interest with respect to a number of points:

1. The scalp distribution of the 40 Hz ERP has been characterized. Most subjects had low amplitude responses at prefrontal sites, and most, but not all subjects had a robust response at fronto-central sites. Subjects varied in whether or not there was a good response at temporal and occipital sites relative to fronto-central sites.
2. The scalp distribution of the response to steady-state auditory stimulation has been described for a range of stimulation rates from 30 to 50 Hz. Subjects generally show a maximal response at one stimulation rate which is at least 0.2 *u*V higher in amplitude at a particular site than at the same site at a different stimulation rate. An "enhancement" effect can thus generally be obtained within this range of stimulation rates. The rate at which an enhanced response is obtained varies across subjects from 30 to 45 Hz, a finding which confirms that of previous investigators (Stapells et al., 1984). The sites on the scalp at which a good following response is obtained generally is the same across stimulation rates. This indicates that the brain is being driven in a similar manner with steady-state stimulation in this range of presentation rates, but with an enhancement in amplitude of the response at one particular rate. Note that fronto-central sites usually stay in phase with each other across stimulation rates.
3. A comparison of scalp distributions for monaural vs binaural stimulation (at 40 Hz) has been provided. Monaural responses are invariably smaller in amplitude and degraded in form compared to the binaural responses, but the sites at which the best following responses are obtained are the same with

both binaural and monaural stimulation. Subjects may show a slight right or a left ear advantage. In addition, the phase variability plots are nearly identical with binaural, right ear or left ear stimulation, indicating that the brain is being driven in a similar manner, in all three cases, from similar generator sites. This finding may reflect the crossing over of sensory neurons to activate bilateral generators of the steady-state response. Apparently this activation is to practically the same extent bilaterally, since no large changes in scalp distribution were obtained with right ear versus left ear stimulation.

4. This study has confirmed the finding of previous investigators of variability of phase and amplitude in the 40 Hz ERP. The use of a multichannel recording system has enabled the characterization of this variability in terms of scalp topography. Amplitude variability was shown to be essentially the same across the scalp. Phase, on the other hand showed some compelling differences in its variability over the scalp. The fronto-central locations (around Cz and Fz) were shown to be quite stable in phase, in contrast to other locations on the scalp. This finding has several implications. First, it indicates that the best locations for recording 40 Hz ERPs with a single channel system are at Cz and Fz (and at positions immediately adjacent to them. Second, this finding very likely reflects on the location of the generator of the response.
5. This study has confirmed that a quite robust response may be obtained at electrode sites over sensory (visual and auditory) cortex. This finding may shed light on the question of whether multimodal sensory systems are activated by 40 Hz auditory stimulation.
6. Although responses of younger and elderly subjects were in general quite similar, the two age groups in this sample could be discriminated fairly

well (in four out of five cases) by the (absolute value) of the difference in amplitude of response between Cz and Pz. In this sample, this seems to index a <u>difference</u> in the activity of the two sites (i.e., that young subjects show a similar response in the two sites, but older subjects display a different response in the two sites), rather than a simple decrease or increase in activity in one of the sites in one of the age groups. In the geriatric sample, three of the five subjects show Fz amplitudes of >0.2 *u*V less than Cz, but one subject shows an Fz amplitude of almost 0.4 *u*V larger than Cz. Of course, with such small N's this index is difficult to interpret, but the fact that the index is significant only at 40 Hz and not at other stimulation rates, and the fact that a significant difference is not found between more distant locations (for example, Cz versus Oz) gives it some credence as a possible analytical tool.

7. There is usually (in 8 out of 10 subjects), an amplitude maximum at one rate which is at least 0.2 *u*V higher than at the same sites at a different stimulus rate. This indicates that the 40 Hz "enhancement" effect can usually be obtained with a range of stimulus rates from 30-50 Hz, although many investigators use extreme rates (for example, 20 versus 40 Hz) to demonstrate the amplitude enhancement effect (Borda, 1984; Schrock, 1985; Sheer, 1987).

The finding that phase of the 40 Hz response is quite stable at fronto-central sites compared to other recording locations is very interesting in the context of previous speculation on the location of the generator site of the response. Since thalamic generators are most likely to be recorded at fronto-central sites (Sheer, 1987), these data are consistent with the hypothesis that a thalamic source is involved in the generation of the response. However, it does not exclude the possibility that sensory cortex is involved in the response. In fact, robust responses are recorded at sites over visual and auditory cortex in many, but not all subjects. According to the Weinberg et al. (1987) model described in the introductory section of this thesis, the 40 Hz ERP is the result of resonance in a system consisting of reciprocally organized thalamo-coticothalamic projections, and a "source" will be obtained wherever the system is sampled.

The findings of this study are consistent with the hypothesis that the effects of both thalamic and sensory cortex sources are being observed in the scalp distribution of the 40 Hz ERP. Additional evidence for this hypothesis is given by previous studies which indicate that 40 Hz visual stimulation will give large amplitude ERPs at sites overlying visual cortex while auditory stimulation gives large amplitude responses at sites near primary auditory cortex (Judd, 1987), and that somatosensory stimulation gives large amplitude responses at sites overlying somatosensory cortex (Galambos, 1982).

If the 40 Hz response is generated by a resonating system of thalamus and primary auditory cortex, why then are the two areas (fronto-central and temporal) not typically in phase with each other in the scalp distributions obtained in this study? Stapells et al. (1987) have shown that phase is sensitive to the signal-to-noise ratio of the recorded signal. Temporal recording sites are likely to be contaminated with temporalis muscle activity, as evidenced by the high amplitude, but noisy responses seen at temporal locations in the scalp distribution of subject D.E. (Fig. 3). An index of the ratio of 40 Hz signal to EEG and muscle noise is required for a more accurate description of the phase relationships at different scalp locations.

Borda (1984) has suggested that the resonance effect in the 40 Hz ERP may involve nonspecific thalamic relay nuclei, so that multimodal systems are activated by stimulation in any one modality. This notion is supported by the scalp distributions obtained in this study. Typically low amplitude responses are obtained at pre-frontal recording sites while large amplitude responses are often obtained at sites overlying primary sensory cortex (temporal, occipital and fronto-central regions). It may be then, that the source system underlying the generation of the auditory 40 Hz ERP includes primary visual and primary somatosensory cortex. Topographic studies using multimodality stimulation are required to answer this question.

The effects of aging on the 40 Hz ERP are subtle. The Cz-Pz index effectively discriminates the majority of the aged subjects from the younger subjects in this sample, but more age-normative data are required to assess and interpret this index. If there are real differences between the two groups in the relationship between the activity of central and parietal brain regions, then it may reflect changes in multimodal thalamic regions at which there is convergence of ascending excitatory sensory information and descending inhibitory information from corticofugal systems.

Aging has been shown to reduce concentrations of glutamic acid decarboxylase (GAD, the rate-limiting enzyme in GABA synthesis) in the human thalamus (McGeer and McGeer, 1976). The thalamic reticular nucleus (n.RT) is a major source of these GABAergic projections and has powerful inhibitory influences on neurons within thalamic relay nuclei (Yingling and Skinner, 1976) causing, for example, reduced auditory responses in the medial geniculate nucleus (MGB) (Shosaku and Sumitomo, 1983). The MGB has been implicated on the basis of lesion studies as a relay to a cortical generator of the Pa component of the middle latency auditory ERP or as a possible Pa generator itself (Woods et al., 1986). Aging has been shown to cause a dramatic increase in the amplitude of the Pa component (Woods and Clayworth, 1986).

Age-related changes in the Cz-Pz index are not readily interpretable in terms of inhibitory influences on sensory systems, but may be an indirect reflection of changes in the tuned resonance characteristics of multimodal thalamocortical systems. This may be manifest as either a release of inhibition over cortical sensory areas (note the extremely large parieto-occipital response in subject N.H., Fig. 4) or simply as a lack of resonance in the system (3 of the five aged subjects have relatively poor parieto-occipital responses compared to the fronto-central response).

Schrock (1985) found that patients with frontal lobe lesions have enhanced amplitude of the 40 Hz ERP. A normal amplitude ERP could be reinstated, however, with the introduction of taped cafeteria noise to one ear. It is known that certain brainstem structures are critically involved in the ability to discriminate auditory information against a noisy background. The olivary/cochlear nucleus of the brainstem and the olivo-cochlear bundle function to improve the auditory signal-to-noise ratio (Whitfield, 1984). These structures are components of centrifugal pathways that have their origins as far back as the cortex, so that selection mechanisms could be initiated at any point along the pathway. Schrock's (1985) finding that the 40 Hz ERP is modulated by environmental noise in frontal lobe patients, suggests that the 40 Hz response is modulated, if not generated, by brain systems involved in improving auditory resolution.

Since hearing function in background noise shows a marked deterioration with age (Davis, 1983), the 40 Hz response, combined with environmental noise to one ear, may be a good index of this type of central hearing loss. It should be noted that subjects in this study were carefully selected for normal hearing and good health and therefore may not represent a random sample of the aged population (16 of 22 aged volunteers for this study were rejected for health reasons, because they were taking some form of prescription drug, or because of diagnosed hearing loss).

To summarize, the intention of this study was to describe the scalp topography of the 40 Hz ERP and to investigate the hypothesis that aging may affect the response. With respect to the scalp topography of the response, it was found that phase of the response is quite stable at fronto-central sites, in contrast to the variability of other recording locations. This finding demonstrates that topographical studies of the 40 Hz ERP may provide insight into the generators of the response. With respect to aging, it was found that young and aged subjects have quite similar ERPs with respect to phase, amplitude and scalp topography. However, an index consisting of the difference between Cz and Fz in amplitude of the response was found to discriminate 4 of the 5 aged subjects from the younger group in this sample.

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