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HUMAN AUDITORY STEADY STATE EVOKED POTENTIALS

by

Roger Dean Linden

A dissertation submitted to the School of Graduate Studies of the University of Ottawa in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Physiology.

Ottawa, Ontario, Canada

September 1985

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

This thesis is dedicated to my parents, Robert F. Linden and Sheila M. Linden without whose support it may have always been a dream rather than reality.

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Vitae

Roger Dean Linden was born in Ottawa, Ontario on April 13, 1956. He attended Queen's University in Kingston, Ontario and graduated with a Bachelor of Science (Honours) in 1979. He studied for a Masters of Science at that institution from 1979 to 1981. From 1982 to 1985 he studied for a Ph. D. in Physiology at the University of Ottawa. His research supervisor was Dr. Terence Picton.

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ABSTRACT OF THE DISSERTATION

Human Auditory Steady State Evoked Potentials.

Roger Dean Linden

Doctor of Philosophy (Physiology)
University of Ottawa, 1985

Human auditory steady state evoked potentials were examined in a series of experiments.

First, these responses were measured during natural all-night sleep in 10 normal hearing young adult subjects. The responses were measured using on-line Fourier analysis. The effects of stimulus rate and intensity were examined during wakefulness and the various stages of sleep. The response is largest at stimulus presentation rates between 30 to 50/s during wakefulness and all stages of sleep. The apparent latency of the response is not different between sleep and wakefulness. As the intensity of the stimulus is increased above threshold the response amplitude increases and the response phase decreases. The response amplitude decreases during sleep. There is no significant difference between the estimated threshold during wakefulness and sleep.

Second, the effects of selective attention upon these potentials were examined in a series of experiments. The first and second experiments

evaluated the effect of attention on the steady state evoked potentials by comparing the responses obtained when subjects attended to increments in intensity to those obtained when subjects ignored the tones and read a book. There were no effects of attention. A third experiment evaluated the effects of attention in a dichotic listening paradigm wherein tones were presented in each ear at a different rate and the responses were recorded using the simultaneous stimulation technique of Fourier analysis. There were clear effects of the physical parameters of the stimulus but there were no effects of attention upon the steady state responses. The late evoked potentials were enhanced by attention. The late event related potential data were also high-pass filtered to analyze the complex event related potential (CERP). The CERP was not affected by attention. The fourth experiment used the same paradigm as the third experiment and one other condition wherein the subjects read a book while tones were presented to both ears. There were no effects of selective auditory attention upon the steady state evoked potentials. The fifth experiment evaluates the effects of attention on these potentials recorded using signal averaging. Again, there were no significant effects of attention.

The literature on the auditory Middle Latency Responses (MLR) is reviewed. There are two types of MLR: the transient and steady state responses. The transient responses are elicited by stimuli presented at a low rate such that there is no overlapping of the responses to subsequent stimuli. The steady state responses are elicited by stimuli presented at a high rate such that there is an overlapping of the responses to subsequent stimuli. Both responses may be recorded using signal averaging. The steady state responses may also be recorded using Fourier analysis. There are probably multiple cerebral sources for the MLR. The brainstem and the primary auditory cortex both contribute to the scalp-recorded transient MLR. The steady state MLR are probably in part composed of the auditory brainstem response and the transient MLR and a contribution from the polymodal area of the neural axis. As the intensity of the stimulus increases the response amplitude of both the transient and steady state MLR increases, reaching a maximum at approximately 60 dB above threshold. Both types of MLR are affected by the frequency, duration and rise-fall of the tones used to elicit a response. Larger amplitudes are recorded to tones of lower frequency, longer duration and decreasing rise times. Binaural stimuli generate larger transient and steady state MLR than monaural stimuli. There is a definite age affect on the MLR and one must therefore be careful when recording these responses from children. The transient MLR are affected by sleep. The steady state MLR amplitude is decreased by sleep but the response phase is not affected by sleep. The transient MLR are probably affected by attention and either adapt or habituate over time. The steady state MLR are not affected by attention and do not habituate. Pharmacologically, the transient MLR amplitude is not affected by muscle relaxants and is decreaed by seditive medication and severely decreased by anesthetic medication. As audiological tools, the transient MLR may be too noisy to estimate threshold. The steady state MLR can assess threshold to within 5-10 dB of those determined behaviourally. Once the generator sites of these responses are clearly defined they may become helpful as a test to assess central auditory dysfunction.

TABLE OF CONTENTS

Introduction

This thesis evaluates the middle latency responses (MLR) of the human auditory evoked potentials. The MLR may be classified, based on the stimulus presentation rate as either transient or steady state responses.

Two major facts may be derived from the presently available literature. First, the MLR can be recorded at low intensities and are therefore helpful in objective audiometry. This is particularly true for the steady state MLR which are larger and therefore easier to recognize. Second, the cerebral source of the MLR is not known. There are probably multiple generators. One of these may be the polymodal area of the brainstem.

The transient responses are elicited when stimuli are presented at a slow rate, such as 10/s, and there is no overlapping of the responses evoked by subsequent stimuli. The steady state MLR are recorded when stimuli are presented at a faster rate, such as 40/s, and the responses to subsequent stimuli overlap. Both transient and steady state responses may be recorded using signal averaging. The steady state response, because of its periodicity may be recorded using Fourier analysis.

Fourier analysis is based on the premise that any waveform may be considered as a linear combinations of sinusoidal waveforms. To extract a particular frequency from a waveform you multiply the waveform by the sine and the cosine of the frequency of interest. This multiplication causes the frequency of interest to be converted to a DC component, other frequencies are converted to AC components, and may be removed with low-pass filtering. This results in two values: an X and a Y component which may be used to calculate the amplitude and phase of the response.

Because of the larger amplitude of the steady state MLR and ease with which these responses may be recorded using Fourier analysis they have important possibilities as a tool in electric response audiometry. However, certain evoked potentials, such as the late auditory components are affected by sleep and selective attention and have been shown to have limited use in objective audiometry. I therefore decided to evaluate the steady state MLR during sleep and in a selective attention experiment.

These experiments were also performed to give us some insight into the generator sites of this response. My working hypotheses were:

(1) If the steady state MLR is generated in a polymodal area such as the reticular formation they should be affected by sleep.

(2) If the steady state MLR is generated in a polymodal area they will be affected by selective attention.

The first paper of the thesis evaluated the effects of sleep on the steady state MLR. To perform this I introduced the sweep technique of steady state analysis. This technique involves rapidly changing a stimulus parameter and recording the response to that change. I examined the effects of stimulus intensity and rate. In the intensity series, the stimulus was presented at 40/s and was swept from a low intensity (-20 dB SL) to a high intensity (60 dB SL) in 3 dB steps. This resulted in amplitude/intensity and phase/intensity plots. These data were used to estimate the subjects threshold during wakefulness and sleep. In the rate series, the stimulus intensity was kept constant (60 dB SL) and the rate was swept from 10/s to 60/s in 2/s increments. This resulted in amplitude/rate and phase/rate plots. The phase/rate plots were used to determine the apparent latency of the responses.

The intensity series demonstrated that the amplitude of the steady state MLR is smaller during wakefulness and does not differ between the various stages of sleep. The phase of the steady state MLR is not sensitive to the change from sleep to wakefulness. The threshold estimated from these data does not differ between sleep and wakefulness.

The rate series demonstrated that the amplitude/rate function observed during wakefulness is preserved during sleep. The overall amplitude is however smaller during sleep. The phase/rate data is not affected by sleep and therefore the apparent latency calculated from this data did not differ between wakefulness and sleep.

I then examined the effect of attention upon the steady state MLR in a series of experiments. To perform this analysis I used both the dichotic listening technique and the stimultaneous stimulation technique of Fourier analysis.

Tones were presented dichotically. In one ear the 1000 Hz tones were presented at a rate of 37/s. In the other ear, 500 Hz tones were presented at a rate of 41/s. The EEG response was amplified and fed into two Fourier analyzers. The Fourier analyzers calculated the amplitude and phase of the response in each ear. The response was displayed as a vector whereby the amplitude of the response was shown by the length of the vector and the phase of the response was shown by its orientation to the x-axis. The attention task was to detect slight increases in the tone frequency in one ear ("targets") and to ignore the tones presented to the contralateral ear. The response to the "targets" were signal averaged for 500 ms after the presentation to ensure selective attention in our paradigm.

The late event-related potentials to the targets demonstrated that there was selective attention in the paradigm. Across all conditions the response amplitude is larger in the attend conditions compared to the ignore conditons. The Fourier analysis data of the steady state MLR demonstrated no effects of attention. However, the amplitude of the response to the 1000 Hz tones was larger than the amplitude to the 500 Hz tones. The response phase was longer for the 500 Hz tones and the 41/s presentation rate. In summary I saw clear effects of the physical parameters of the stimulus but no significant effect of attention.

The late event related potentials data to the targets were high-pass filtered and Fourier analyzed to evaluate the Complex Event Related Potentials (CERP). The CERP are not affected by attention.

In a final experiment I measured the response using simultaneous signal averaging and Fourier analysis. The EEG response fed into the Fourier analyzer was also fed into a signal averager. The steady state MLR recorded using signal averaging demonstrated no effects of attention. The steady state MLR recorded using Fourier analysis demonstrated no affects of attention. The late event related potentials were clearly larger to the attended targets.

In summary, I have shown the following:

(1) The amplitude of these responses are decreased during sleep. The phase appears not to be affected by sleep.

(2) Central to the 40/s presentation rate is whether this amplitude enhancement is preserved during sleep. I have shown that the amplitude enhancement is preserved during sleep.

(3) The estimated threshold is not different between sleep and wakefulness.

(4) The steady state MLR is not affected by selective attention.

(5) These steady state MLR may be recorded using the sweep method of Fourier analysis and the simultaneous stimulation technique of Fourier analysis. Although these techniqes have been applied in the visual system this is the first time they have been applied to the auditory system.

With respect to my working hypotheses on generator localization:

(1) The steady state MLR are affected by sleep and may therefore be generated in part by an area that is involved in sleep such as the reticular formation.

(2) My hypothesis that these responses would be affected by selective attention proved not to be true. Wherever they are generated they appear to be more affected by arousal than attention.

This dissertation consists of three papers examining human auditory steady state evoked potentials. Each paper is presented in the format required by the Journal in which it has been published in or will be submitted for publication to.

The first paper evaluates the effect of sleep on the human auditory steady state evoked potentials. This paper was published in Ear and Hearing.

The second paper evaluates the effects of attention on the steady state MLR. This paper has been written following the format required by the journal, Electroencephalography and Clinical Neurophysiology.

The third paper is a review of the literature on auditory middle latency responses. This paper has been written following the format of the Journal of Clinical Neurophysiology. It is an attempt to clarify muddy waters. The literature is vague and difficult to follow. Using some minor experiments and collating the reports in the literature I have attempted to present an understandable summary of the literature on the auditory MLR.

in Ear and Hearing

HUMAN AUDITORY STEADY STATE EVOKED POTENTIALS DURING SLEEP*

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Abstract

The human auditory steady state evoked potentials were recorded during all-night sleep in 10 subjects. The effects of stimulus rate and intensity on these potentials were measured using on-line Fourier analysis. The amplitude of the response was greatest at stimulus rates of 30-50/s. Although the response amplitude was lower during sleep, the rate at which the amplitude was greatest did not change between sleep and wakefulness. As the intensity was increased above threshold the amplitude of the response increased linearly. The responses recorded during wakefulness showed a larger amplitude change with increasing intensity than during sleep. The estimated thresholds for the responses, however, did not differ significantly between wakefulness and sleep.

Key Words: Auditory evoked potentials
Fourier analysis
Middle latency responses
Steady state potentials
Sleep

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Introduction

Auditory evoked potentials are important tools in the clinical assessment of hearing. There are two kinds of auditory evoked potentials: transient responses and steady state responses. Transient responses are evoked by an auditory stimulus that is presented at a rate sufficiently slow that the response to one stimulus has finished before the next stimulus occurs. Transient responses are classified on the basis of their latency as fast, middle, slow and late[6]. The middle latency responses (MLR) occuring between 10 and 100 ms are usually recorded using stimulus rates of 10/s or less.

Steady state responses are evoked when stimuli are presented at a sufficiently high repetition rate to cause an overlapping of the responses to successive stimuli[31]. Until recently, the auditory steady state responses were not widely studied. Campbell et al.[3] described auditory steady state responses to tones presented at rates of up to 32 Hz. They reported the response amplitude increased linearly as the intensity of the stimulus increased, with an intercept approximately equal to subjective threshold. In 1977 Cohen[4] described a "following response" to tones presented at rates between 20 and 100/s. In 1981 Galambos and his colleagues[9] described the auditory 40 Hz potential. They demonstrated that when stimuli were presented at rates of 30-50/s the amplitude of the response was 2-3 times greater than the amplitude of the transient MLR to stimuli presented at rates of 10/s. Stapells and his colleagues[34] replicated this work and demonstrated that these 40 Hz steady state responses could be recorded using Fourier analysis.

The literature is very unclear about the effect of sleep on the auditory MLR. Mendel and Goldstein[20] initially reported that the transient MLR was stable over a 24 hour waking period and in various stages of sleep. In 1971, Mendel and Goldstein[21] found that the latencies of the major peaks remained constant across the different stages of sleep and that the amplitudes were larger during stages REM and 2 than during stages 3 and 4. Mendel and Kupperman[23], however, reported no significant amplitude differences between REM (rapid eye movement) and non-REM sleep, and Mendel[19] found little difference in the latency or amplitude of the MLR between light (stages REM and 2) and deep (stages 3 and 4) sleep. Brown and Shallop[2] reported that components Pb and Pc of the transient MLR decreased in amplitude during sleep. The literature on the steady state MLR is more consistent. Galambos [7] stated the 40 Hz response was about half the amplitude in sleep compared to the awake state. Brown and Shallop[2] and Shallop and Osterhammel[32] reported that the response during sleep was approximately one third that during wakefulness. Klein[14] also found that the amplitude of the steady state response was smaller during sleep than during wakefulness.

The auditory MLR has received a great deal of attention as a possible tool for determining frequency-specific auditory thresholds. The thresholds for recording transient MLRs to clicks and tones correlate well with behavioral thresholds[10,22,25,35,36]. During sleep the transient MLRs have been recorded to within 10-20 dB SL[15,19]. Despite these reports Stapells[33] found the transient MLRs too variable to use in assessing thresholds. Several investigators have reported that the steady state MLR is accurate in determining subjective threshold using both averaging[1,5,7,9,12,14,16,32,33] and frequency based analyses[17,18,34].

This study examined the effects of sleep on the auditory steady state MLR. Recordings were made throughout a night of natural sleep in ten subjects. We evaluated the responses using Fourier analysis while sweeping either the intensity or the rate of the stimulus through a range of values and plotting graphs of the effects of these parameters on the response[26,28,29,31,34]. The threshold of the response in each of the different sleep stages was estimated from the data obtained during the intensity sweeps.

Methods

Subjects

Ten subjects (4 males, 6 females) participated in the study. All subjects had thresholds below 20dB HL at 500 Hz, no history of audiological or neurological problems, and no drug or alcohol dependency. The age of the subjects ranged from 23 to 35 years (mean 25). The subjects entered the laboratory approximately one hour before their normal evening bedtime and slept through the night on a bed in a sound-attenuated chamber.

Stimuli

The stimuli used in the study were 500 Hz tonebursts (4 ms rise-fall, 2 ms plateau) presented to the subject through a specially designed (Starkey Laboratories) behind-the-ear hearing-aid containing a Knowles ED-197 wide bandpass receiver. A #13 plastic tube (1.9 mm inside diameter), approximately 40 mm in length was employed to conduct the sound from the speaker to the tip of individually fitted ear molds. The frequency response of this system was calibrated using a Bruel and Kjaer 2209 sound level meter and a 2 cm^3 hearing aid coupler. A 0.2 V RMS input signal produced an approximately flat response (94-104 dB SPL) from 0.1 to 4 kHz. This response curve is comparable to those reported in the literature[13]. To verify stimulus input, the hearing aid case contained a broadband sub-miniature Knowles EA-1934 microphone connected to the ear mold with a second #13 tube. This provided a means of monitoring the waveform of the stimulus in the ear canal and allowed us to verify that stimulus levels were constant despite movement of the subject during the night.

Sleep Staging

Electrophysiological recordings were obtained from gold-plated cup electrodes attached with saline gel and collodion-impregnated gauze. Inter-electrode impedances at 10 Hz were less than 5 kOhms. Electrodes at Cz and Oz were used to record on-going electroencephalographic (EEG) signals using as reference an electrode on the mastoid ipsilateral to stimulation. Electrodes placed lateral to the outer canthus of each eye were used to monitor the electrooculogram (EOG). The electrode on the left side was placed slightly higher than eye level and the electrode on the right side was placed slightly lower than eye level. Each of the eye electrodes was referenced to the electrode placed on the mastoid contralateral to the eye. Electromyographic (EMG) activity was monitored between left and right sub-mental electrodes. The EEG and EOG were amplified with a bandpass of 0.16-30 Hz (6 dB/octave slope). The EMG was amplified using a bandpass of 5-100 Hz. These electrophysiological signals were written out on paper at a speed of 10 mm/s. The EEG was staged according to Rechtschaffen and Kales [27]. Stages were grouped into the following categories: Awake PM while the subjects were awake before they slept; Awake AM in the morning when the subjects were woken up; Stage 2 Early while the subjects were in stage 2 in the first half of the night; Stage 2 Late while the subjects were in stage 2 in the last half of the night; Slow Wave while the subjects were in either stage 3 or stage 4; and REM while the subjects were in REM sleep.

Steady State Responses

The EEG recorded from Cz to the mastoid ipsilateral to stimuli was also amplified with a bandpass of 5-1900 Hz (6 dB/octave slope) and fed to a laboratory-constructed Fourier analyzer[30,34] which calculated the phase and amplitude of the EEG at the frequency of stimulus repetition. A computer-controlled sine-wave generator triggered the tonebursts (at 0° phase) and served as the reference signal for the Fourier analyzer. A computer controlled the rate and the intensity of the stimulus, and calculated the average amplitude and phase of the EEG activity detected by the Fourier analyzer. The phase was calculated as the phase of the reference signal minus the phase of the EEG response. Our experiments used the sweep technique of Fourier analysis to determine the effect of stimulus intensity and rate on the steady state potentials during sleep[26,28,29,30,31,34]. The computer swept either the intensity or rate of the stimulus. Figure 1 illustrates the sweep technique in analyzing the effect of stimulus intensity. The computer increased the intensity in 3 dB steps every second, calculated the amplitude and phase of the response at each intensity, averaged the data from ten sweeps together, and then plotted out the resultant amplitude-intensity and phase-intensity functions. Each subject's behavioral threshold (SL) for the 40/s tones presented through the hearing-aid device were determined prior to sleep, and the intensity of the stimulus was swept from -21 to 60 dB SL at a constant 40/s stimulus-rate. The rate sweep differed from the intensity sweep in that the intensity was kept constant at 60 dB SL while the stimulus-rate was swept from 10 to 60 tones per second with 2/s increments every second. The amplitude and phase of the responses were averaged using vector-averaging over 10 sweeps of either stimulus rate or intensity. Recorded sweeps were classified according to the stage of sleep. Recordings occuring during transitions from one stage to another or when a definite classification could not be made were not analyzed. Each stage had between 10 to 60 sweeps averaged. Some subjects did not have sufficient data to analyze in all stages. Some Awake AM data were incomplete because of the time constraints of early morning appointments.

-insert figure 1 about here-

Threshold Determination

The thresholds for the steady state response were estimated from the data obtained during the intensity sweep. The data were modelled as having a low amplitude (noise level) and random phase below threshold and a linear increase in amplitude and a linear decrease in phase with increasing intensity above threshold. A possible threshold was postulated at each intensity from -15 dB SL to +51 dB SL and the data were fit to the model using linear regressions. The actual threshold was estimated as the intensity at which the data were best fit by the model. This best fit was determined on the basis of the least sum-of-squares deviation between the data and the model. The data were analyzed using amplitude alone, phase alone, or an equally weighted combination of amplitude and phase. This analysis of threshold also provided the slopes of the suprathreshold regression lines for both amplitude and phase.

Statistical Analysis

The data were analyzed using two-way (stage X intensity or stage X rate) repeated measures analyses of variance (ANOVA) and linear regressions. Greenhouse-Geiser[11] corrections were used to compensate for violations of the repeated-measures assumptions. Post Hoc analyses were done using Tukey honestly significant differences (HSD)[11]. Results were considered significant at p<0.01.

Results

Rate

(a) Amplitude

Figure 2 illustrates the grand mean vector-averaged data for the response amplitude at different stimulus-rates across the sleep stages. Data from every stage were not available for all subjects. The number of subjects represented in the grand mean data are 10 for Awake PM, 10 for Stage 2 Early, 10 for Stage 2 Late, 9 for Slow Wave, 4 for REM sleep and 6 for Awake AM.

-insert Figure 2 about here-

In the Awake PM and Awake AM a broad amplitude peak is consistently recorded around 40 tones per second with variable subharmonic peaks at rates of about 10 and 20 tones per second. During sleep, the tracings show a generally lower amplitude but a similar morphology with a maximum at rates of 30-50/s. To examine the significance of these data an ANOVA across every second stimulus rate (12,16...60 tones/s) and four of the stages (Awake PM, Stage 2 Early, Stage 2 Late, Slow Wave) was performed for the eight subjects with recordings in all of these stages. The response amplitude differed across stimulus-rate (F=10.44; df=12,84; p<0.01) and stage (F=6.45; df=3,21; p<0.01) with an interaction between rate and stage (F=2.20; df=36,252; p<0.01). Post hoc analysis of the main effects showed that the response was largest at the 30-50/s rates, and smaller during sleep than wakefulness with no significant differences between sleep stages. The interaction was due to a greater effect of stage at the peaks than at the troughs of the graph. The average rate at which the maximum amplitude was recorded across stage is presented in Table 1. This did not differ significantly as a function of stage of sleep (F=0.80).

-insert Table 1 about here-

REM sleep was not included in the statistical analysis because a rate response recorded during REM was obtained from 4 subjects only. For the 4 subjects from which REM data were obtained the data were analyzed across stages REM, Stage 2 Late and Slow Wave sleep. The amplitude of the response was significantly different as a function of stimulus presentation rate (F=3.17; df=12,36; p<0.01) for all stages. There was no significant difference between the stages Slow Wave, Stage 2 Late and REM (F=4.35;

df=2,6; p>0.01) and no significant interaction between stage and rate (F=0.68).

(b) Phase

Figure 3 illustrates the grand mean data for stimulus rate and response phase across sleep stage. In all stages there is a linear increase in phase as the stimulus-rate is increased from 20 to 50 tones per second. To examine this relationship during sleep an ANOVA across stimulus-rate (between 30 and 46 tones/s) and stage (Awake PM, Stage 2 Early, Stage 2 Late, Slow Wave) was performed for the eight subjects where all four stages were recorded. The response phase differed significantly with stimulus rate (F=6.57; df=8,56; p<0.01), was not significantly different across stage (F=4.88; df=3,21; 0.01<p<0.05)) and showed no significant interaction between rate and stage (F=1.00). The phase of the response increased linearly across all stages as the stimulus-rate was increased. The relationship between phase and stimulus-rate was used to calculate the apparent latency of the response[28]. For each stage of sleep the apparent latency was determined by calculating the slope of the phase/rate function and dividing the slope by 360. Table 1 presents the average apparent latencies for the different sleep stages. An ANOVA across sleep stage (Awake PM, Stage 2 Early, Stage 2 Late, Slow Wave) for the apparent latency of the eight subjects with all the stages showed no significant effect of sleep stage (F=1.51; dF=3,21; p>0.01).

-insert figure 3 about here-

Intensity

(a) Amplitude

Figure 4 illustrates the results of the intensity series in wakefulness. The tracings on the left of the figure are the superimposed responses for 9 subjects. The Awake AM and Awake PM recordings were combined. Each tracing is the vector-average of 40 zooms in stimulus intensity. The tracings on the right of the figure represents the grand mean vector-averaged data from all the subjects. A low level response with random phase is recorded until the subject is able to hear the stimulus; as the intensity of the stimulus increases above this threshold, the amplitude increases and the phase decreases.

-insert Figure 4 about here-

The grand mean amplitude data for the intensity sweep at each of the stages is illustrated in Figure 5. Data across every sleep stage were not available for all subjects. Awake PM, Stage 2 Early, Stage 2 Late and REM data were obtained from 10 subjects. Slow Wave data were recorded from 7 subjects. Awake AM data were recorded from 9 subjects. The general trends were an increase in response amplitude as the intensity of the stimulus increased above threshold and a decrease in amplitude during sleep. To examine these relationships an ANOVA was performed between the response amplitude values for every second intensity level more than 12 dB SL

(12,18... 60 dB SL) and five stages (Awake PM, Stage 2 Early, Stage 2 Late, Slow Wave, REM). Values between -21 to 9 dB SL were not included in the analysis because these intensities were below or near threshold. The response amplitude differed significantly across intensity ($F=8.44$; $df=8,48$; $p<0.01$) and stage ($F=15.09$; $dF=4,24$; $p<0.01$) with no significant interaction. Across all stages the recorded amplitude increased as the intensity of the stimulus increased. Post Hoc analysis revealed the amplitude of the response differed between wakefulness and sleep but did not differ across sleep stage. A specific comparison between Stage 2 Early and Stage 2 Late showed no significant difference at 60 dB SL ($F=0.01$).

-insert figure 5 about here-

The subthreshold response amplitude was statistically analyzed by comparing the -21, -15, -9, -6 dB SL amplitude values across stage (Awake PM, Stage 2 Early, Stage 2 Late, Slow Wave, REM). These subthreshold measurements provided an estimate of the background noise level in the recordings. As expected, there was no significant difference in the amplitude across the different subthreshold intensities ($F=0.06$). The background noise was significantly different across sleep stage ($F=5.59$; $df=4,24$; $p<0.01$). Post Hoc analysis revealed that the background noise was significantly lower during sleep than during wakefulness with no significant differences across sleep-stages.

To examine if gender affected the response, the amplitude of the response to the 60 dB SL stimulus was compared in the Awake PM and Slow Wave state and analyzed according to gender. There was no significant effect of gender (F=0.25) and no interaction between gender and sleep-stage(F=0.28).

(b) Phase

The grand mean vector-averaged data for the phase of the response during the intensity sweep are illustrated in Figure 6. To examine the effects of intensity and sleep stage on the phase of the response, ANOVAs were run on the phase values across intensity (12,18... 60 dB SL) and stage (Awake PM, Stage 2 Early, Stage 2 Late, Slow Wave, REM). The response phase showed a significant effect of intensity (F=4.25; df=8,48; p<0.01) and stage (F=4.62; df=4,24; p<0.01) with no interaction(F=1.00). As the intensity of the stimulus increased, the phase of the response decreased. Post hoc analysis revealed that the phase of the response was larger in sleep than in wakefulness but that this difference was only significant when comparing Slow Wave sleep and Awake PM. The phase of the response at 60 dB did not differ as a function of gender (F=1.14; df=1,5; p>0.01).

-insert Figure 6 about here-

(c) Threshold

The thresholds were estimated from the data obtained during the intensity sweep. A typical subject's response for the intensity sweep is illustrated in Figure 7.

- insert Figure 7 about here-

The mean and standard deviation of the threshold determined on the basis of amplitude alone, phase alone and a standardized combination of amplitude and phase are presented in Table 2. Using the phase alone results in a threshold estimate closest to the behavioural threshold. The threshold determined with amplitude alone, (F=1.35; df=4,36; p>0.01), phase alone (F=1.01; df=4,36; p>0.01) and a standardized combination of amplitude and phase (F=.79) did not differ significantly across stage of sleep.

-insert Table 2 about here-

The effects of stimulus intensity on the slope of the amplitude and phase functions at intensities greater than 21 dB SL (i.e. above the range of threshold for the steady state responses) are presented in Table 3. The phase slope did not differ significantly as a function of stage (F=0.13). The amplitude slope approached significance as a function of stage (F=3.95; df=4,32; 0.01<p<0.05) with decreasing slopes during sleep.

-insert Table 3 about here-

Discussion

The effects of stimulus rate on the amplitude of the MLR[7,8,9,34] is similar during wakefulness and sleep. Although the amplitude of the response is smaller during sleep, the maximum amplitude is still recorded when stimuli are presented at rates of 30-50 tones/s. The effects of stimulus rate on the phase of the response also did not change during sleep. This stability across stage of sleep is clearly indicated in the apparent latency of the response which did not change as a function of stage. Because of the broad amplitude maximum recorded in response to stimuli presented at rates of 30-50 tones/s we feel confident that the initial 40/s stimulus rate proposed by Galambos, Makeig and Talmachoff[9] is appropriate for studying the response in all stages of sleep or wakefulness. Inter-subject variability in the optimal stimulus presentation rate within the range of 30-50 tones per second does exist, but, because of the broad range of maximum amplitude we feel small variations in stimulus rates around 40/s will not have significant effects on the average responses.

The amplitude of the response increases as the intensity of the stimulus increases. A similar stimulus-intensity/response-amplitude function occurs across all stages of sleep, but the slope of the suprathreshold intensity-amplitude relationship is lower during sleep. The phase of the responses decreases as the suprathreshold intensity of the stimulus increases. A similar intensity-phase relationship occurs in all stages of sleep and wakefulness.

The results of this study have shown that steady state evoked potential audiometry shows promise in objective audiometry. First, there is no difference in the response as a function of gender or duration of the testing period. Second, although the recorded amplitude values are smaller during sleep, it is still possible to estimate thresholds during sleep that are close to behavioral thresholds. These findings are probably related to the decreased level of background EEG noise during sleep, and the consistency of the phase relationship despite the decreased amplitude. Because of the variability of the data, it is possible that we may have missed a 10 dB change in threshold between sleep and wakefulness. It is doubtful, however, that the change would be greater, provided that sufficient averaging is performed to recognise the small responses near threshold.

One problem with auditory electrophysiological testing is obtaining reliable frequency-specific information[6,24]. The steady state MLR can be used to assess thresholds at frequencies other than 500 Hz[33]. It is possible therefore that an electrophysiological audiogram can be obtained using the intensity-sweep technique at the different audiometric frequencies. The sweep technique does not require expensive averaging equipment, since a Fourier analyzer can be constructed with a few integrated circuits[30]. Careful consideration must be given to the intersubject variability in threshold estimation. The observed standard deviation of about 20 dB in threshold estimation is too high for audiometry. It is possible that the estimations would be more accurate if they were based on sweeps that had been averaged over more than the 10 or 20 usually used in the present study.

The generator site of the steady state MLR is still unknown. Galambos[8] has postulated that, because of the interactions with other modalities, the response may be generated from the rostral reticular formation or thalamus. Wherever the steady state MLR are generated, this study has shown that the site is particularly sensitive to changes between sleep and wakefulness but much less affected by changes between sleep stages.

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Table 1. Effects of stimulus rate on the auditory steady state responses

	RATE AT MAXIMUM AMPLITUDE (/sec)	APPARENT LATENCY (msec)
AWAKE PM	34 ± 12	36 ± 12
STAGE 2 EARLY	35 ± 11	32 ± 7
STAGE 2 LATE	33 ± 7	35 ± 8
SLOW WAVE	28 ± 7	31 ± 7
	NS	NS

Table 2. Thresholds for recognizing the auditory steady state responses during sleep (dB SL)

	MODEL		
	AMPLITUDE	PHASE	BOTH
AWAKE PM	22 ± 21	12 ± 19	15 ± 25
STAGE 2 EARLY	24 ± 25	-1 ± 11	20 ± 26
STAGE 2 LATE	23 ± 24	4 ± 9	8 ± 19
SLOW WAVE	37 ± 17	5 ± 13	11 ± 23
REM	21 ± 23	5 ± 20	17 ± 23
	NS	NS	NS

Table 3. Effects of stimulus intensity

	AMPLITUDE SLOPE (nV/dB)	PHASE SLOPE (°/dB)
AWAKE PM	18 ± 15	-1.7 ± 2.4
STAGE 2 EARLY	8 ± 9	-1.6 ± 1.5
STAGE 2 LATE	10 ± 8	-1.8 ± 2.7
SLOW WAVE	6 ± 6	-2.1 ± 1.6
REM	13 ± 8	-1.5 ± 2.4
	p=0.01	NS

Figures

Figure 1. The sweep technique to assess the effects of intensity on the steady state MLR. The Fourier analyzer measures the EEG energy at the frequency of stimulus presentation. The stimulus generator (S) is triggered by an oscillator (O) at a constant repetition rate (f Hz). The subject's EEG is fed into the Fourier analyzer to be multiplied (M) by the sine and the cosine of the stimulus repetition frequency. These multiplications convert the f Hz component into a steady DC output; all other frequency components are converted to AC output. The AC outputs are removed with a low-pass filter (F). The remaining DC outputs are used by the computer to calculate the amplitude and phase of the EEG activity at f Hz. The computer increases the intensity of the stimulus while calculating the amplitude and phase of the steady state response at f=40/s. The data are stored on disk to be averaged and plotted. The phase data are plotted such that values less than 180 degrees have 360 degrees added to their value.

Figure 2. Amplitude/rate function for the auditory steady state evoked potentials using the sweep technique. The responses represent the grand mean data obtained from the 10 subjects for Awake PM, Stage 2 Early and Stage 2 Late. The responses recorded during Slow Wave sleep were from 9 subjects. Responses were recorded from 4 subjects during REM sleep. Six subjects were tested when the subjects were awake in the morning. The broad maximum amplitude of the response occurred when stimuli were presented at rates of

30-50 tones/s. As well, there is a general decrease in amplitude in sleep.

Figure 3. The phase/rate functions for the same grand mean responses presented in Figure 2. The phase increases with increasing stimulus rate. The slope of this response, reflected in the apparent latency, does not differ significantly as a function of stage of sleep.

Figure 4. The amplitude/intensity and phase/intensity functions obtained using the sweep technique while the subjects were awake. The upper left figure shows the superimposed amplitude/intensity responses for the ten subjects. The upper right figure shows the grand mean vector-averaged data for all subjects. Both the superimposed and grand mean data show a low noise level below threshold and an increase in amplitude as the intensity increases above threshold. The lower left figure shows the superimposed phase/intensity responses for all subjects. The lower right figure shows the grand mean vector-averaged data for all subjects. Both the superimposed and grand mean data illustrate that below threshold the phase is random and above threshold the phase of the response decreases linearly as the intensity of the stimulus increases.

Figure 5. The grand mean data for the amplitude/intensity function across sleep stage for the 10 subjects. The number of subjects from which responses were recorded as a function of stage were: Awake PM=10; Stage 2 Early=10; Stage 2 Late=10; REM=10; Slow Wave=7; Awake AM=9. The response amplitude across all stages was low below threshold and as the intensity of the stimulus was increased above threshold the amplitude increased. The amplitude of the response decreased during sleep, but was not different

across stage of sleep.

Figure 6. The grand mean data for the phase/intensity function across sleep stages for the 10 subjects. The number of subjects from which data were recorded during each stage were the same as in Figure 5. At all stages the phase was random below threshold. As the intensity of the stimulus increased above threshold, the phase decreased regularly. The slope of the suprathreshold intensity-phase function did not change significantly with stage.

Figure 7. The intensity amplitude and phase functions from a single subject during wakefulness and stage 4 sleep. The background noise of the recording, illustrated in the dashed line parallel to the abscissa of the amplitude response decreases during sleep. The slope of the amplitude/intensity function above threshold was larger during wakefulness. The phase of the response phase was random below threshold and decreased as the intensity was increased above threshold. The threshold estimated using a standardized combination of amplitude and phase was 6 dB SL during stage 4 sleep and 15 dB SL during wakefulness.

Figure 1

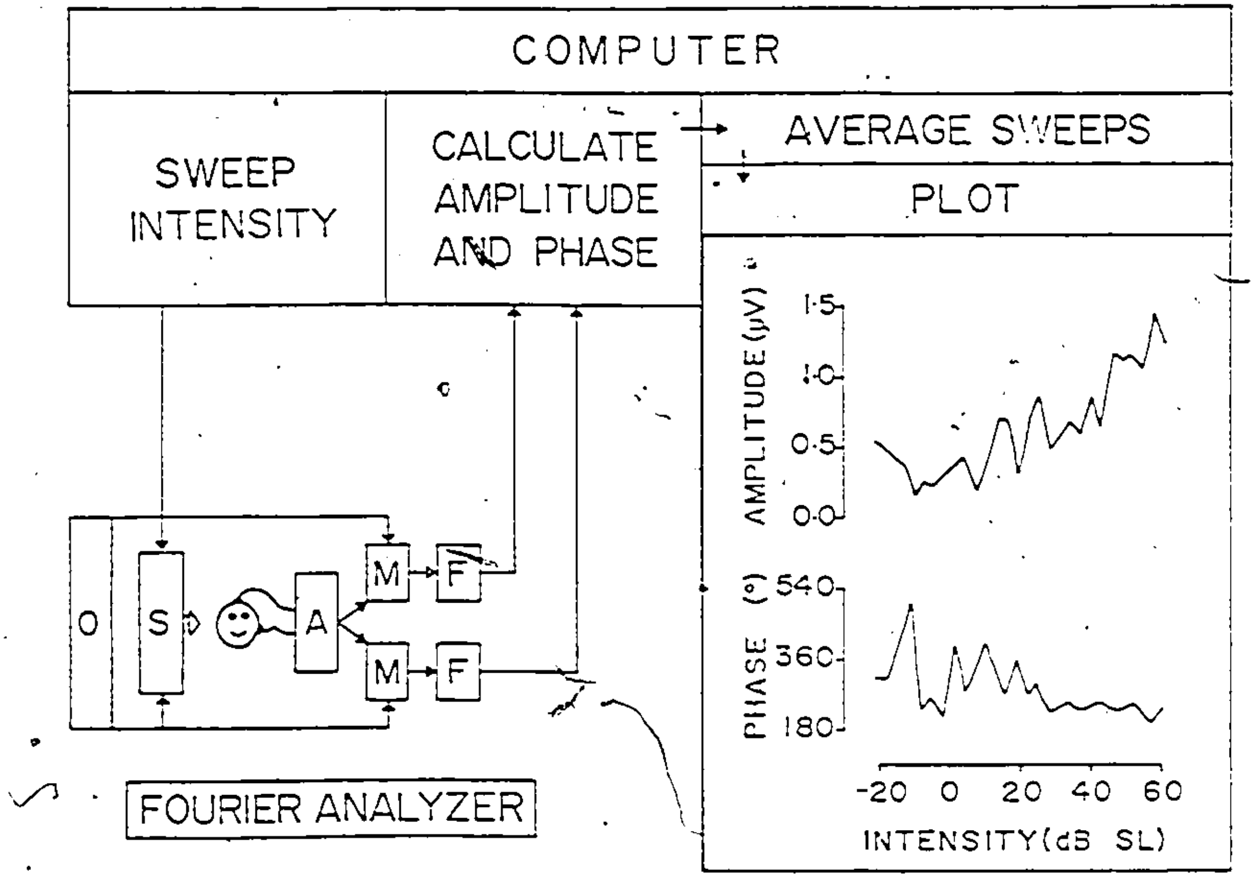
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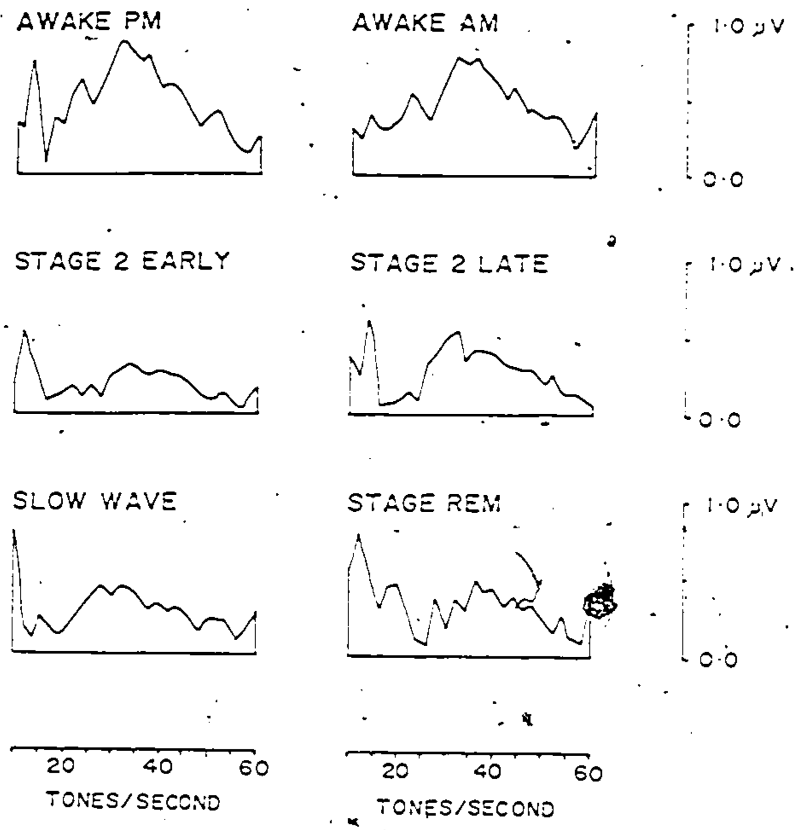
Figure 2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SLOW WAVE
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TONES/SECOND
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TONES/SECOND

Figure 3

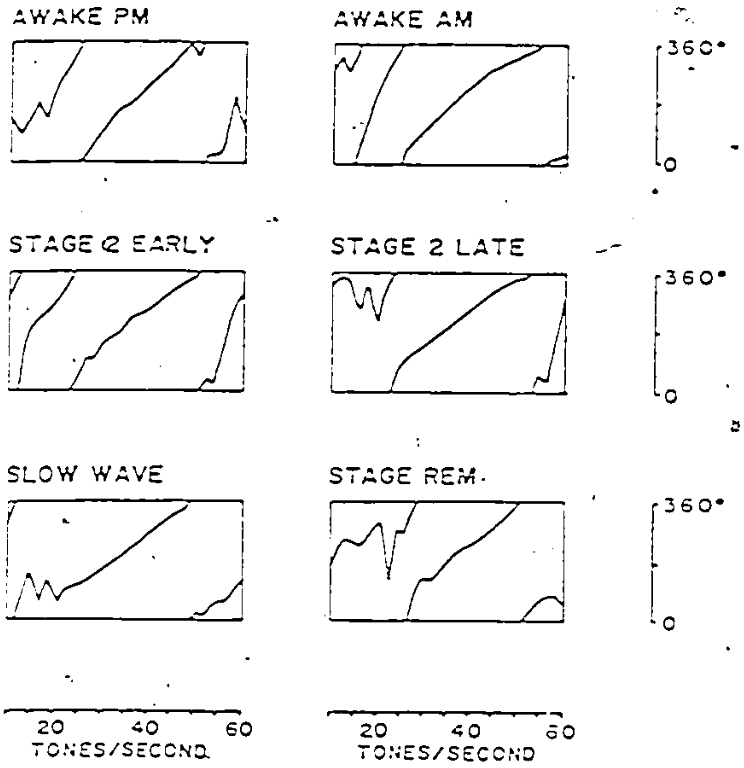
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Figure 4

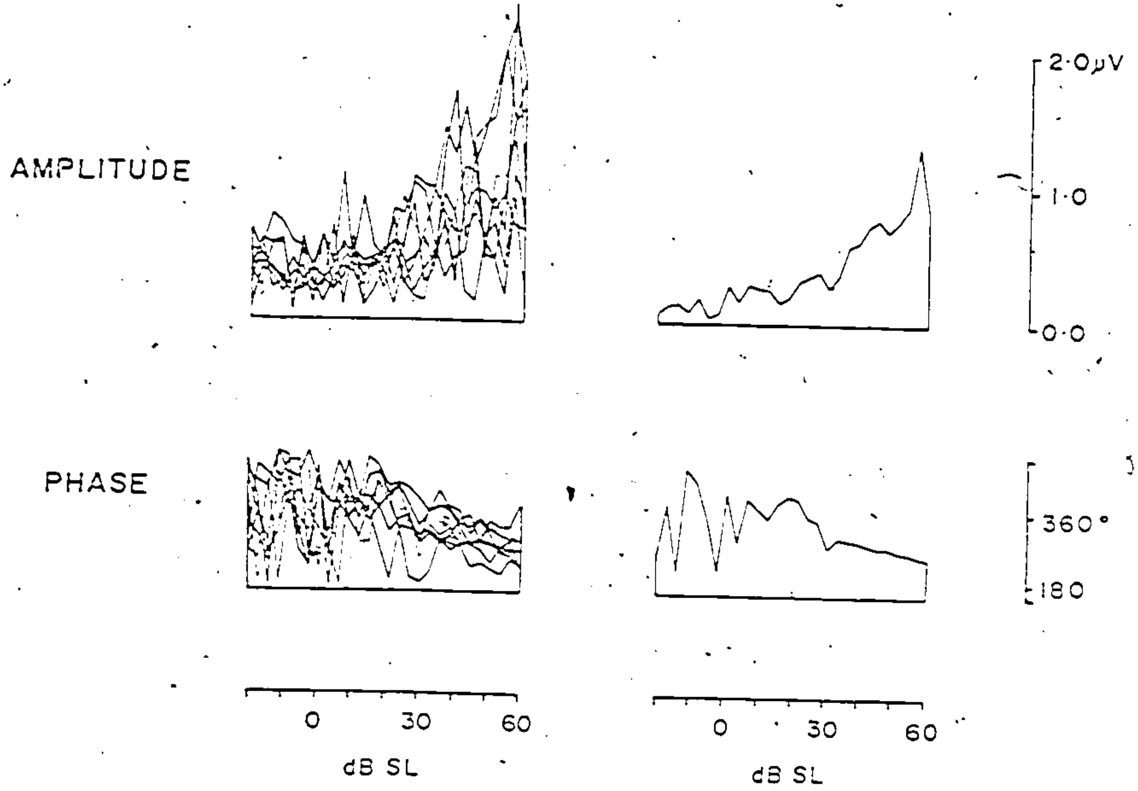

Figure 5

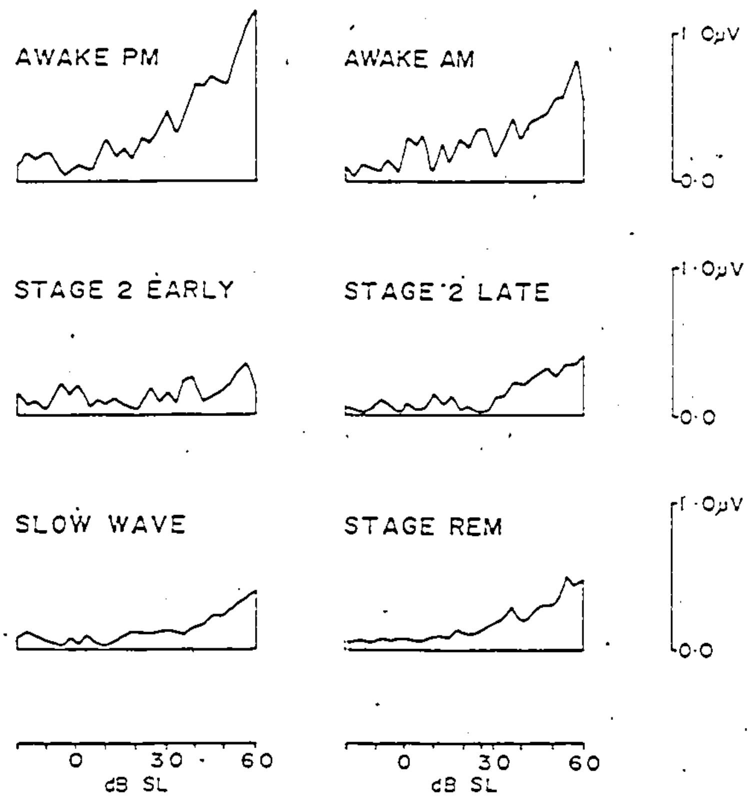
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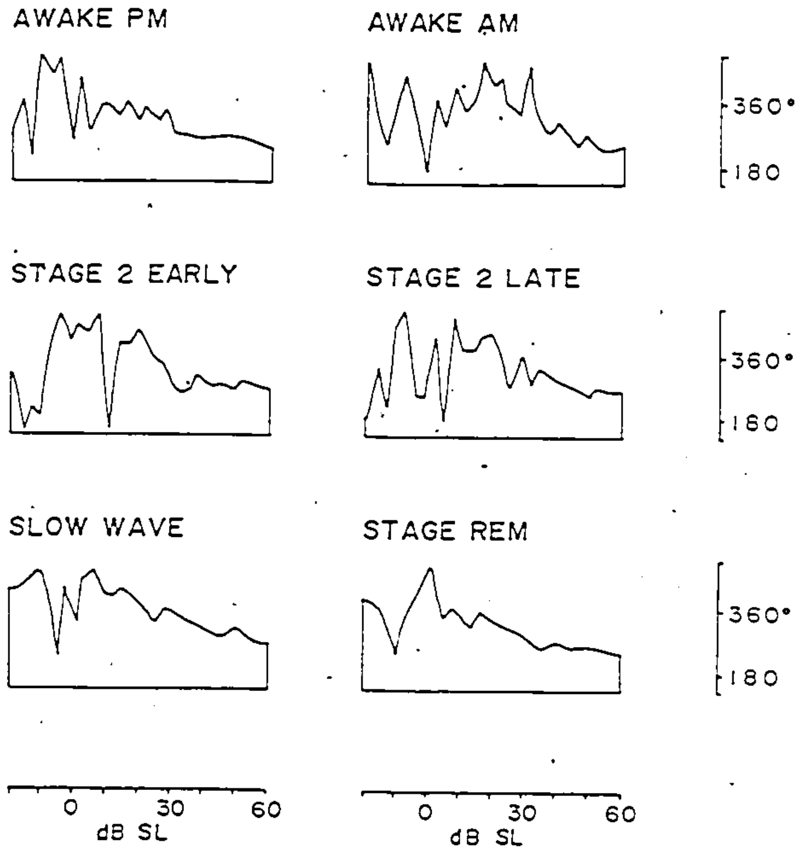
Figure 6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AWAKE AM
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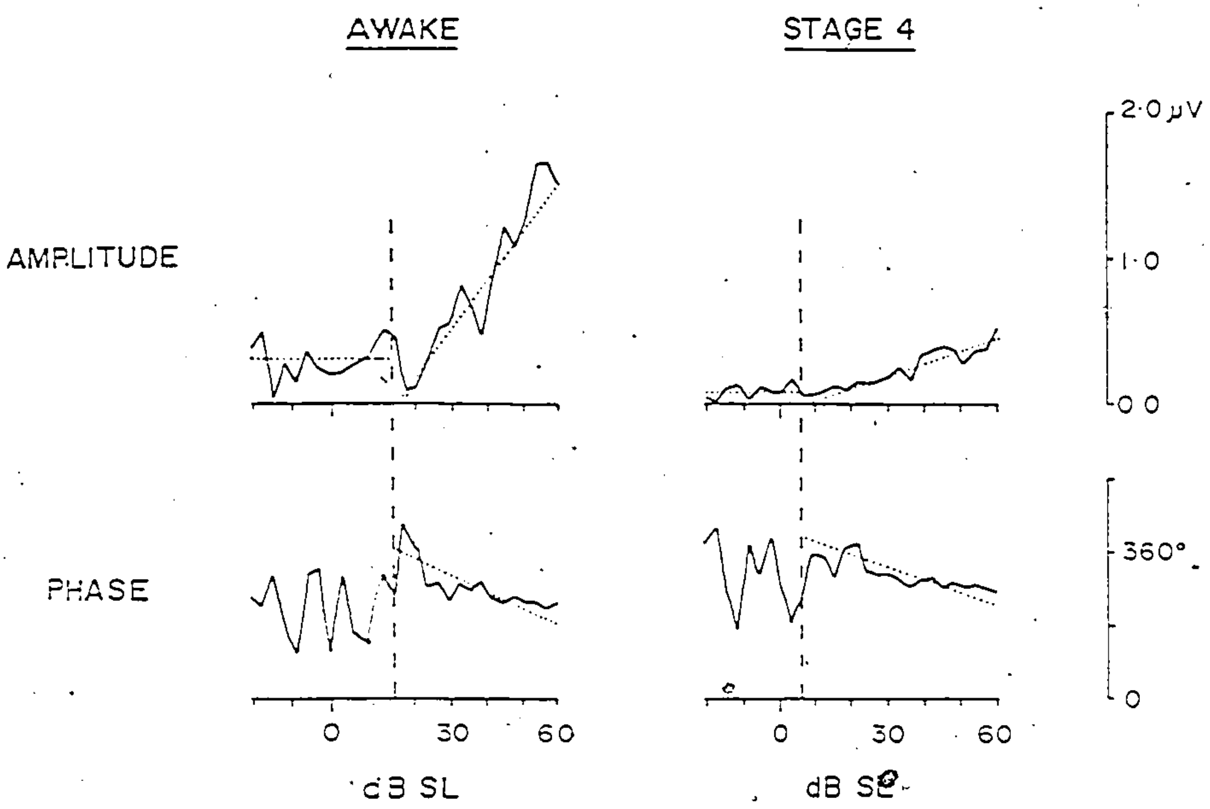
Figure 7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To be Submitted to Electroencephalography and Clinical Neurophysiology *

HUMAN AUDITORY STEADY STATE EVOKED POTENTIALS:

EFFECTS OF ATTENTION

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Auditory evoked potentials may be classified on the basis of their latency as early (0-10 ms), middle (10-50 ms) and late (50-500 ms) responses (Picton et al. 1974). Selective auditory attention causes definite changes in the late auditory evoked potentials (Hillyard and Picton 1979). There is some controversy about the effects of attention on the middle latency responses. Hillyard et al. (1973) and Picton and Hillyard (1974) initially reported that the middle latency responses (MLR) were unaffected by selective attention. Recently, however, several papers (Kadobayashi et al. 1981; McCallum et al. 1983; Hillyard, in press) reported changes in the MLR with attention.

The auditory MLRs may be classified according to their stimulus presentation rate as either transient or steady state (Stapells et al. 1984). "Transient" responses are obtained when stimuli are presented at a sufficiently slow rate such 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 (Regan 1982). Steady state MLRs recorded at stimulus rates of 30-50/s have been studied recently as a possible clinical tool in objective audiometry (Galambos et al. 1981; Stapells et al. 1984). These steady state MLRs are attenuated in amplitude during sleep (Linden et al. 1985). Because of the controversy of whether the MLRs are affected by attention, and because it is important clinically to know whether the steady state MLR can change with attention, we examined the effect of attention on the human auditory steady state MLR.

Because of its periodicity both signal averaging and frequency-based techniques such as Fourier analysis may be used to analyze the steady state MLR (Stapells et al. 1984). We therefore used signal averaging to measure the effects of attention on the late components and both averaging and Fourier analysis to examine the effect of attention on the steady state MLR in several experimental paradigms. The methods and results are presented in four separate sections according to the particular stimulus protocol or analysis technique used.

A. Intensity sweeps

Schwent et al. (1976) reported that the effect of selective attention on the auditory evoked potentials was greater when stimuli were less intense. The first experiment, therefore, evaluated the effects of attention on the steady state MLR at different intensities. The intensity of the tones was swept across a range of intensities and the responses evaluated using Fourier analysis at each intensity.

Methods

Eight subjects (2 female, 6 male) ranging in age from 27 to 40 years participated in this experiment. During the one-hour experimental session, the subject sat on a comfortable chair in a sound-attenuated chamber. In one subject (RDL) responses were recorded on five separate days.

Tonebursts (4ms rise-fall, 2ms plateau) with a frequency of 500 Hz were presented monaurally through a TDH-49 earphone at a rate of 40/s. The EEG recorded from Cz referenced to the mastoid ipsilateral to stimulation was amplified with a bandpass of 5-1900 Hz (6dB/octave slope) and fed to a laboratory Fourier analyzer (Regan 1977; Stapells et al. 1984) which calculated the amplitude and the phase of the EEG at the frequency of stimulus repetition with an integration time of about 250 ms (time constant 75 ms). Figure 1 illustrates the basic principles of this Fourier analysis. A sine-wave generator triggered the tonebursts and served as the reference signal for the Fourier analyzer. A computer controlled the intensity of the stimulus and calculated the average amplitude and phase of the EEG activity detected by the Fourier analyzer. The phase was calculated as the phase of the reference signal minus the phase of the EEG response ("phase delay").

-insert Figure 1 about here-

The experiment used a sweep technique to analyze the effects of stimulus intensity (Regan 1982; Nelson et al. 1984; Linden et al. 1985). The computer swept the intensity of the stimulus from -20 to 40 db nHL (10-70 dB peSPL). The intensity was increased in 5 dB steps with a time interval between increments that varied between 500 to 1000 ms. The computer calculated the amplitude and phase of the response at each intensity, averaged the data from 40 sweeps, and then plotted out the resultant amplitude-intensity and phase-intensity functions. Because of the ambiguity associated with the periodicity of the phase (i.e 10° may also be 370°), and because the typical near-threshold phase values were 315°, phase values less than 135° were increased by 360°.

The data were modelled as having a low amplitude and a random phase below threshold with a linear increase in amplitude and a linear decrease in phase above threshold. A threshold was postulated at each intensity and the data were fit to the model using linear regressions. The accuracy of the fit was calculated on the basis of the least sum-of-squares deviation between the data and the model using an equally weighted combination of amplitude and phase. The intensity at which the data were best fit by the model provided an estimated threshold.

In the ATTEND condition, the subject counted the number of intensity increments above their subjective threshold. In the IGNORE condition, the subject read a book and ignored the stimuli. The responses to two ATTEND and two IGNORE conditions were examined. The order of the conditions was randomized.

The suprathreshold and subthreshold data were separately analyzed using a two-way (attention by intensity) repeated measures analysis of variance (ANOVA) (BMDP, 1981). The amplitude and phase of the response to the 20, 25, 30, 35 and 40 dB nHL tones were used to analyze the suprathreshold data. The amplitude and the phase of the responses to the -20, -15 and -10 dB nHL tones were used to analyze the subthreshold (background noise) data. The thresholds estimated by the linear regression model were compared using a t-test. Results were considered significant at $p<0.01$.

Results

The number of intensity increments counted by the subjects provided an estimate of the behavioral threshold. The mean sensation level calculated in this fashion was -3.8 dB nHL (26.2 pe SPL) with a range of -15 dB nHL to + 10 dB nHL.

Figure 2 shows the superimposed grand mean data for the eight subjects in the ATTEND and IGNORE conditions. Each tracing is the result of 640 sweeps of stimulus intensity. The amplitude of the response to the suprathreshold tones demonstrated a significant effect of stimulus intensity

(F=5.90; df=4,28; p<0.01), no significant difference between the ATTEND and IGNORE conditions (F=0.00) and no interaction between intensity and condition (F=0.55). The phase of the response to the suprathreshold tones demonstrated a significant effect of stimulus intensity (F=6.13; df=4,28; p<0.01), no significant difference between the ATTEND and IGNORE condition (F=0.27) and no significant interaction (F=0.17). The subthreshold response amplitude was examined to assess the general noise level. There were no significant differences between the ATTEND and IGNORE conditions (F=1.44; df=1,6; p>0.01).

-insert Figure 2 about here-

The mean threshold estimated using the linear regression model was -6.6 dB nHL (S.D.=9.4) for the ATTEND condition and -4.7 dB nHL (S.D.=9.5) for the IGNORE condition (t=-0.41; P>0.01).

Because of the variability of threshold between subjects we did not include the low intensity suprathreshold results in the analysis of variance. A t-test of the responses at 10 dB nHL, however, revealed no significant differences between the ATTEND and IGNORE conditions for either the amplitude (t=-0.59; p>0.01) or phase (t=-0.003; P>0.01).

These results demonstrated no effect of attention upon the auditory steady state evoked potentials. However, at the intensities near threshold the variability of threshold between subjects may have obscured any possible effect of attention. We therefore evaluated a single subject on five different days using averages of 80 sweeps per day per condition. This subject's sensation level was -5 dB nHL. The ANOVA was computed using all intensities between 10 and 40 dB nHL. The grand mean data for this subject are illustrated in Figure 3. The amplitude of the response to the suprathreshold tones showed a significant effect of intensity (F=12.31; df=5,20; p<0.01), no significant effect of attention (F=0.20) and no interaction (F=1.06; df=5,20; p>0.01). The phase showed a significant effect of intensity (F=14.45; df=5,20; p<0.01), no significant effect of attention (F=1.30; df=1,4; p>0.01) and no interaction (F=0.34).

-insert Figure 3 about here-

The estimated threshold was -3.0 dB nHL (S.D.= 12.0) for the ATTEND condition and -1.0 dB nHL (S.D.= 11.7) for the IGNORE condition (t=-0.24; p>0.01).

B. Dichotic listening

The dichotic listening technique allows the study of selective attention independent of any changes in arousal (Hillyard et al. 1973). In this experiment the subjects attended to the tones in one ear in order to detect occasional changes in tonal frequency while ignoring the tones presented to the contralateral ear. The simultaneous stimulation technique (Regan and Heron 1969; Regan 1982) was used to assess the responses independently in each ear. The technique uses two Fourier analyzers each tuned to a specific rate of stimulation (either 37 or 41/s).

Methods

Five female and five male subjects ranging in age from 22 to 38 years participated in this experiment. All subjects reported normal hearing.

Tonebursts of 10 ms duration (4 ms rise-fall, 2 ms plateau) and 85 dB peak SPL intensity were presented dichotically through TDH-49 earphones. The tones were presented at rates of 37/s in one ear and 41/s in the contralateral ear. The frequency of the standard tones was 500 Hz in one ear and 1000 Hz in the other. Within the 500 Hz channel the frequency was occasionally changed to 535 Hz for 60 ms; within the 1000 Hz channel the frequency was occassionally changed to 1050 Hz. These frequencies were chosen on the basis of pilot experiments demonstrating that they could be detected with an accuracy of about 85%. The target duration was set at 60 ms so that three tones would occur when the train of stimuli were presented at either 37/s or at 41/s. For 4 subjects who could not accurately detect the 535 Hz targets, the frequency was changed to 545 Hz. The subjects counted the number of frequency changes or "targets" in the attended channel over a block of approximately 2 minutes. The targets were presented to the attended or ignored ears with an equal probability of 50 %. Targets were presented randomly at a mean interval of 1000 ms and a range of 650 ms to 1350 ms. A total of 100 attended and ignored targets were presented in each block.

The electrophysiological recordings were obtained using gold-plated cup electrodes attached with saline gel and collodion-impregnated gauze. Inter-electrode impedences at 10 Hz were less than 5 kOhms. The EOG and EEG were amplified with a bandpass of 0.16-30 Hz (6 dB/octave). The late evoked potentials to the target stimuli were recorded with signal averaging. These potentials were recorded from vertical electro-oculograms, Fz, Cz, and Pz (referenced to linked mastoids) with a sweep time of 500 ms. Responses contaminated by muscle artifact or eye movement were rejected before averaging. The ERP data was low-pass filtered using a digital boxcar filter at 10 Hz prior to identifying the peaks. Four peaks were marked: peak 1, the maximum negativity between 50-200 ms; peak 2, the maximum negativity after peak 1 between 150-250 ms; peak 3, the maximum positivity between 250 and 400 ms; peak 4, the maximum positivity after peak 3 between 350-500 ms.

The latencies of the late components used to ensure selective attention were analyzed using a 4-way repeated measures ANOVA for each of the 4 peaks. Levels of analyses were: attention (attend vs ignore), rate (37/s vs 41/s), tone frequency (500 Hz vs 1000 Hz), and ear (left vs right). The amplitude of the ERP data was analyzed using a 5-way repeated measures ANOVA with the same levels used in the analysis of the peak latencies with the added level of electrode location (Fz, Cz, Pz).

The steady state MLR to the 37/s and 41/s stimuli were simultaneously recorded by Fourier analysis. The EEG recorded from Cz to inion was also amplified with a bandpass of 5-1900 Hz (6dB/octave) and fed to two laboratory-constructed Fourier analyzers. These Fourier analyzers calculated the amplitude and phase of the EEG at 37/s and 41/s. To ensure that the Fourier analyzers could discriminate between the two frequencies (37/s and 41/s) we mixed 37/s and 41/s sine waves (at various amplitudes) with 30-50 Hz noise and sent this signal to both Fourier analyzers. The resultant amplitude and phase were within 4% of the actual values over the range 0.2 to 1 uV. The integration time of the Fourier analyzers was approximately 250 ms (time constant 75ms).

Figure 4 illustrates the simultaneous stimulation and dichotic listening technique in analyzing the effect of attention. In one ear the subject attended to a train of 500 Hz tones presented at a rate of 41 /s and counted the 535 Hz targets within this train of standard tones. The subject ignored the 1000 Hz and 1050 Hz tones presented to the contralateral ear at a rate of 37/s.

-insert Figure 4 about here-

For 10 of the subjects, the Fourier analyzers measured the amplitude and the phase of the response before each attended and non-attended target was presented. In addition, for 5 of the subjects, the Fourier analyzers measured the amplitude and the phase of the response 500 ms after each attended and non-attended target was presented.

The Fourier analysis amplitude and phase data were separately analyzed. The pre-target Fourier analysis data (amplitude and phase) were analyzed using a 4-way repeated measures ANOVA. The levels examined were: attention, rate, tone frequency and ear.

For the five subjects with pre-target and post-target data, a 5-way repeated measure ANOVA was performed using the same levels as in the pre-target with an additional level comparing the pre-target samples to the post-target samples.

For all 10 subjects data a 5-way repeated measures ANOVA was performed using the same levels as in the first pre-target analysis with an added level of "random sampling". When the EEG was sampled before the target in one channel, the other Fourier analyzer simultaneously sampled the EEG randomly with respect to any target in that channel.

Results

Figure 5 illustrates the grand mean data for the late transient evoked potentials collapsed across ears. The responses are the ATTEND and IGNORE tracings from Cz.

-insert Figure 5 about here-

The latency of the first negative peak demonstrated no significant effect of attention ($F=1.03$; $df=1,9$; $p>0.01$), rate ($F=0.00$), tone frequency ($F=2.21$; $df=1,9$; $p>0.01$), ear ($F=3.10$; $df=1,9$; $p>0.01$) and no significant interaction between any of the levels of the analysis.

The amplitude of the first negative peak demonstrated a significant main effect of attention ($F=13.91$; $df=1,9$; $p<0.01$). There was no significant main effect of electrode location ($F=3.52$; $df=2,18$; $p>0.01$), rate ($F=0.00$), tone frequency ($F=4.17$; $df=1,9$; $p>0.01$), or ear ($F=0.33$). There was an interaction between the electrode location and attention ($F=9.38$; $df=2,18$; $p<0.01$). The collapsed cell amplitudes demonstrated that the attention effect was greatest at Fz and Cz. This interaction remained significant ($p<0.01$) when the data were scaled (normalize technique) to remove attention effects (McCarthy and Wood, 1985).

The latency of the second negative peak demonstrated no significant main effect of attention ($F=0.22$), rate ($F=0.60$), tone frequency ($F=4.35$; $df=1,9$, $p>0.01$) or ear ($F=1.36$; $df=1,9$; $p>0.01$). Interactions between the attention and tone frequency levels of the analysis ($F=15.31$; $df=1,9$; $p<0.01$) and attention and ear levels ($F=14.33$; $df=1,9$; $p<0.01$) were present in the latency analysis of the second negative wave. These interactions were not easily interpretable and may have been caused by the arbitrary picking of a peak when none was present in the ignore condition.

The amplitude of the second negative peak demonstrated a significant main effect of attention ($F=20.69$; $df=1,9$; $p<0.01$). There was no significant effect of electrode location ($F=3.14$; $df=2,18$; $p>0.01$), rate ($F=0.16$), tone frequency ($F=0.83$; $df=1,9$; $p>0.01$), or ear ($F=1.61$; $df=1,9$; $p>0.01$). A significant interaction was present between the electrode location and attention levels of the analysis (F=8.94; df=2,18; p<0.01). After scaling the data (normalize method) to remove the attention effects the interaction remained significant (p=0.01) (McCarthy and Wood, 1985).Collapsed cell means of the electrode location and attention levels demonstrated that when the subjects were attending, the second negative peak was maximum at Fz and Cz. While ignoring the incoming targets, there was no difference in the amplitude recorded as a function of electrode location.

The latency of the first positive peak demonstrated no significant effect of attention (F=0.38), rate (F=0.26), tone frequency (F=7.19; df=1,9; p>0.01), or ear (F=0.19) and no interaction between any of the levels of the analysis. The amplitude of the first positive peak was significantly affected by electrode location (F=7.66; df=2,18; p<0.01) demonstrating a maximum at Cz, approached significance as a function of attention (F=7.42; df=1,9; 0.01<p<0.05) with the collapsed cell means for the ATTEND condition being larger than the IGNORE condition at Cz and Pz. There was no significant effect of rate (F=2.34; df=1,9; p>0.01), tone frequency (F=0.00), or ear (F=0.48). There were no significant interactions.

The latency of the second positive peak showed a significant effect of attention (F=12.85; df=1,9; p<0.01). The latency was longer for the IGNORE condition. There was no significant effect of rate (F=2.02; df=1,9; p>0.01), tone frequency (F=0.02), ear (F=0.50) and no significant interaction between any of the levels of the analysis. The amplitude of the second positive peak showed a significant main effect of electrode location (F=6.78; df=2,18; p<0.01), and attention (F=23.99; df=1,9; p<0.01). There was no significant main effect of rate (F=0.28), tone frequency (F=3.00; df=1,9; p>0.01) or ear (F=0.88; df=1,9; p>0.01). There was a significant interaction between the electrode location and attention (F=7.06; df=2,18;

p<0.01). The interaction was caused by the measurement showing a significantly greater enhancement with attention at Pz than at the other electrodes. The interaction was not significant after the data was scaled to remove attention effects (p=0.02) (McCarthy and Wood, 1985).

The pre-target amplitudes for the steady state MLR demonstrated no significant effect of attention (F=0.35), rate (F=2.09; df=1,9; p>0.01), or ear (F=3.85, df=1,9; P>0.01). There was a significant effect of tone frequency (F=33.60; df=1,9; p<0.01). The responses to the 1000 Hz tone were slightly larger than the responses to the 500 Hz tone. There were no significant interactions. The phase data demonstrated no significant effect of attention (F=0.33), or ear (F=0.09). There was a significant effect of rate (F=91.91; df=1,9; p<0.01), the response at 37/s showing a shorter phase delay than at 41/s, tone frequency (F=78.76; df=1,9; p<0.01), the response at 1000 Hz showing a shorter phase delay than at 500 Hz. There were no significant interactions between any of the levels of the analysis.

The two other ANOVAs showed similar effects of rate and frequency. There were no significant main effects of attention in any of the analyses and no attention related interactions. There were no differences between pre- and post-target measurements or between pre-target and random samples.

Figure 6 illustrates the grand mean results for the Fourier analysis data. Because there was no significant effect of ear we collapsed the grand mean data across ears for the figure. Polar plots are used to demonstrate both the amplitude and phase measures.

-insert Figure 6 about here-

C. Complex Event Related Potentials

Makeig (1985) proposed that changes in the amplitude and phase of the steady state MLR could be evoked by changes in the stimuli. He referred to these changes as the Complex Event Related Potentials (CERP) the term "complex" relating to the real and imaginary dimensions of the steady state response. Makeig reported time locked modulations in the CERP in response to omitted clicks in a train of standard clicks. We therefore extracted from our late components the steady state response and assessed whether there were any changes in this as the subject detected the attended targets.

Methods

The data from the dichotic listening experiment were used to analyze the CERP. Because there was no effect of ear we collapsed the data across ears. The data were high-pass filtered at 10 Hz (Figure 6). The filtered data were then Fourier analyzed at the frequency of the stimulation for 500 ms after the target was presented using a moving 42.5 ms window. There were no consistent changes in the response with attention. We measured the average amplitude and phase of the response separately within two time windows (100-150 ms and 175-225 ms) and analyzed these responses statistically. These windows were chosen on the basis of visual analysis of our grand mean data and of the data from Makeig (1985). A four way repeated measures ANOVA was performed: latency X attention X tone frequency X presentation rate.

The CERP analysis was performed post hoc. The filters for recording the late components had not been adjusted appropriately for measuring the steady state response. The 30 Hz low-pass filter attenuated the amplitude of the responses at 37 and 41 Hz by approximately 50% and increased the phase delay by approximately 120°.

-insert Figure 7 about here-

Results

There was no significant difference betweeen the average amplitude measured in each latency window (F=0.00) nor was there significant effects of attention (F=0.77), tone frequency (F=0.06) or rate (f=0.86). There were no significant interactions.

There was no significant difference between the average phase measured in each latency window (F=0.13). The average response phase showed a significant effect of tone frequency (F=14.49; df=1,9; p<0.01) and presentation rate (F=33.07; df=1,9; p<0.01). The response phase was longer for the 500 Hz tone and the 41/s presentation rate. There was no significant effect of attention (F=0.07) and no significant interactions. Figure 7 illustrates the grand mean results of the analysis of the steady state MLRs imbedded in the late transient responses.

-insert Figure 8 about here-

D. Effects of visual attention

There are several reports in the literature that suggest visual attention may decrease the amplitude of the early auditory evoked potentials in animals (Oatman 1976; Oatman and Anderson 1977) and in human subjects (Lukas 1980, 1981). Picton et al. (1981) reported that in a similar experiment to the Lukas (1980, 1981) studies that visual attention did not effect the early auditory evoked potentials. Because of these conflicting reports, we specifically examined the effect of visual attention upon the auditory steady state evoked potentials.

Methods

Five subjects participated in this experiment. All subjects reported normal hearing. The experimental set up was identical to that used in the dichotic listening experiment. Because we had found no significant effects of ear, we presented the 1000 Hz tones to the right ear at a presentation rate of 37/s and presented the 500 Hz tones to the left ear at 41/s. The experiment consisted of three conditions (a) counting the targets presented to the left ear and ignoring the incoming targets to the right ear (b) counting the targets presented to the left ear and ignoring the stimuli delivered to right ear (c) reading a novel and ignoring all auditory stimuli in both ears.

The first experiment in the dichotic listening series demonstrated that during the attend condition the late components had a negative amplitude maximum at Cz and a positive amplitude maximum at Pz. To ensure selective focussing on one channel we therefore measured the maximum negative peak recorded at Cz within 50 to 250 ms and the maximum positive peak recorded at Pz within 250 to 500 ms. Since the data from the previous experiment did not clearly distinguish separate peaks in these latency ranges, we only measured one peak. The ERP data were analyzed using two-way repeated measures ANOVAs: side (left, right) by condition (ATTEND, IGNORE, READ). The "side" manipulation involved rate, frequency and ear. The amplitude and phase of the Fourier analysis data were analyzed separately with similar two-way repeated measures ANOVAs

Results

Analysis of the late components revealed that the latency of the negative peak showed no significant effect of side ($F=2.67$; $df=1,4$; $p>0.01$), or condition ($F=0.33$) and no significant interaction between side and condition ($F=0.23$). The amplitude of the negative peak demonstrated no significant effect of side ($F=0.30$), approached significance for condition ($F=4.81$; $df=2,8$; $.01<p<.05$) and no interaction between side and condition ($F=0.52$). Because of this "approach" to significance we examined the data in the READ and IGNORE conditions and in the IGNORE and ATTEND conditions in separate two-by-two analyses. The READ and IGNORE conditions demonstrated no significant effect of side ($F=0.14$) or condition ($F=0.08$) and no significant interaction ($F=0.68$). The ATTEND and IGNORE analysis demonstrated an approach to significance of condition ($F=9.74$; $df=1,4$; $.01<p<.05$). There was no significant effect of side ($F=0.12$) and no significant interaction ($F=0.63$).

The latency of the positive amplitude maximum recorded at Pz showed no significant effect of side ($F=0.01$), or condition ($F=0.56$) and no significant interaction ($F=0.92$). The amplitude of the maximum recorded at Pz demonstrated no significant effect of side ($F=3.17$; $df=1,4$; $p>0.01$), a significant effect of condition ($F=14.73$; $df=2,8$; $p<0.01$) and no significant interaction ($F=0.58$). A further analysis of only the READ and IGNORE conditions revealed no effect of side ($F=4.73$; $df=1,4$; $p>0.01$), or condition ($F=1.60$; $df=1,4$; $p>0.01$) and no significant interaction ($F=0.04$). The separate analysis of the ATTEND and IGNORE conditions demonstrated a significant effect of condition ($F=21.12$; $df=1,4$; $p=0.01$). There was no significant effect of side (F=1.90; df=1,4; p>0.01) and no significant interaction (F=0.81). Figure 9 illustrates these results.

-insert Figure 9 about here-

The amplitude of the Fourier analysis data showed no significant effect of side (F=0.88), or condition (F=0.88) and no significant interaction (F=1.77; df=2,8; p>0.01). This is illustrated in figure 9 where the length of the steady state evoked potential (SSEP) vectors do not differ between conditions. The phase of the Fourier analysis data showed a significant effect of side (F=400.06; df=1,4; p<0.01), no significant effect of condition (F=2.44; df=2,8; p>0.01) and no significant interaction (F=0.34). Figure 9 shows that the 500 Hz, 41/s right ear tones have a longer phase delay than the 1000 Hz, 37/s left ear ~~tones~~. There are no differences between the ATTEND, READ, and IGNORE conditions.

E. Simultaneous signal averaging and Fourier analysis.

In all of the previous studies in this paper we analyzed the steady state evoked potentials using Fourier analysis. Stapells et al. (1984) have reported that the auditory steady state MLR analyzed with signal averaging and Fourier analysis give approximately equivalent results. Because evoked potential studies of attention have, however, used signal averaging, we decided to study the effects of attention on the steady state evoked potentials recorded by averaging.

Methods

Seven subjects participated in this experiment. The paradigm was identical to that used in the secon[illegible] exper[illegible] in this series. As well as being analyzed on the Fourier analyzer, the EEG at Cz was averaged on a Tracor Northern (TN3000) signal averager triggered at the onset of the tonebursts. The duration of the averaging sweep was 100 ms. These evoked potentials could only be recorded from one side at a time. Averaged late evoked potentials were obtained for ATTEND and IGNORE conditions for both sides. The late transient evoked potentials were scored with the same method used in the visual attention experiment. The amplitude of the late transient evoked potentials was analyzed using a three-way repeated measures ANOVA: averager -if the signal averager was used for the recording or not; side -right (1000 Hz, 37/s) vs left (500 Hz, 41/s); attention -attend vs ignore. The amplitude and phase of the Fourier analysis data were separately analyzed in a similar fashion. The amplitude of the steady state response obtained by averaging was measured as the mean peak-to-peak amplitude of the first three negative-positive deflections. These amplitudes were analyzed using a two-way repeated measures ANOVA (attention by side).

Results

The amplitude of the negative peak demonstrated an approach to significance of attention (F=7.13; df=1,6; $0.01<p<0.05$). There was no significant effect of averager (F=0.49) or side (F=0.00).There were no interactions. The amplitude of the positive peak demonstrated a significant effect of attention (F=27.98; df=1,6; $p<0.01$). There was no significant effect of averager (F=0.55) or side (F=0.11) and no significant interactions.

The amplitude of the Fourier analysis data demonstrated no significant effect of attention (F=7.43; df=1,6; p>0.01), side (F=3.20; df=1,6; p>0.01), or averager (F=2.87; df=1,6; p>0.01) and no significant interaction between any of the levels of the analysis. The phase of the Fourier analysis data demonstrated no significant main effects of attention (F=10.01; df=1,6; p>0.01) or averager (F=0.02). There was a significant main effect of side (F=173.43; df=1,6; p>0.01) and a significant interaction was present between the attention and averager levels of the analysis (F=19.70; df=1,6; p<0.01). Collapsed cell means demonstrated that while attending, the phase was inexplicably shorter when the signal averager was analyzing the data. There were no other significant interactions. The effect of side was due to the 41/s, 500 Hz side has a longer phase delay than the 37/s, 1000 Hz side.

The peak-to-peak amplitude of the signal averaging data showed no effect of side (F=1.79; df=1,6; p>0.01), or attention (F=0.99) and no significant interaction (F=0.17). Table 1 presents amplitude values for the Fourier analysis and signal averaging data while the subjects were attending or ignoring the targets.

-insert Table 1 about here-

For both recording measures there was no difference between the ATTEND and IGNORE conditions. The signal averaging data were slightly larger than the Fourier analysis data. This may be explained by noise superimposed on the signal averaging data which would enhance the amplitude of the peak-to-peak measurements (Stapells et al., 1984).

Figure 10 illustrates the grand mean results of this experiment. The late transient evoked potentials data show that selective focusing of attention was achieved during the experiment since the amplitudes of the negative and positive peaks were greater when the subjects were attending to the targets. The Fourier analysis data illustrates that the resultant vectors were not different between the ATTEND and IGNORE conditions. However, as in the previous experiments, an effect of side was present with the phase being longer for the 500 Hz tones presented at 41/s. The averaged steady state responses for the ATTEND and IGNORE conditions were superimposable, indicating no effect of attention.

-insert Figure 10 about here-

Discussion

The results of the intensity sweep experiments demonstrate that the amplitude, phase and threshold of the human auditory steady state MLR, recorded using Fourier analysis, are unaffected by attention to the auditory stimuli. The amplitude, phase and estimated threshold of the response do not change between attending or ignoring. Spydell et al. (1985) reported that they examined in one subject the effects of attention on the steady state MLR using Fourier analysis. They found that the phase and power of the responses were unaffected by changes in attention. Their preliminary report supports our findings.

Naatanen (1967) reported several problems with experiments such as the sweep experiments. Changes in general arousal between "attend" and "ignore" conditions or prior to predictable stimuli may confound the effects of selective attention. The solution to these problems is to present unpredictable sequences of stimuli to attended and ignored channels (Hillyard and Picton 1979). Our dichotic listening experiments showed no effects of attention on the auditory steady state evoked potentials. These results could not be confounded by changes in general arousal.

Attention caused highly significant changes in the late transient responses to the detected targets. An amplitude enhanced negativity was followed by an amplitude enhanced positivity. The negative waves recorded at 100 and 200 ms had similar scalp distributions. Furthermore, there was no clear negativity in the ignore conditions in some subjects. Therefore the negative wave may represent a combination of a processing negativity (Naatanen 1982) and the N2 occurring with target detection. The early positive wave was often difficult to recognize and because of its central amplitude maximum it may represent P3a (Squires et al. 1975). The late positive wave has a scalp distribution of a P300 wave (Picton and Hillyard 1974; Ritter et al. 1979). Furthermore, this wave had a similar latency to the button press response time which we had measured in pilot studies as 400 ms (Ritter et al. 1079; Fitzgerald and Picton 1983).

We analyzed the effects of attention on the "complex event related potential" reported by Makeig (1985). Our analysis of the steady state response embedded in the late event related potential data revealed no effect of attention. Makeig (1985) found changes in the amplitude and phase of the steady state response during the perception of an omitted stimulus by one subject. Our target detection was associated with a negative-positive late evoked potential similar to the potentials recorded during the detection of an omitted stimulus. Nevertheless, we were not able to measure any consistent changes in the simultaneously recorded steady state responses.

However, we had fewer trials in the average, a less defined target and individual differences were recorded. If there a possible attention effect was present it would be very small.

Our visual attention experiment demonstrates that visual attention does not effect the human auditory steady state MLR. The amplitude and phase of the Fourier analysis data are not affected by auditory or visual attention. Because Lukas (1980, 1981) and Picton et al. (1981) found conflicting results on the effect of visual attention on the early brainstem components more work is required to properly interpret the relationship between the efferent auditory pathway and attention.

Because of the larger amplitude of the steady state MLR compared to the early auditory brainstem response (ABR), the steady state MLR show great promise as a useful clinical tool in objective audiometry (Galambos et al. 1981; Stapells et al. 1984; Linden et al. 1985; Kileny and Shea 1985). Furthermore, these potentials may be analyzed using frequency based techniques such as Fourier analysis. Fourier analysis provides a rapid, inexpensive assessment and is amenable to such techniques as sweeping stimulus parameters and simultaneous stimulation. This paper introduces the simultaneous stimulation technique of steady state systems analysis to the auditory system. By using non-harmonically related repetition frequencies, audiometric analysis of several tone frequencies may by analyzed simultaneously. The interactions between different frequencies will have to be examined before such simultaneous stimulation can be used clinically.

Central to the issues of electric response audiometry is the important task of being able to use these tools on children and sedated subjects. Davis et al. (1983) reported that in young sedated children the auditory steady state MLR are not recognizable at 30 dB nHL stimulus levels. However, Suzuki and Kobayashi (1984) reported, that in young children, the amplitude maximum for the steady state MLR occurs when stimuli are at 20/s i.e a subharmonic of 40/s. If this technique is to be used in children the threshold should be determined using the optimum stimulus presentation rate. Also, a frequency based analysis providing amplitude and phase of the data would give us some insight into the use of the steady state MLR as a clinical tool because of the superior performance of the phase in calculating threshold (Makeig and Galambos, 1984). Age normative optimal stimulus presentation rate data is required. This may be quickly and efficiently obtained using the sweep technique (Linden et al. 1985).

The origins of the auditory steady state evoked potentials are unknown. Galambos (1982) suggested that because of an interaction between responses to somatosensory and auditory stimuli, the steady state responses may be generated from a region where sensory modalities converge, such as the rostral reticular formation or polymodal thalamus. The sensitivity of the response to sleep and because of the intricate relationship between the reticular formation and sleep, this gave further evidence to the reticular formation as a possible generator site. Spydell et al. (1985) reported that patients with midbrain/thalamic lesions had steady state MLRs with abnormally delayed phases and that patients with temporal lobe lesions had normal steady state MLR. They therefore proposed a non-cortical origin for the steady state MLR. Therefore the steady state MLR may in fact provide a valuable electrophysiological tool to measure the polysensory area of the neural axis, and as Galambos (1982) suggested, may open a new window to view the nervous system. Wherever the response is generated it is relatively resistant to change. Although its amplitude decreases during sleep its phase and apparent latency remain unchanged (Linden et al. 1985; Jerger et al.

1985). Furthermore, attention to the stimuli does not affect the response.

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Table 1

	Rate=37/s		Rate=41/s	
	Attend	Ignore	Attend	Ignore
Signal Averaging	.74	.73	.67	.64
Fourier Analysis	.65	.63	.60	.60

Amplitude values in microvolts

Running title: Effects of attention on auditory evoked potentials

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Key Words: Auditory evoked potentials
Attention
Fourier analysis
Middle latency potentials
Steady state potentials

Summary

The human auditory steady state evoked potentials were examined during several different tasks requiring attention. Both Fourier analysis and signal averaging were used to measure the responses at stimulus rates between 37 and 41/s. There was no effect of attention on the amplitude and phase of the steady state evoked potentials when subjects either counted successive increments in stimulus intensity or read a book. In a dichotic listening task, there were clear changes in the late transient evoked potentials with selective attention but no changes in the steady state responses. Furthermore, the steady state potentials during reading were not different from those obtained while the subjects were selectively attending to the auditory stimuli in one ear. There is therefore no evidence that the auditory steady state responses are affected by attention.

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Figure 1 Principles of the Fourier analysis. The subject receives an auditory stimulus (S) presented at f Hz. The subject's EEG is amplified (A) and then fed into a Fourier analyzer where it is multiplied (M) by the cosine and sine of the stimulus repetition frequency. This multiplication results in a mixture of DC and AC outputs. The f Hz component of the EEG is converted by the multiplication to the DC output. Noise of the EEG is converted by the multiplication to the AC output which is removed with a low-pass filter. Two DC output values are obtained, an X and Y component. These two values are used to determine the amplitude $[amp=(X^2+Y^2)^{1/2}]$ and phase $[phase=\tan^{-1}Y/X]$ of the response at the stimulus repetition frequency. The amplitude is represented by the length of the vector and the phase delay is represented by the vector orientation relative to the X and Y axis.

Figure 2 Grand mean data showing the amplitude/intensity and phase/intensity functions using the intensity sweep technique. The subjects were either attending (ATTEND) or ignoring (IGNORE) incoming, monaurally presented auditory stimuli. These equally weighted grand mean data are from 8 subjects. The data are vector-averaged and each tracing represents 640 sweeps of stimulus intensity. Below threshold, the amplitude is low and the phase is random. As the intensity of the stimulus increases above threshold, the amplitude increases linearly and the phase decreases. Below threshold, because of the randomness of the data, the phase tracings for the ATTEND and IGNORE conditions are dissimilar. Above threshold, the ATTEND and IGNORE conditions have similar responses.

Figure 3 The grand mean data from a single subject tested on 5 different occasions using the intensity-sweep technique. Each amplitude/intensity and phase/intensity function is the response from 400 sweeps of stimulus intensity. Below threshold, the amplitude and phase for both the ATTEND and IGNORE conditions are random. Above threshold, the amplitude and phase are similar for the IGNORE and ATTEND conditon.

Figure 4 Simultaneous stimulation and dichotic listening technique used to evaluate the effect of attention on the human auditory steady state MLR. Two stimulus generators (STIM) presenting tones of 500 and 1000 Hz are triggered by oscillators (OSC) at repetition rates of 37/s and 41/s respectively. The subject's EEG is amplified (AMP) and fed into separate Fourier analyzers to be multiplied by the sine and the cosine of the stimulus repetition frequencies. These multiplications result in two independent vectors giving the amplitude and the phase of the response at each stimulus repetition frequency.

Figure 5 The grand mean late event related potentials (ERP) recorded using signal averaging to demonstrate selective attention to one channel. The figure represents the responses during the ATTEND and IGNORE conditions for the 500 Hz and 1000 Hz tones presented at the 37/s and 41/s presentation rates. The tracings are the grand mean responses recorded from Cz in ten subjects. Negativity at Cz is represented by an upward deflection. The evoked potentials to the ATTENDed targets are larger than the evoked potentials to the IGNOREd targets. The data are collapsed across ears because there was no significant difference between ear of delivery.

Figure 6 The grand mean Fourier analysis data for the dichotic listening experiment collapsed across ears. The phase delay is longer for the 41/s presentation rate and for the 500 Hz tone frequency. The response is larger for the 1000 Hz tone frequency. There is no difference between responses obtained while subjects were attending and those obtained while subjects were ignoring the stimuli.

Figure 7 The grand mean steady state MLR superimposed on the late ERP components. The ERP data recorded from the vertex were high-pass filtered at 10.35 Hz. This filtering removed the transient responses and left the superimposed steady state response at the periodicity of the stimulus rate. The responses from the ATTEND and IGNORE conditions are similar.

Figure 8 Steady state responses imbedded in the late event related potentials analyzed with Fourier analysis. The upper tracings show the late event related potentials to the ATTENDed and IGNOREd targets. Imbedded in the responses are the smaller steady state responses at the periodicity of the stimulus rate. The lower tracings represent the results of a Fourier anlalysis of these embedded data after the larger transient responses had been removed by filtering (of figure 7).

Figure 9 The effect of visual attention upon the steady state evoke potentials (SSEP) for 5 subjects. On the left are the vectors representing the Fourier analysis steady state evoked potentials (SSEP). The reponse phase is longer for the 500 Hz tone presented at 41/s. The amplitude and phase of the response is not different between responses obtained when subjects are attending to incoming stimuli (ATTEND), ignoring incoming stimuli (IGNORE) or reading a book (READ). On the right are the transient, late event related potentials (ERP). The ERP are larger during the ATTEND condition than in the IGNORE and READ condition therefore illustrating that selective attention was achieved during the experiment. Note the similarity between the ERP data during the IGNORE and READ conditions.

Figure 10 The grand mean data for the steady state evoked potentials (SSEP) measured using simultaneous signal averaging and Fourier analysis. The tracings represent the data from 7 subjects. The subjects attended (ATTEND) to targets in one ear and ignored (IGNORE) targets presented to the contralateral ear. The tracings on the left are the responses measured using signal averaging. There is no difference between the responses obtained while the subjects were attending or ignoring incoming stimuli. In the middle are the Fourier analysis data. The response phase for the SSEP is longer for the 41/s presentation rate and 500 Hz tone condition. There is no difference between the ATTEND and IGNORE codition in the responses measured with Fourier analysis. The late event related potentials (ERP) are on the right. They are larger for the ATTEND condtion than the IGNORE conditon therefore demonstrating selective attention.

Figure 1

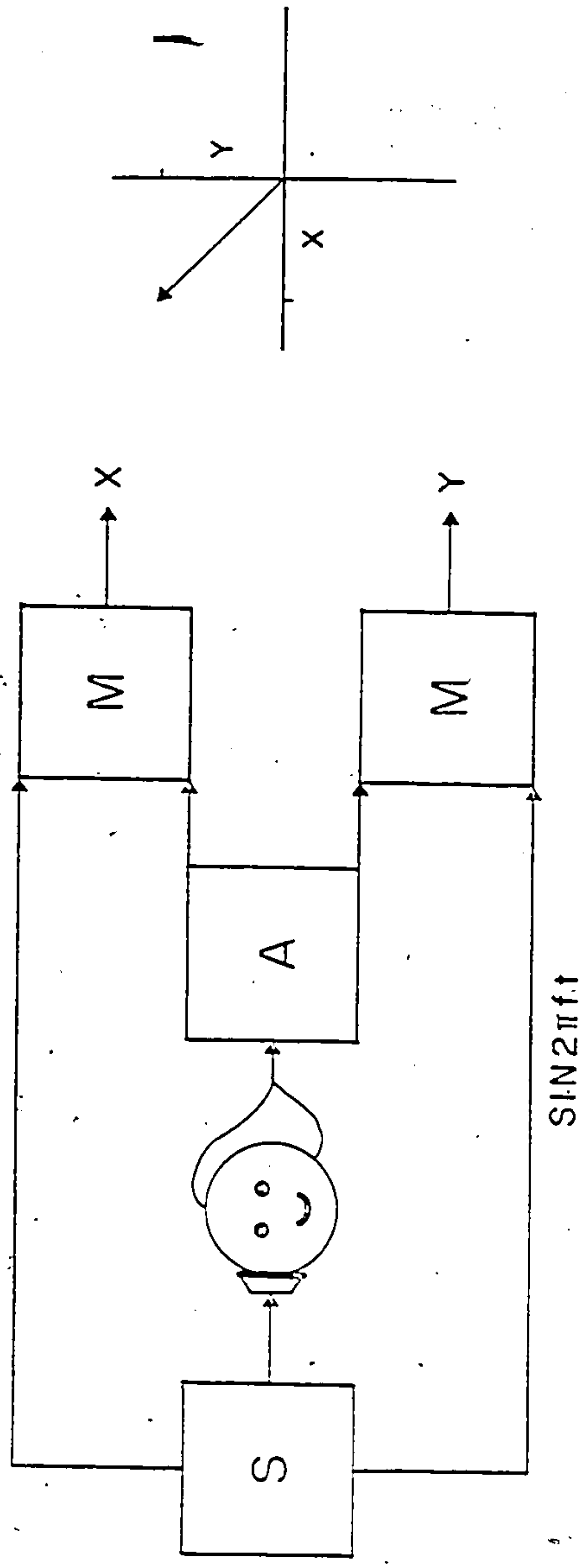


Figure 2

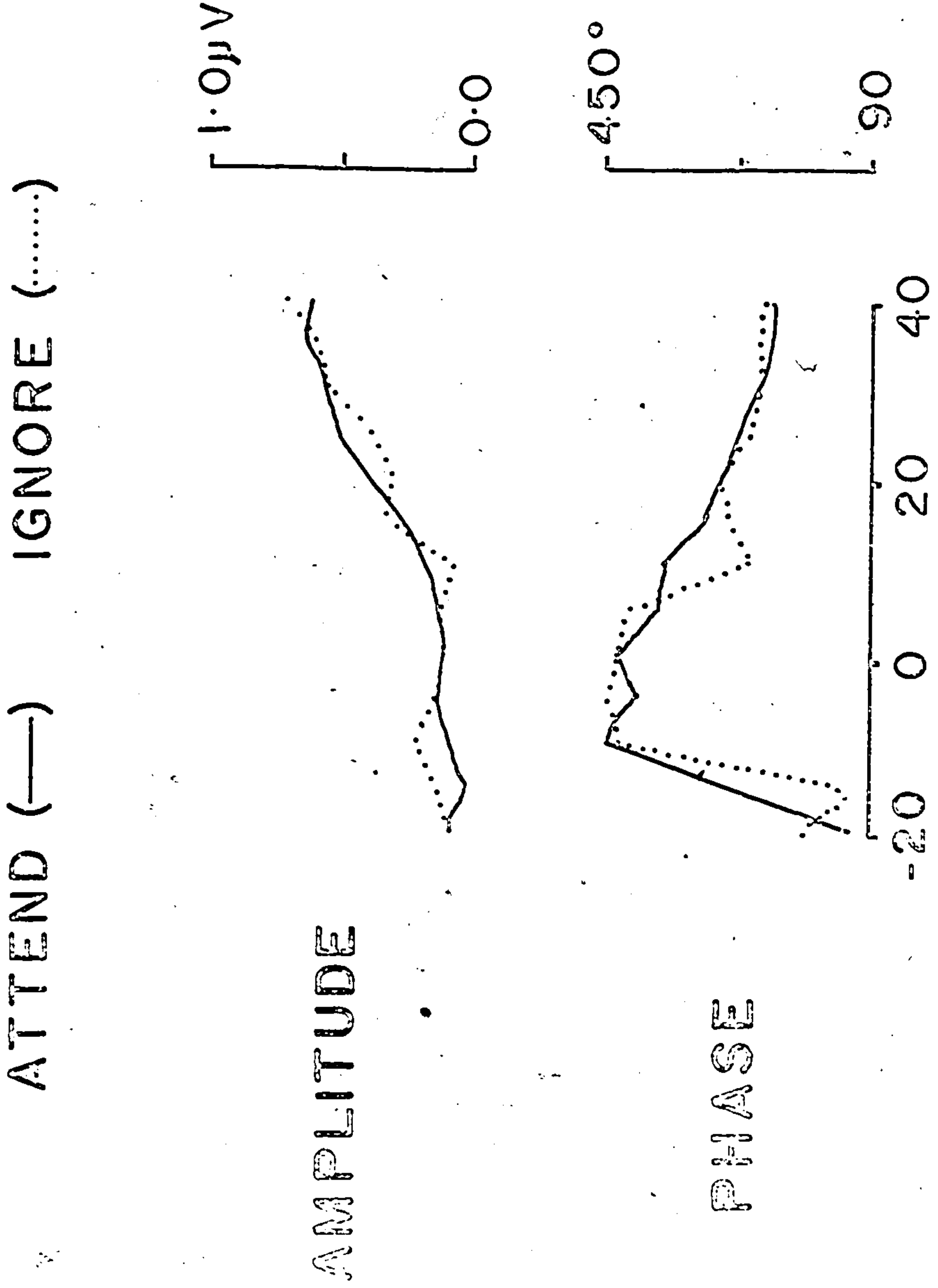


Figure 3

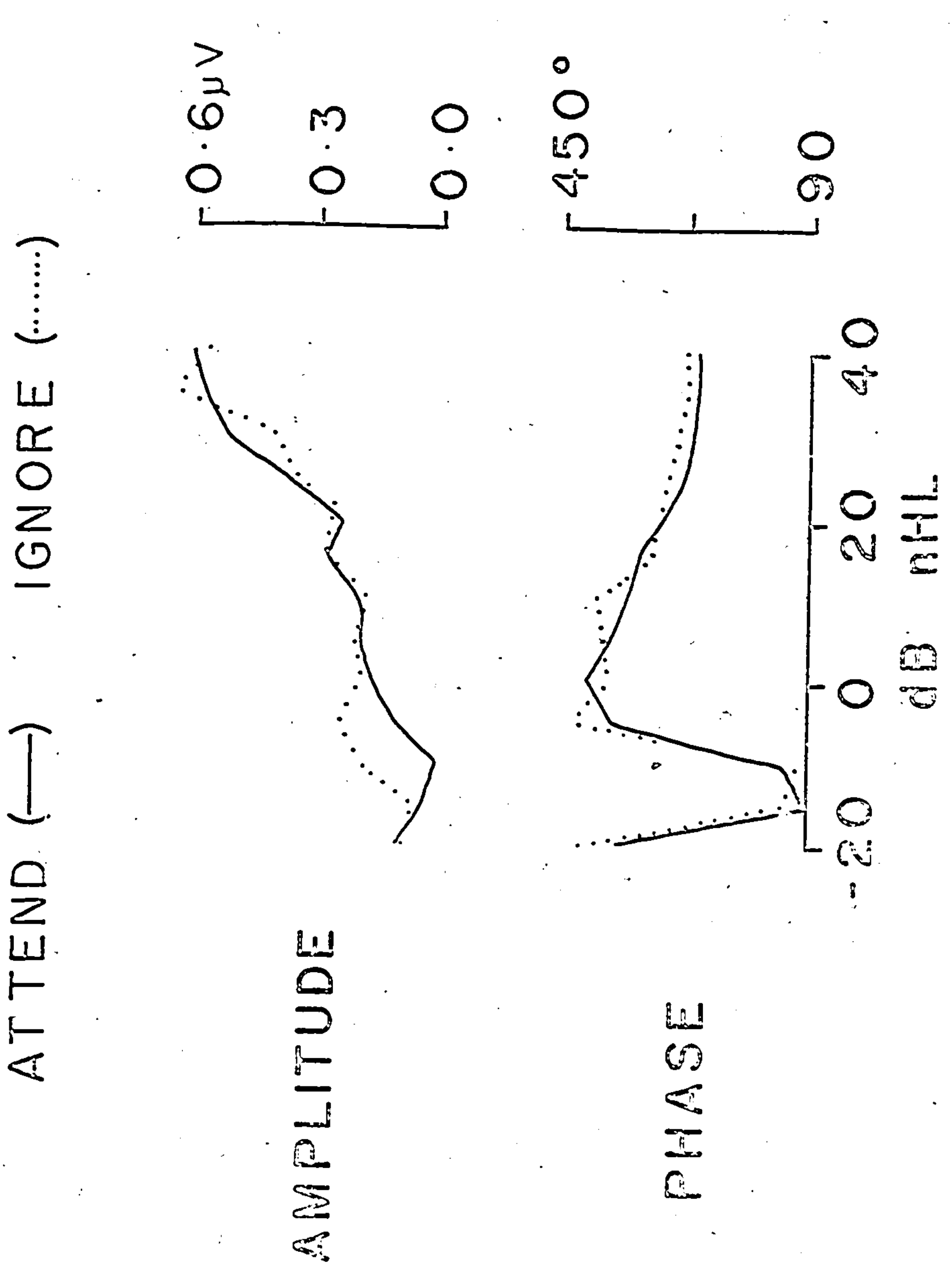

ATTEND (——)
IGNORE (……)
AMPLITUDE
0·6µV
0·3
0·0
PHASE
450°
90
-20
0
20
40
dB nHL

Figure 4

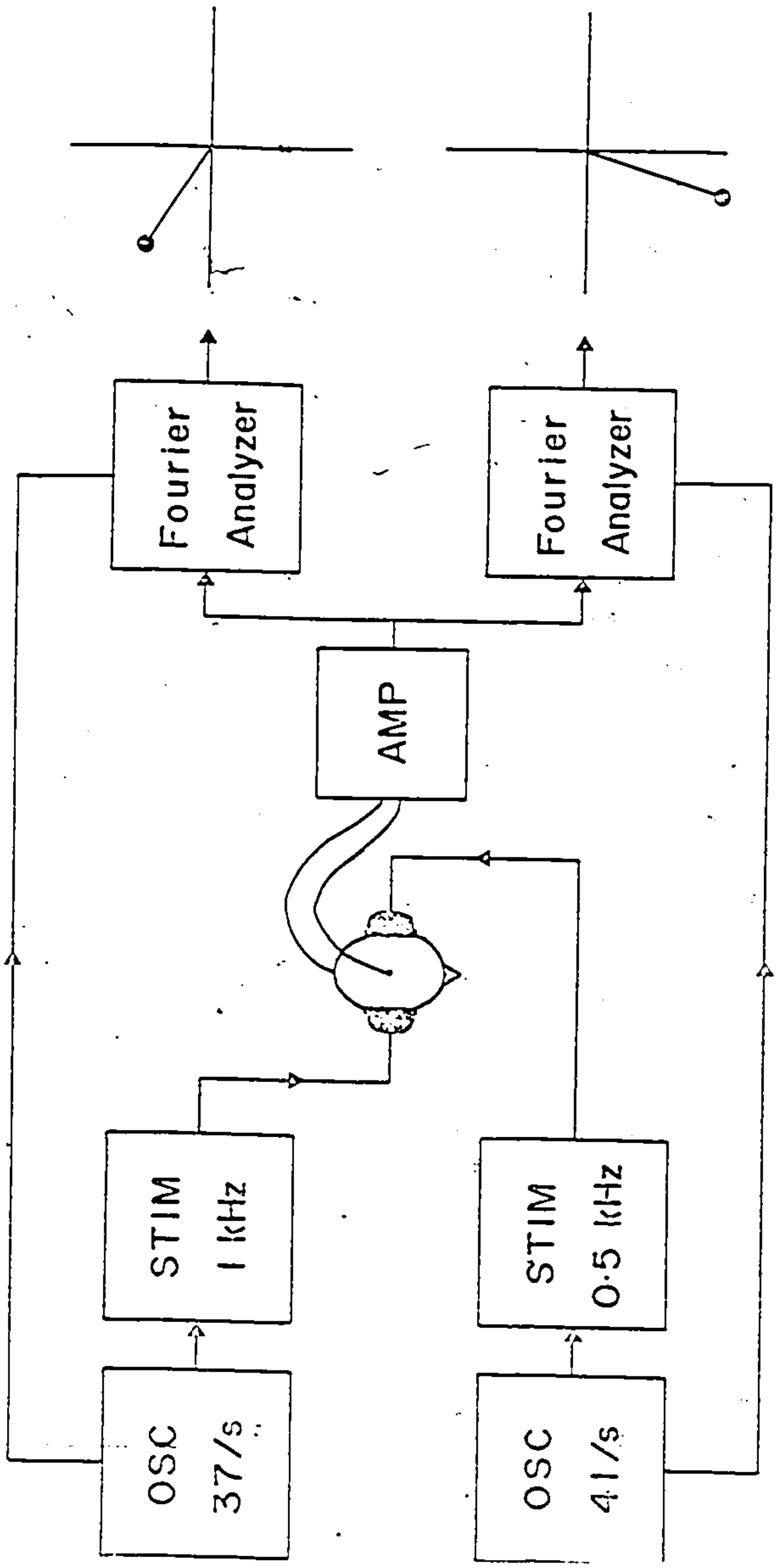

Fourier Analyzer
Fourier Analyzer
AMP
STIM 1 kHz
STIM 0·5 kHz
OSC 37/s
OSC 41/s

Figure 5

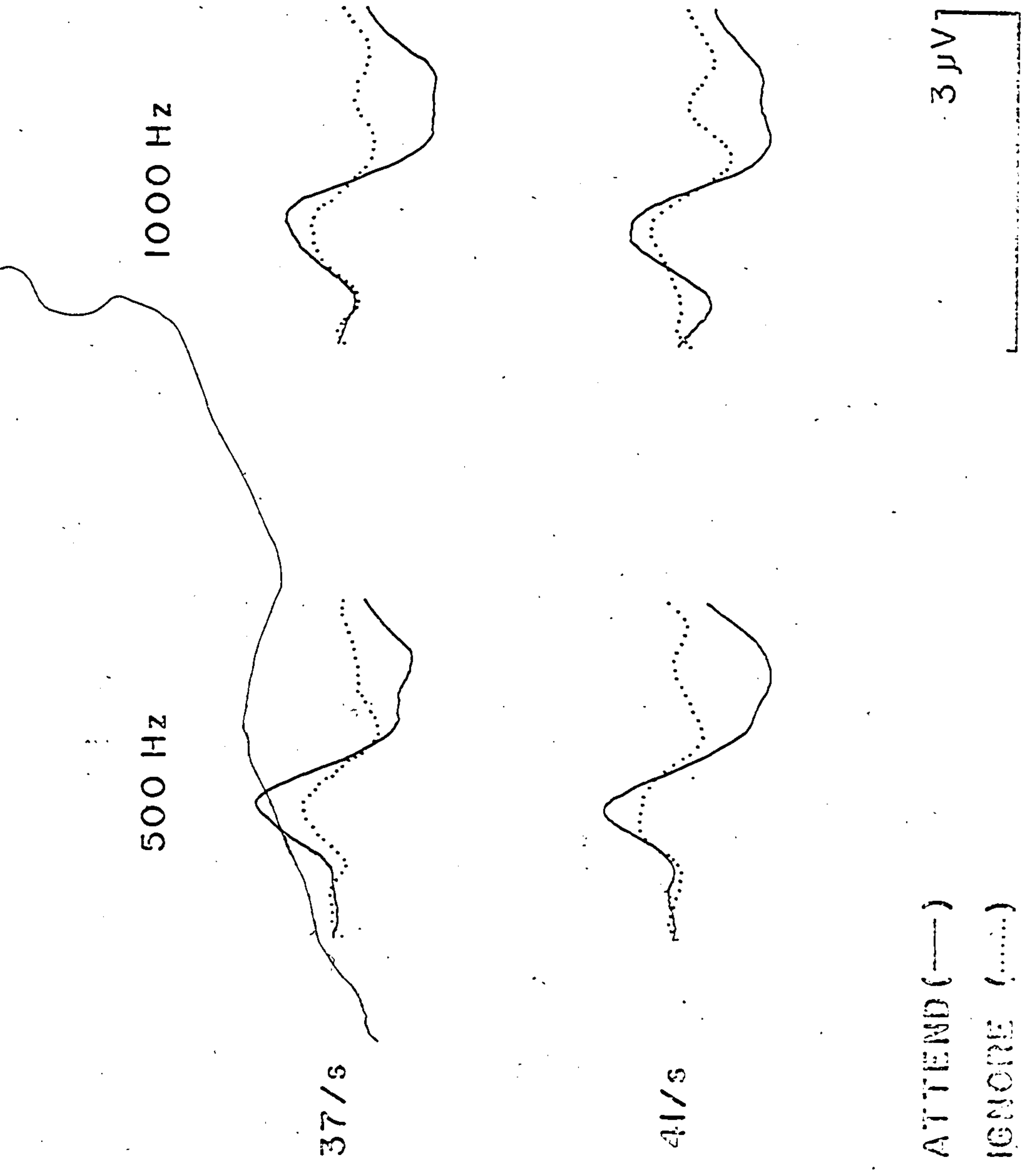


Figure 6

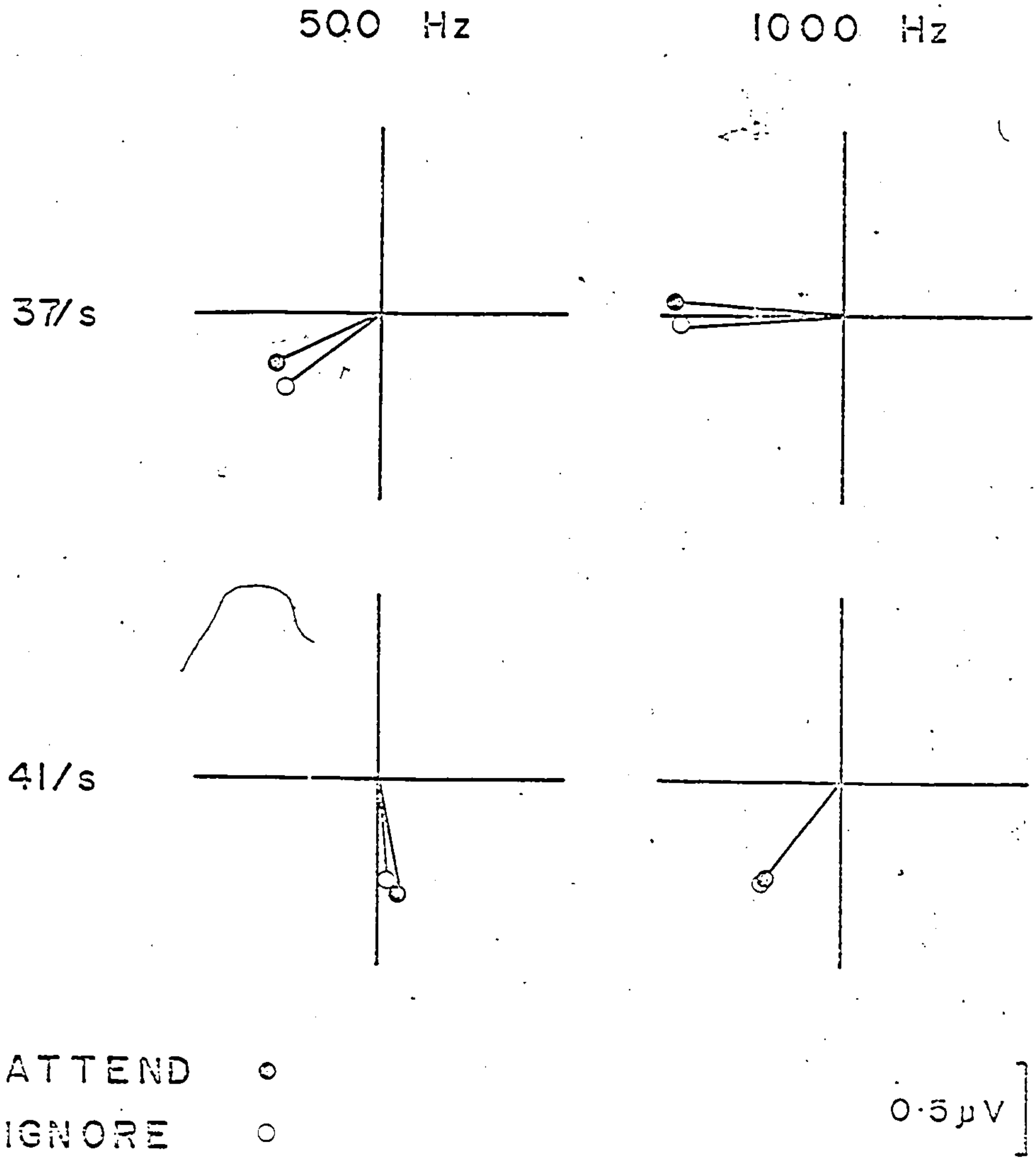


Figure 7

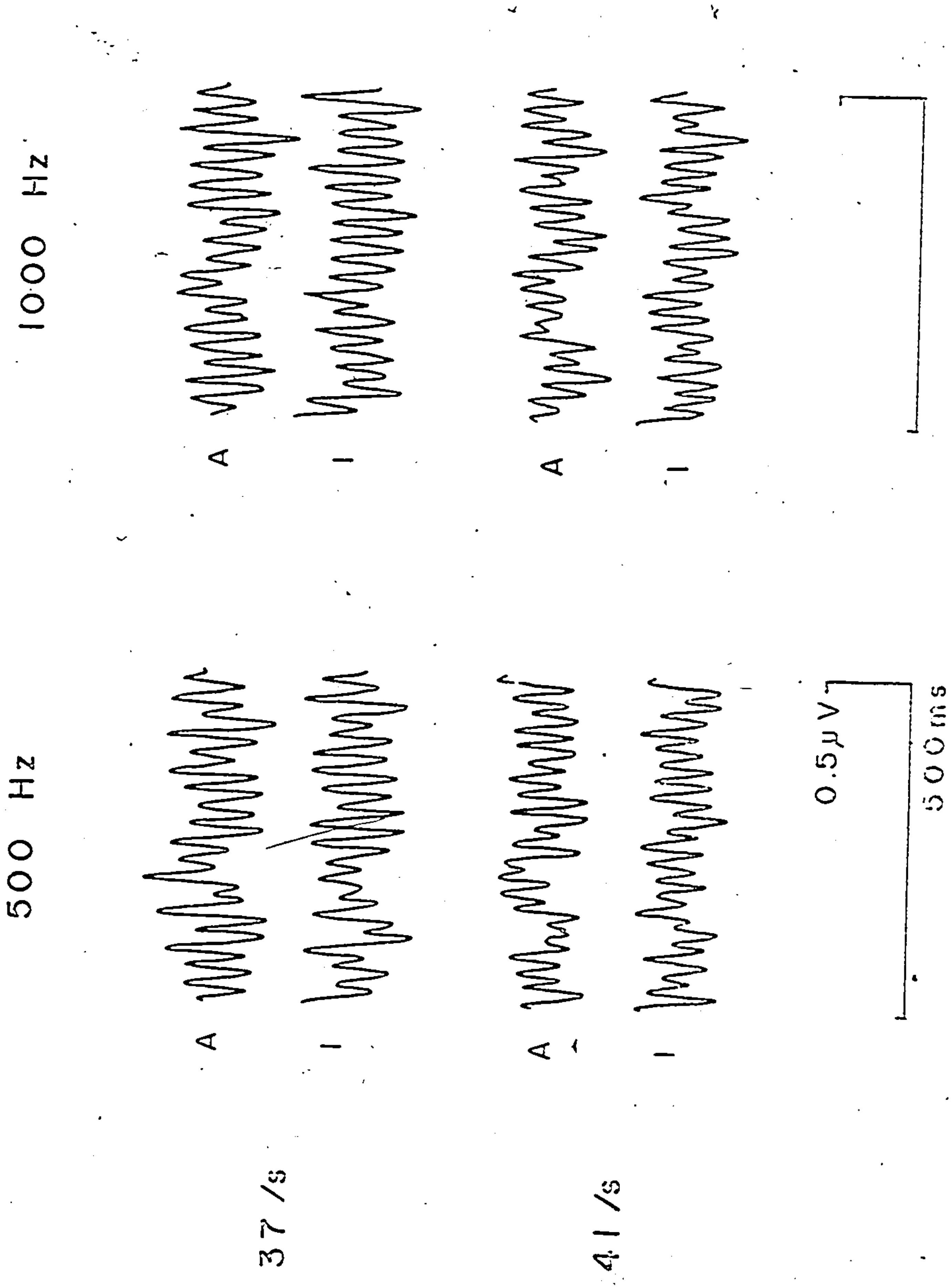


Figure 8

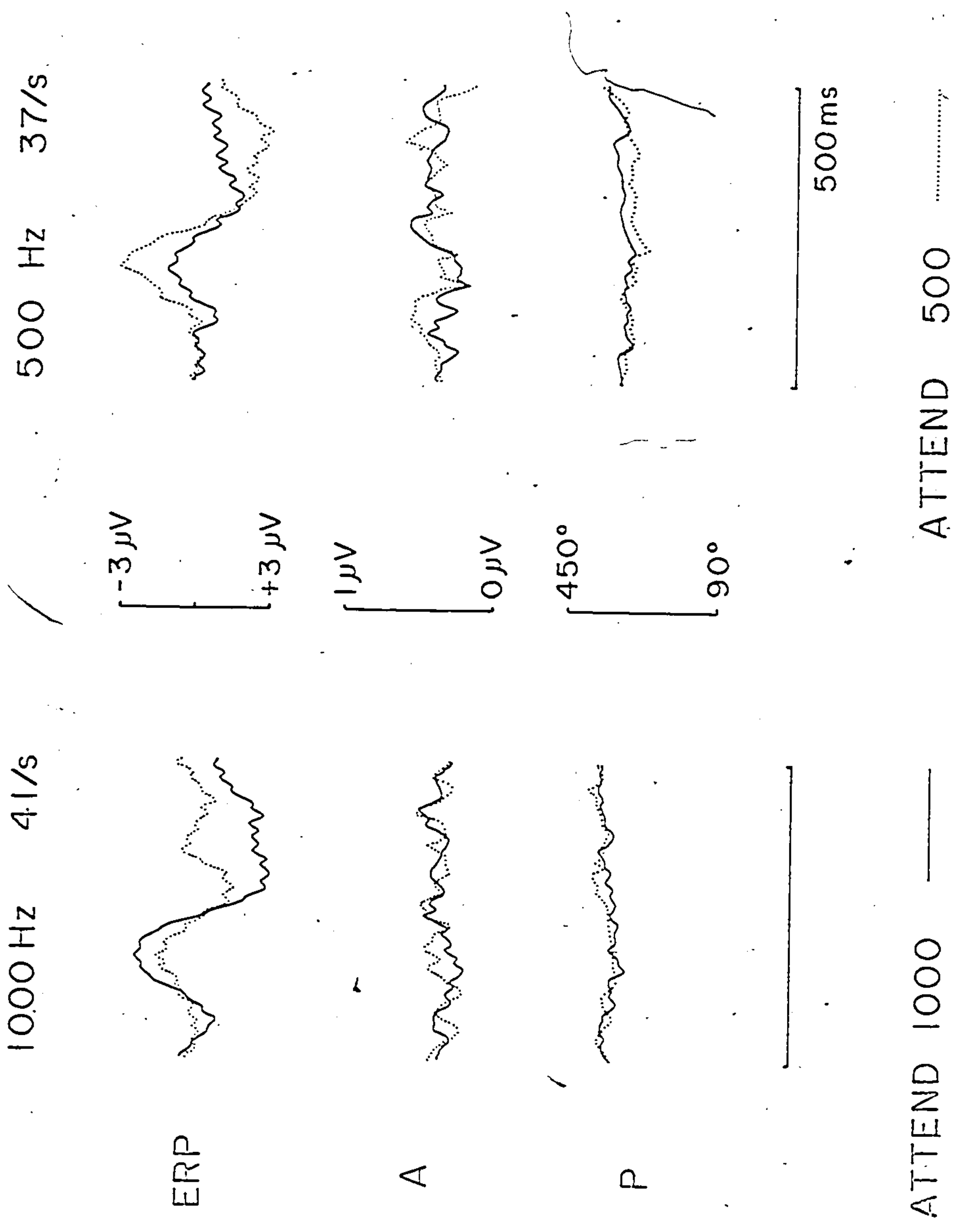

500 Hz 37/s
1000 Hz 41/s
ERP
A
P
-3 μV
+3 μV
1 μV
0 μV
450°
90°
500ms
ATTEND 500
ATTEND 1000

Figure 9

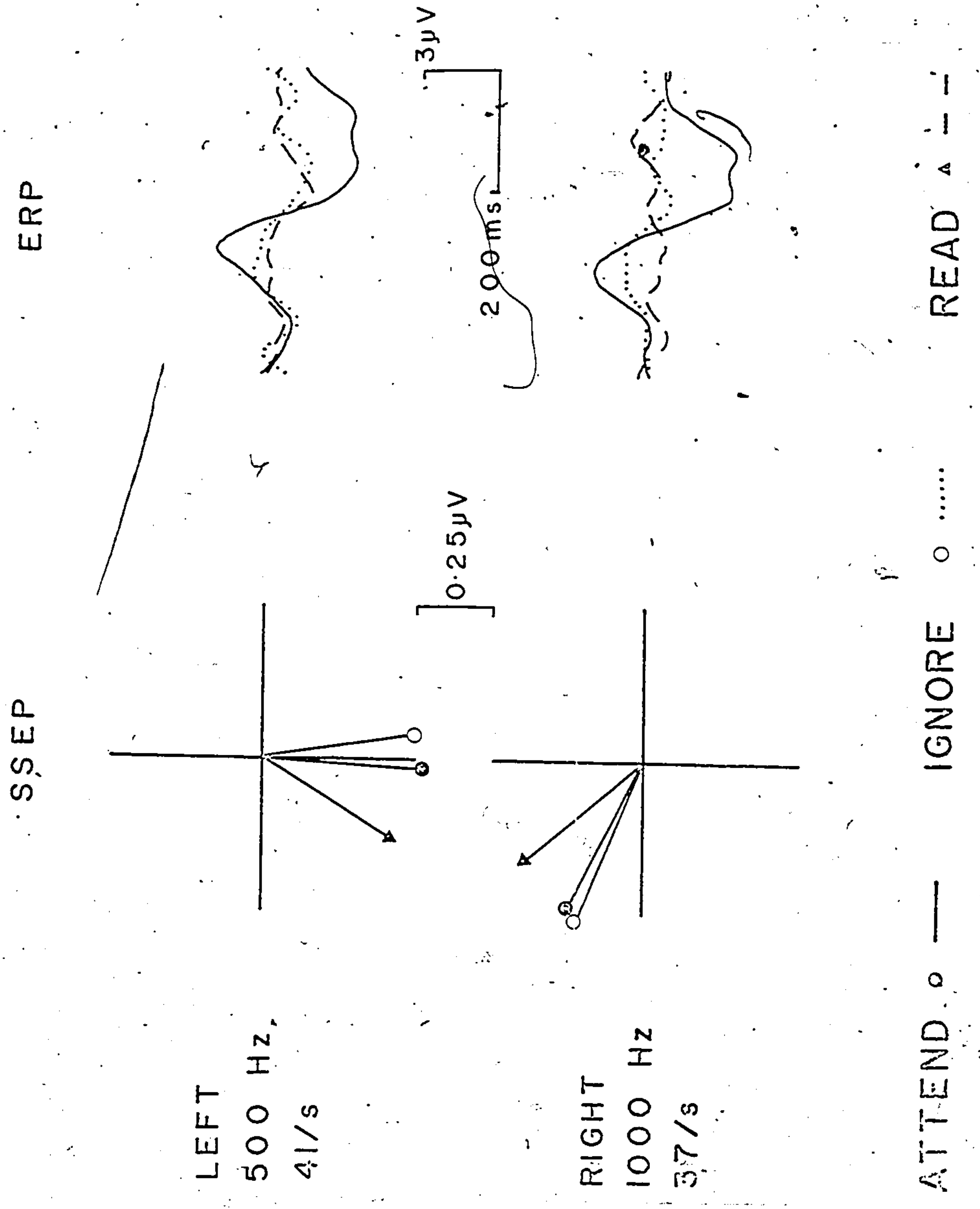
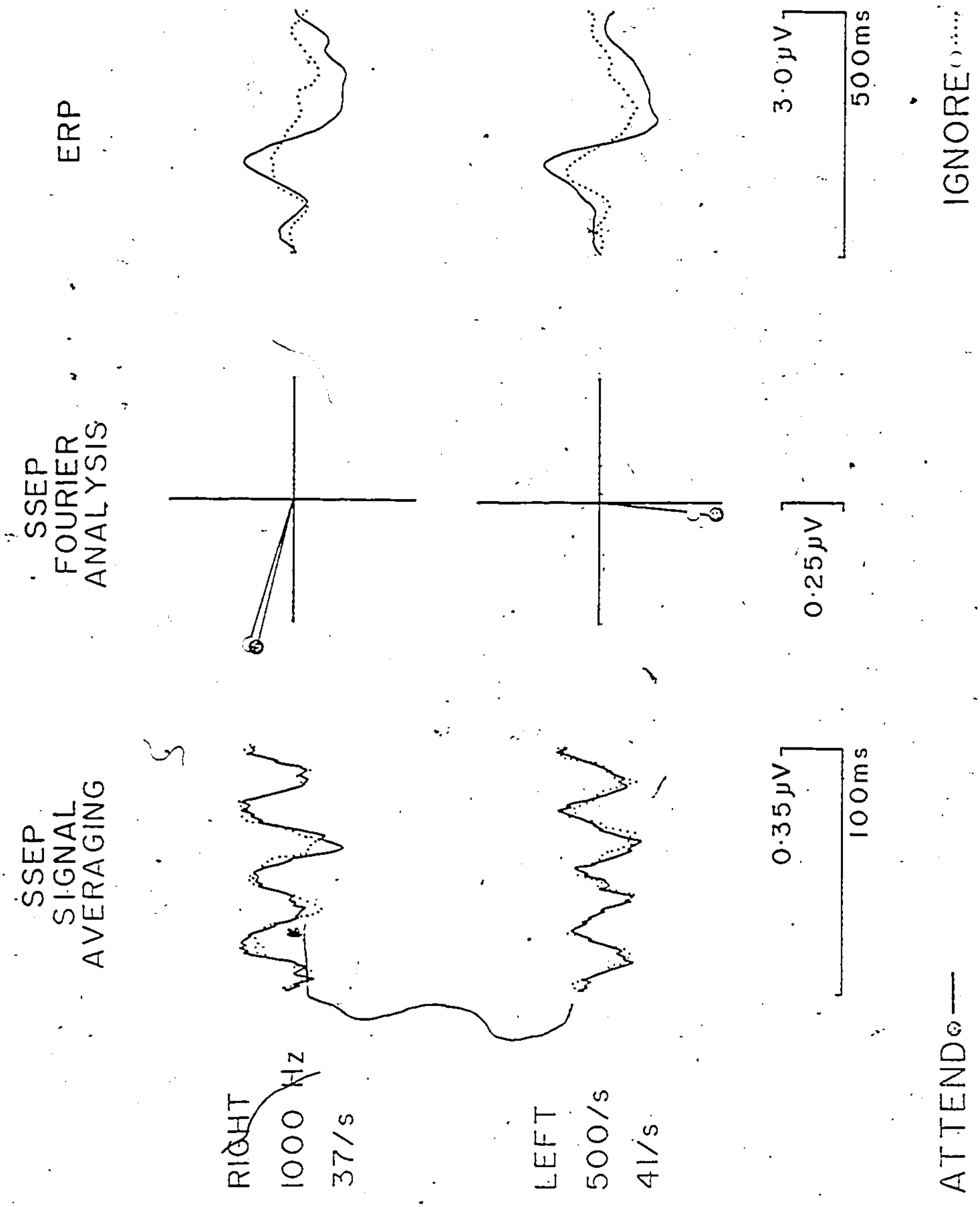

ERP
SSEP
3µV
200ms
0·25µV
LEFT
500 Hz,
41/s
RIGHT
1000 Hz
37/s
ATTEND ○ ——
IGNORE ○ ......
READ △ — —

Figure 10


SSEP SIGNAL AVERAGING
SSEP FOURIER ANALYSIS
ERP
RIGHT 1000 Hz 37/s
LEFT 500/s 41/s
0·35µV
100ms
0·25µV
3·0µV
500ms
ATTEND
IGNORE

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Human Auditory Middle Latency Evoked Potentials

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Running title: Auditory middle latency responses

Summary: Auditory evoked potentials are useful clinical tools. They are classified on the basis of the latency of their components as early (0-10 ms), middle (10-50 ms) and late (50-500 ms) responses. On the basis of the stimulus presentation rate, the middle latency responses (MLR) may be classified further as transient and steady state responses. Both transient and steady state MLR may be recorded using signal averaging. Steady state MLR may also be recorded using Fourier analysis. As the intensity of the auditory stimulus is increased the amplitude of the MLR increases and the phase of the steady state MLR decreases. Therefore, these responses may be used to estimate response threshold. The steady state response may estimate threshold to within 10 dB of those determined behaviourally provided the subject is awake. The transient MLR may be too noisy to estimate threshold in awake subjects. Threshold estimates may be improved using the transient MLR while the subjects are sleeping. The transient MLR are affected by sleep and may be affected by attention. The steady state MLR are not affected by attention and the response amplitude decreases during sleep but the phase of the response is not affected by sleep. Both transient and steady state MLR are affected by the age of the subject. Once the generator sites of the MLR is known the responses may become helpful in assessing central auditory dysfunction.

Key words: Evoked potentials
Middle latency
Transient
Steady state

Introduction

On the basis of their latency, the human auditory evoked potentials can can be divided into early (0-10ms), middle (10-50 ms) and late (50-500 ms) components (Picton et al., 1974; Davis, 1976). This paper reviews the auditory middle latency responses (MLR). According to the rate of stimulus presentation, Regan (1982) has distinguished "transient" and "steady state" evoked potentials. Transient responses are recorded when stimuli occur at a sufficiently slow rate that the response to one stimulus is complete before another stimulus is applied. Steady state responses are recorded when stimuli occur at a sufficiently high rate that the response to one stimulus overlaps the responses to subsequent stimuli. In a linear system transient and steady state evoked potentials are equivalent. If the system is non-linear, however, the steady state potentials are not predictable from the transient responses. This paper reviews both the transient and the steady state auditory MLR. Figure 1 compares the transient MLR (recorded at 10/s) to the steady state MLR (recorded at 40/s).

-insert Figure 1 about here-

History

Geisler and his colleagues (1958, 1960) were the first to report the transient MLR recorded from the human scalp. They observed a vertex-positive peak recorded at approximately 30 ms in response to a click stimulus. The threshold of these responses was similar to the threshold determined behaviourally. Early acceptance of these responses as a clinical tool in electric response audiometry was blocked by a report by Bickford et al., (1964) that these responses were myogenic. Although these responses were later shown to be sensitive to myogenic reflex potentials because they may be recorded during complete muscle paralysis they are partially neurogenic in nature. Goldstein and Rodman (1967) reported a vertex negative peak recorded between 20-24 ms, a vertex positive peak recorded between 31-35 ms and a vertex negative peak recorded between 46-50 ms. The amplitude of these responses varies from 0.5 to 3.0 uV.

Geisler (1960) and Chatrian et al., (1960) were the first to report the steady state MLR, noting an amplitude enhanced plateau when stimuli were presented at rates of 30/s to 50/s. Schimmel et al., (1974, 1975) reported a periodic steady state MLR to clicks presented at rates of 10-200/s. Campbell et al., (1977) using clicks and 90-100% amplitude-modulated tones described steady state MLR at stimulus rates of 6-32/s. Sine-wave modulated tones showed an amplitude enhancement at rates of 24/s. Square-wave modulated tones and clicks had an amplitude maximum at stimulus rates between 12-16 /s. Cohen (1977) found an amplitude plateau maximum when stimuli were presented at 35/s to 45/s and suggested that wave V of the early brainstem components caused this amplitude enhancement. Because of the periodicity of the responses, Cohen suggested that templates may be used to score the responses.

In 1981, Galambos et al. sparked renewed interest in the steady state MLR. They found that when stimuli were presented at rates between 10-60/s an amplitude enhancement occurred when stimuli were presented at rates of approximately 40/s. This amplitude enhancement of the MLR may be explained by the fact that the major negative-positive deflections of the transient MLR are separated by 25 ms. Stimulating every 25 ms (40/s) would cause the later peaks and troughs of one response to align with the earlier peaks and troughs of the response to the next stimulus resulting in an enhancement of the combined response. This response has been termed the 40 Hz event related potential (Galambos et al., 1981), the "high rates response" (Makeig, 1985) or the steady state MLR (Stapells et al., 1984).

RECORDING PARAMETERS

(i) Signal averaging

The transient MLR is recorded using signal averaging. A sweep of 50-100 ms is used and averaging is carried out over 500 to 2000 trials. There are three main peaks: Na (20-24 ms), Pa (31-35 ms) and Nb (46-50 ms) (Goldstein and Rodman, 1967). Mendel and Goldstein (1969) reported two earlier peaks and called them No (8-10 ms) and Po (10-13 ms). These earlier peaks are difficult to isolate because they may represent a filtered distortion of wave V and the aftergoing negative wave in the earlier auditory brainstem response (ABR) (Picton and Fitzgerald, 1983). McFarland et al., (1977) reported later peaks Pb (47-56 ms), Nc (58-68 ms) and Pc (72-80 ms) when narrow filter settings (25-175 Hz) are used. These may represent filter-distortions of the late components of the auditory evoked potentials.

The steady state MLR have also been recorded using signal averaging (Galambos et al., 1981; Stapells et al., 1984). The steady state MLR resembles a sinewave. Separate peaks are not identified and the response is measured in terms of the amplitude and phase of the average waveform.

(ii) Filtering effects

The transient MLR are particularly sensitive to filter settings (Scherg, 1982; Suzuki et al., 1984). Scherg (1982) found that analog filters may affect the transient MLR by altering the waveform and even creating new peaks. Decreasing the low pass filter settings results in the removal of the early peaks and an increase in the latency of the remaining peaks. Increasing the high pass filter settings causes a decrease in the latency of the peaks. Because of the phase-shifts caused by analog filters, increasing the filter slope distorts the recorded waveform and may cause the creation of new peaks. One answer to these problems is to use zero-phase shift digital filters. If digital filtering is unavailable, transient MLR should be recorded using a wide bandpass (such as 10-1000Hz) and a low filter slope (6 dB/octave) (Scherg, 1982; Suzuki et al., 1984). Such a wide band recording allows the simultaneous recording of the early auditory brainstem response (ABR) and the MLR (Scherg, 1982 a,b; Scherg and Volk, 1983; Ozdamar and Kraus, 1983).

Kileny (1983) examined the effects of high and low pass filtering on the steady state MLR. When low pass cutoff frequencies are extended from 100 to 1500 Hz the ABR is included in the response. When high pass cutoff frequencies are changed from 30 to 5 Hz the peaks of the response are sharper and the phase of the response shifts. Bandpass filters are recommended to be set at 10-100 Hz (Galambos et al., 1981).

(iii) Fourier analysis

Because of the periodicity of the steady state response, frequency based techniques such as Fourier analysis may be used to measure the responses (Regan, 1977; Stapells et al., 1984). Fourier analysis is diagramatically represented in Figure 2. The stimuli are presented at a presentation rate of f Hz. To extract from the EEG a particular frequency, the EEG is multiplied by the sine and cosine of that frequency. These multiplications cause the components of the EEG at that frequency to be converted to a steady DC output; all other frequencies are converted to an AC output. The AC output is removed by low pass filtering. The DC offset values are used to compute the amplitude and the phase of the response. These calculations are based on the following formulae: amplitude=$(X^2+Y^2)^{1/2}$; phase=$\tan^{-1} Y/X$. This proceedure is effectively narrow-band filtering at one frequency. Phase-locked amplifiers work on the same principle, however, many of the commercially available phase locked amplifiers use square waves in their multiplications instead of sine and cosine waves. The product of the square wave multiplication consists of the activity at the stimulus rate plus other frequencies used in making up the square wave signal.

-insert Figure 2 about here-

If frequencies other than the stimulus rate are required, a more detailed analysis of the response may be obtained by running algorithms such as the Fast Fourier Transform (FFT) on the waveform. The Fourier transform effectively calculates the amplitude and phase of the signal at a range of frequencies rather than at one particular frequency. The Fourier transform provides a frequency spectrum of the waveform. Although it provides more detail on the frequency composition of the response the Fourier transform is computationally more complex than simple Fourier analysis. Furthermore the FFT analysis is closely determined by the digitization rate; the stimulus must be locked to the digitization or the energy at this frequency may not be properly measured (Picton et al., 1984). The analyzer can be used in the sweep techniques and the simultaneous stimulation techniques, both of which decrease the time required to obtain response information.

The sweep technique of Fourier analysis allows a rapid analysis of the response across a range of values for one stimulus parameter (Regan, 1972; Nelson et al., 1984). Stapells et al., (1984) introduced the use of the sweep technique in the analysis of the auditory steady state MLR. Figure 3 illustrates this technique to evaluate the effects of varying the stimulus presentation rate. The computer controls the stimulus rate. The stimulus is presented, the EEG is sampled by the Fourier analyzer and the computer calculates and stores the amplitude and the phase of the response for that particular rate. The computer then increases (or decreases) the presentation rate, samples the responses,stores etc. At the end of the sweep there is a series of amplitude and phase values for each stimulus presentation rate. Another sweep is then initiated, completed, stored and finally the values for each rate are vector averaged. The resultant amplitude/rate and phase/rate functions can then be plotted. Other parameters may also be swept. One obvious parameter to be swept in an audiological test is stimulus intensity therefore providing amplitude/intensity and phase/intensity functions which may be used to estimate the subjects response threshold (Linden et al., 1985; Rodriguez et al., 1985).

-insert Figure 3 about here-

Regan and Heron (1969) introduced the simultaneous stimulation technique of steady state systems analysis to the visual system. Linden et al., (1985) applied this technique to the auditory steady state MLR in an attention task. Tones were presented to each ear at different presentation rates. These rates should be non-harmonically related. A Fourier analyzer was set to each presentation rate. The technique can be used to assess the auditory analysis going on simultaneously in different sensory channels. Thus the responses to different ears or to stimuli of different tonal frequencies can be simultaneously assessed. More than two channels can be assesed simultaneously although one must be careful to rule out physiological interactions between different channels.

ORIGINS

The attempted localization of the auditory evoked potentials generator sites have included many approaches. Scalp distribution studies, examining the scalp muscle reflexes, animal studies, human intracranial recordings, human lesion studies and magnetoencephalographic recordings have all been used to try and localize the generator sources of the MLR.

(i) Scalp distribution

The auditory MLR are usually recorded between an electrode at the vertex and one on the mastoid or earlobe. The choice of reference site for recording the scalp distribution of transient MLR is important. Several reports exist wherein a nose reference was used (Vaughan and Ritter, 1970; Cohen, 1982). However a non-cephalic reference has been advocated because activity recorded at the nose may alter the response (Kooi et al., 1971; Wolpaw and Wood, 1982).

The transient MLR have a widespread scalp distribution recorded maximally at the vertex (Picton et al., 1974; Goff et al., 1977; Streletz et al., 1977). Several reports indicate a phase reversal across the Sylvian fissure. Vaughan and Ritter (1970) reported that when the components of the transient MLR were identifiable there was a reversal of the components recorded with electrodes placed above and below the sylvian fissure referenced to an electrode placed on the nose. Strelet: et al., (1977) examined the topography of the transient MLR using a non-cephalic reference. Electrodes were placed on the mastoid, ear, nose, and along the sagittal and coronal planes. They reported a phase reveral of the transient MLR recorded with a coronal array and a latency shift recorded in an anterior to posterior series of leads. Furthermore they found activity at the nose, ear and mastoid. Wood and Wolpaw (1982) used an extensive 20 electrode array over one hemisphere and mapped the responses to contralateral stimuli. A non-cephalic reference was used. Two frontocentral positive peaks were recorded at 30 and 50 ms. These peaks were inverted in temporal regions. Cohen (1982) mapped the transient MLR in a coronal array using a nose-reference. Seven equidistant elecrodes were placed in a row starting at the midline, 25 % anterior to Cz and extending to the mastoid. Between the fourth and fifth electrode the Pa (28.1 ms) component was inverted for all the subjects. Na and Nb were observed to invert occasionally along the electode array. Because the transient MLR phase reversal has been observed using a nose reference and a non-cephalic reference it is not probable that the reversal is caused by activity at the nose. The tracings on the left of Figure 4 show the scalp topography of the transient MLR. Our data from 10 subjects does not indicate a phase reversal along a coronal array. The Na peak does decrease in amplitude and the latencies of the peaks decrease from responses recorded at the vertex to responses recorded below the sylvian fissure. A possible explanation for this difference may be the state of the subjects. We made sure that our subjects were awake. Cohen (1982) reported that some of his subjects were asleep. Wood and Wolpaw (1982) did not comment on the state of arousal of their subjects. Sleep does affect the transient MLR. The response is different along a vertex to mastoid coronal array however amplitude decrements and latency shifts may be misinterpreted as phase reversals.

-insert Figure 4 about here-

There are several conflicts in the literature on the effect of ipsilateral versus contralateral recordings. Peters and Mendel (1974) recorded the transient MLR recorded between Cz-A1, Cz-A2, C3-A1 and C4-A2. They reported no difference between the ear of delivery and the response amplitude and latency measured at the vertex (Cz-A1, Cz-A2) or at the lateral placed electrodes (C3-A1, C4-A2). Kevanishvili et al., (1979) examined the transient MLR recorded from the ipsilateral and contralateral side of the head to the ear stimulated. The responses were recorded between an electrode placed on the central region of the skull and both earlobes. They found differences between the transient MLR recorded from stimulation to the ipsilateral ear and contralateral ear. The responses were larger if recorded from the side of the head contralateral to the ear stimulated. Celesia (1976) recorded the transient MLR from the lateral surface of the cortex referenced to a gold-plated alligator clip attached to the exposed bone and found that the responses to stimuli to the ear contralateral to the recording site were larger than responses elicited from stimulating the ear ipsilateral to the recording site. Lee et al. (1984) reported similar results recorded from subdural electrodes referenced to an elecrode attached to the skin over the fifth cervical vertebrae. Ozdamar and Kraus (1983) found that the amplitude of Na was symmetrical, but appeared larger when recorded over the contralateral temporal lobe. Woods and Clayworth (1985) recorded the transient MLR from the vertex, ipsilateral mastoid to the ear stimulated and from electrodes placed midway between C3 to T3 and between C4 to T4 referenced to a balanced non-cephalic reference at the base of the neck. They reported that the Na component recorded from electrodes placed contralateral to the ear stimulated had a shorter latency and a larger amplitude. The Pa and Nb components demonstrated no effects of ear of delivery. A maximal response recorded from stimuli presented to the contralateral ear may be explained anatomically by enhanced projection to the contralateral auditory cortex (Ravizza and Belmore, 1978). Different effects of ear of delivery upon different components of the transient MLR suggests different generator sites for these components (Woods and Clayworth, 1985).

The topography of the steady state MLR has not been studied in as much detail as the transient MLR. A widespread frontocentral maximum topography has been reported (Makeig, 1985). Figure 4 shows the topography of the steady state MLR. Cohen et al., (1973) reported a polarity reversal between C4 and T4. We have found that the periodicity of the steady state MLR has a widespread scalp distribution. Although not readily discernible in the individual tracings the grand mean data demonstrates that along a coronal line the phase of the response shifts (Figure 4).

-insert Figure 4 about here-

(ii) Scalp muscle reflexes

Early acceptance of the MLR as a clinical tool was clouded because they were thought to be myogenic (Bickford et al., 1964; Mast, 1965). Bickford

(1972) reported on a number of scalp muscle reflexes in response to auditory stimuli of sufficient magnitude. There are four main scalp muscle reflexes: frontalis, inion, postauricular and temporalis. Picton et al., (1974) reviewed the characteristics of these reflexes. The frontalis, inion and temporalis reflexes are all affected by changes in muscle tension. The inion reflex is initiated through vestibular rather than auditory connections (Townsend and Cody, 1971).

The postauricular reflex is recorded at a latency of approximately 12 ms (Bochenek and Bochenek, 1976). There are two peaks, a mastoid negative peak (12-15 ms) and a positive wave (12-18 ms). These responses will not contaminate the MLR if the reference mastoid electrode is placed on a low mastoid position (Yoshie and Okudaira, 1969). Figure 5 illlustrates the postauricular muscle reflex recorded at different mastoid locations.

-insert Figure 5 about here-

By using an electrode placed on a low mastoid position and ensuring that the subject is relaxed, the myogenic contribution to the MLR may be minimized.

(ii) Animal work

Kiang et al., (1961) first recorded the transient MLR in animals using an implanted electrode in the cat auditory cortex. A positive peak followed by a negative peak was recorded within 50 ms after the auditory stimulus was presented. Arezzo et al., (1975) studied the transient MLR recorded intracranially in the Rhesus monkey and suggested the recorded peaks were generated in the primary auditory cortex. Kaga et al., (1980) found that the transient MLR in cats are similar to those of humans except that the latencies of the peaks are shorter. They demonstrated that during laminar analysis a dipole was observed in the cat area A1 (auditory cortex). Lesioning experiments of A1 and the adjacent cortex demonstrated that a small anterior A1 lesion abolished Pa without affecting earlier components. Lesions adjacent to this small area had no effect upon the transient MLR.

Buchwald et al., (1981) examined the effect of click rate, pentobarbital anesthesia and lesions on the transient MLR recorded in cats from the scalp and from depth recordings. The scalp recordings were between the vertex and referenced to the neck, pinna or paw. The depth recordings were made between the barrel to wire or the barrel referenced to the pinna. They reported three positive waves: wave A (17-25 ms), wave B (35-45 ms) and wave C (50-75 ms). The waves are sensitive to presentation rate, disappearing as presentation rates are increased to 10/s. Furthermore, all the waves disappear when pentobarbital is administered. Wave A remained after hemispherectomy, therfore suggesting its origin is not in the auditory cortex or auditory association cortex. Ablation of the suprasylvian gryrus, ectosylvian gyrus and frontal lobes did not affect wave C. Hemispherectomy abolished wave C. They proposed that their data supports the hypothesis that components before 25 ms are recordings of a diffuse medially placed ascending auditory system. This secondary system is in addition to the standard lemniscal pathway and may consist of a reticular-midthalamus-association cortex loop. Hinman and Buchwald (1983) examined the cat wave A of the transient MLR comparing depth evoked potentials and scalp recorded evoked responses from the brainstem and thalamus. Potentials were recorded from the midbrain (cuneiform nucleus) to the level of the intralaminar thalamic nuclei (centralis lateralis and center median). Scalp and depth recorded responses were diminished in amplitude during sodium pentobarbital anesthesia. Bilateral aspiration of the inferior colliculus did not affect wave A therefore suggesting that it is mediated by non-lemniscal connections. Responses from the intralaminar thalamic nuclei, centralis lateralis and center median, were enhanced after bilateral removal of the inferior colliculus. These observations led Hinman and Buchwald to propose that wave A represents a secondary ascending auditory pathway projecting from the midbrain reticular formation to the thalamus.

Farley and Starr (1983) reported that the cat transient MLR polarities and latencies corresponded well with human data. They postulated that cat peaks (P10-N13-P17-N22-P31-N41) assigned to human peaks (P12-N22-P25-N28-P30-N45). Furthermore, as the intensity of the stimulus was increased, the amplitude of the response increased and the latency decreased.

McGee et al., (1983) and Kraus et al., (1985) reported a triphasic MLR in guinea pigs recorded optimally from the contralateral cortex. Peak A at 11 ms, B at 18 ms and C at 29 ms. The unanesthetized guinea pigs had diminished responses recorded from the ipsilateral hemisphere and vertex. Wave A and C were recorded maximally at different locations over the temporal lobes, suggesting they have different generator sites. Wave C was more sensitive to anesthesia than wave A.

Kraus et al., (1985) examined the transient MLR in anesthetized non-human primates. They reported a negativity similar to the Na recorded in humans except having a slightly earlier latency. Later components were variable but the authors postulated they may be homologous to the human Pa (30ms) and Pb (65ms) components.

Yoshida et al., (1985) examined the steady state MLR recorded from the scalp of guinea pigs. They reported on the scalp distribution, effects of pentobarbital and ablation experiments. Screw electrodes were placed in the skull and referenced to an implanted silver wire. Responses were recorded maximally from the vertex and from the temporal area contralateral to the area stimulated. Pentobarbitol administration reduced the amplitude of the temporal response but did not affect the vertex response. Removal of the cortex contralateral to the ear stimulated eliminated the temporal response but did not affect the vertex response. Bilateral removal of the cerebral cortex did not affect the midline response. The vertex component remained after the removal of the inferior colliculus and after decerebration. Decerebration altered the response, yet a steady state response was still present. These data suggests a number of generator sites may contribute to the steady state response.

Several reports indicate the amplitude of the MLR decrease as the presentation rate increases in cats (Buchwald et al., 1981; Hinman and Buchwald, 1983). Although presentation rates of 20/s (harmonic of 40/s) cause a decrease in the response amplitude recorded at the vertex, the figures suggest that recording from the "ectosylvian cortex" and "medial geniculate body" are amplitude enhanced (Buchwald et al., 1981).

Galambos postulated that, because of a scalp recorded interaction between tactile and auditory stimuli, the steady state MLR are generated in the rostral reticular formation or thalamic region described by Buchwald et al., (1981). This hypothesis was based on the fact that midbrain reticular neurones receive converging sensory inputs (Steriade and Deschenes, 1984).

(iii) Human intracranial recordings

Several early reports on auditory evoked responses recorded from the human cortex exist (Heath and Galbraith, 1966; Celesia et al., 1968; Puletti and Celesia, 1970). These responses were within the same latency range as the scalp recorded MLR. Celesia and Puletti (1971) recorded the transient MLR from the exposed auditory cortex in conscious, drowsy patients and in anesthetized patients. The components they called the primary components are commensurate with the scalp recorded MLR. The responses from the anesthetized patients were similar in morphology, but smaller in amplitude and longer in latency than potentials recorded from the scalp. Hashimoto (1982) examined the transient MLR recorded directly from the human midbrain and proposed that No, Po and Na are generated in the inferior colliculus. Lee et al., (1984) studied the transient MLR in man using a rectangular array of (16-32 electrodes) subdural electrodes placed over the mid and posterior perisylvian region. They reported that these potentials may be recorded from the banks of the Sylvian fissure. The observed waveforms had a morphology similar to those reported by Celesia and Puletti (1971) with the largest component being the primary P2 (28 ms). This component was hypothesized to be the scalp recorded Pa component. The maximum amplitude was at 1 or 2 electrodes in the array with steep potential gradients at adjacent electrodes. This drop in potential may indicate localization of the generator site of these signals. Binaural stimulation produced larger responses than monaural stimulation. Stimulating the ear ipsilateral to the recording site produced smaller responses than contralateral stimulation. The amplitude of all components increased as the intensity of the stimulus increased. Barbiturate anesthesia caused a decrease in amplitude and an increase in latency but the general morphology of the components remained unchanged.

A detailed analysis of the steady state MLR in vivo has yet to be performed. Lee et al., (1984) performed a rate series on two of their subjects. In contrast to the results recorded at the scalp, the steady state MLR recorded subdurally were greatly diminished in amplitude compared to responses obtained from stimuli presented at lower rates.

(iv) Human lesions

Another method used to try and localize generator sites of auditory evoked potentials is to examine the responses in patients with confirmed brain lesions. Parving et al., (1980) reported that a patient suffering from auditory agnosia due to bilateral temporal lobe lesions had a normal transient MLR peak Pa latency and configuration. Graham et al.,(1980), however, found that a patient who had cortical deafness from bitemporal emboli, did not have transient MLR. Ozdamar et al., (1982) examined the transient MLR in a subject with bilateral temporal lobe lesions involving areas 41 and 42. The patient showed no behavioral response to sound. ABR and transient MLR were recorded while the subject was sleeping or resting quietly, sedated with chloral hydrate. Normal early ABRs were recorded. Pa (30 ms) was absent to either left or right ear stimulation. Because sleep affects the transient MLR it is difficult to determine whether the lack of response was a function of sleep in this case.

Kraus et al., (1982) examined the transient MLR from 22 patients (sedated with chloral hydrate) who had cortical lesions of the left or right hemisphere and in two patients with lesions in both hemispheres. Na and Pa components to 60 and 70 dB nHL click were measured. They found that the Na, Pa responses recorded from the vertex were within normal range regardless of the location of the lesions. In general, they reported that Pa amplitude was smaller in patients. Two patients had abnormal responses. One patient with bilateral temporal lobe lesions did not have any MLR. A second patient who had a left temporal lobe lesion that extended to the thalamic radiation had a delayed Pa in recordings from the vertex. They also measured the coronal potentials with an electrode placed halfway between the vertex and the ipsilateral mastoid. They found a decrease in the response amplitude over the injured hemisphere. Because of this data from patients with temporal lobe lesions affecting the auditory cortex demonstrating abnormal Pa responses they postulated that the transient MLR are generated from two vertical oriented dipoles located in the vicinity of the auditory cortex. Kileny and Berry (1983) examined the transient MLR recorded from two children (7 months, 33 months) with bilateral temporal lobe lesions. Both patients had normal early components and recognizable MLR. The 33 month old child was tested at 11 months and was found not to have MLR initially, but at 33 months transient MLR were recognized. The observation at 11 months could be explained by a maturation effect.

Kileny et al., (1985) compared transient MLR obtained from normal subjects, patients with temporal lobe lesions and patients with cortical lesions in areas other than the temporal lobe. Temporal lobe lesions affected the Na-Pa complex particularly if the response was elicited by ipsilateral stimulation to the damaged hemisphere. Patients with temporal lobe lesions in both hemispheres had abnormal Pa components measured at all scalp locations. Patients with lesions in areas not involving the temporal lobes had normal transient MLR. These data indicate that the transient MLR are at least in part generated in the primary auditory cortex. One problem with this hypothesis is that, when these responses are recorded from the scalp they are maximal at Cz. However, two vertically oriented dipole sources in the temporal lobes may sum at the vertex and create an enhanced sum (Vaughan and Ritter, 1970; Ozdamar and Kraus, 1983).

Spydell et al., (1985) examined the steady state MLR in patients with midbrain lesions and in patients with temporal lobe lesions using Fourier analysis. There were no abnormalities in the response amplitude. They reported that the response phase did not differ between normal subjects and subjects who had cortical lesions. However, subjects who had midbrain lesions had shorter phase values than those obtained from normal subjects.

These studies have shown that the transient MLR is partially generated from the primary auditory cortex. At least one of the generator sites of the steady state MLR is situated in the midbrain-thalamic area.

(v) Magnetoencephalography

Auditory evoked potentials are extracellular volume conducted potentials. Conversely, neuromagnetic recordings are thought to be generated from intracellular currents (Romani et al., 1982). The human auditory evoked magnetic field has a 50 ms component postulated to be equivalent to the transient MLR at 50 ms, possibly Nb (Farrel et al., 1980). The generator source for this potential was reported to lie 3 cm deep in the region of the sylvian fissure. Zimmerman et al., (1981) hypothesized the "orientation of an equivalent dipole source tipped away from the vertical by an amount consistent with the dipole being oriented perpendicular to the lateral fissure". These reports support the hypothesis that the later waves of the transient MLR are generated in the primary auditory cortex.

Romani et al., (1982) examined the magnetic evoked fields to stimuli at different presentation rates. They observed an enhanced amplitude maximum at high presentation rates (28-40 Hz). The response phase increased linearly as the stimulus presentation rate was increased above 20/s. The apparent latency calculated from the magnetic phase data was 19 ms, slightly shorter than the 36 ms reported by Linden et al., (1985). This may be explained by the different intensities and stimuli used in the two studies. Romani et al., (1982) reported that the steady state evoked current dipole for auditory, visual and somatosensory modulation lies perpendicular to the fissure projection.

From these data one may suggest several generator sources contribute to the transient MLR. The primary auditory cortex from both hemispheres contributes to the later waves (Pa) and beyond. The earlier peaks are probably generated from the midbrain-thalamus areas and may have myogenic contributions. The steady state MLR appear to have multiple generators. The reticular formation, thalamus and auditory cortex are possible candidates.

STIMULUS PARAMETERS

(i) Stimulus presentation rate

When stimuli are presented between rates of 1 to 10/s the amplitude of the MLR does not change (Goldstein et al., 1972; McFarland et al., 1977). Kodera et al., (1978) reported that the peak-to-peak amplitude between wave V and the Na wave remained constant as stimulus rates were increased from 10 to 31/s. However, the Na-Pa and Pa-Nb amplitude decreased as the stimulus rate was increased over this range. Galambos et al. (1981) reported an enhancement of the MLR amplitude at stimulus rates of 35-45/s. Figure 6 illustrates the MLR amplitude-rate and phase-rate functions. There is an amplitude enhanced plateau at stimulus rates of 30-50/s. The response phase increases linearly as rate increases above 30/s.

-insert Figure 6 about here-

Regan (1972) introduced the "apparent latency" measurement for steady state responses recorded using Fourier analysis. The apparent latency is the latency of the dominant component making up the response. It can be calculated if the steady state response is recorded over a range of stimulus rates. The apparent latency is the slope of the phase/rate function divided by 360°. The apparent latency of the data presented in Figure 6 is 36 ms. This value was calculated using the response phase between 30-55/s.

The apparent latency of the steady state MLR may also be estimated from the responses recorded using signal averaging. Diamond (1977) proposed that as the interstimulus interval (ISI) decreases, the time between equivalent peaks should also decrease. Therefore, drawing a line through the related peaks at different ISIs to the abscissa gives a latency value for the steady state response. Stapells et al., (1984) applied this technique to the steady state MLR and found that both calculations provide approximately equivalent results

(ii) Stimulus intensity

The amplitude of the transient MLR increases and the latency decreases as the intensity of the stimulus increases (Madell and Goldstein, 1972);

Thornton et al., 1977; Picton et al., 1977). However, Ozdamar and Kraus (1983) report that the major peaks of the transient MLR, elicited with a click stimulus, have the same latency regardless of the stimulus intensity and that the amplitude of Pa reaches a maximum at 50-60 dB HL. The response amplitude reaches a plateau at approximately 60 dB SL and therefore testing delivering greater stimulus intensities may not provide more useful information.

The amplitude of the steady state MLR increases as the intensity of the stimulus increases (Galambos et al., 1981; Stapells et al., 1984). Figure 7 illustrates this relationship for 500 Hz and 2000 Hz tones.

-insert Figure 7 about here-

The latency of the steady state responses can be calculated from the intensity data obtained from both signal averaging and Fourier analysis (Galambos et al., 1981; Stapells et al., 1984). For the 500 Hz tones the latency to the first positive peak decreases and the phase of the Fourier analysis data becomes shorter with increasing stimulus intensities. For high-frequency tones (2000 Hz and 4000 Hz) there is much less change in phase with intensity.

(iii) Tone frequency

Thornton et al., (1977) reported that the transient MLR elicited using tonebursts of varying frequencies (250, 1000, 4000 Hz) had increased peak-latencies and larger amplitudes for the lower frequencies.

The larger amplitude for the lower frequency tonebursts is more evident for the earlier peaks of the transient MLR. McFarland et al., (1977) found similar results using tone pips. When clicks are the eliciting stimulus the transient MLR have shorter latencies and larger amplitudes (Zerlin et al., 1973; Maurizi et al., 1984). The latency change with frequency may represent travel time along the basilar membrane. The larger amplitude to low frequency tones probably represents more neuronal activity because both high-frequency and low-frequency parts of the basilar membrane may be activated.

The steady state MLR have a similar stimulus-frequency/response-amplitude relationship (Galambos et al., 1981; Stapells et al., 1984). As the frequency of the tone is increased the amplitude and latency of the steady state responses decreases. Furthermore, the apparent latency, calculated from data obtained using low and high frequency different tones is longer for low frequency tones (Stapells et al., 1984). Therefore, possibly representing travel time along the basilar membrane from the basal high-frequency area to the apical low-frequency area.

(iv) Tone duration

Early reports in the literature were vague as to the exact effects tone duration had on the transient MLR. The latency of the transient MLR is unaffected by the tone stimulus duration (Lane et al., 1971; Skinner and Antinoro, 1971). Lane et al. (1971) used 1000 Hz tones with plateau durations of 20 and 40 ms. Skinner and Antinoro (1971) used 1000 Hz tones with durations varying from 1 to 50 ms. The amplitude may be affected by the duration of the stimulus. Lane et al., (1971) reported that the Nb-Pb amplitude is larger with longer stimulus duration. Skinner and Antinoro (1971) reported no effects of duration on the response amplitude for any of the transient MLR peaks. Vivion et al., (1980) reported that increasing the stimulus duration from 10 to 30 ms resulted in an increase of 1-3ms in the latency of all the transient MLR components and caused a reduction in the response amplitude.

Kileny (1983) demonstrated that as the tone plateau duration was increased from 4 to 8 ms, the latency of the steady state MLR remained unchanged but the response amplitude increased. The duration may only be increased so far or you can exceed the 50% duty cycle.

(v) Rise-fall time

Stimulus rise-fall times is important in electric response audiometry. Although shorter rise-fall times cause a greater spread of acoustic energy in the stimulus they also result in greater synchronization of the response. Early studies of the effect of changes in the stimulus rise-fall times (10 us-25 ms) on the transient MLR demonstrated no effect on the latency of the responses and the amplitude increased with decreasing rise-time (Lane et al., 1971; Skinner and Antinoro, 1971). Beiter and Hogan (1973) proposed using 5 ms rise-fall times rather than a 10 ms rise-fall time. Kodera et al., (1979) reported that as the stimulus rise-fall time increases, the Na and Pa latencies increase and the amplitudes decrease. Later studies reported that increasing the stimulus rise-fall times caused an increase in the latency and an attehuation of the amplitude of the transient MLR (Kodera et al., 1979; Vivion et al., 1980). Beattie et al., (1984) examined the effect of varying the rise-fall time on the transient MLR recorded within the first 25 ms after the stimulus. They found that increasing the rise-fall time from 1 to 4 ms caused an increase in the latency and no change in the detectability of the responses. Kileny (1983) reported that the latency of the steady state MLR increases as the rise-fall time of the stimulus is increased from 4-8 ms. Therefore, a satisfactory combination of detectability and frequency specificity may be obtained using a 5 ms rise-fall time.

(vi) Binaural Interaction

The transient MLR are larger when recorded in response to binaural stimuli than in response to monaural stimuli. The difference between the binaural response and the sum of the monaural responses is a measure of the binaural interaction. Dobie and Berlin (1979) recorded the responses to monaural stimuli from both ears, recorded the response from binaural stimuli, summed the monaural responses and subtracted the summed response from the binaural response. The resultant of this subtraction is called the binaural interaction (BI) component (figure 8). The binaural response is smaller than summed response. The binaural interaction components of the transient MLR start at the latency of Pa and consists of two negative peaks (Dobie and Norton, 1980; Berlin et al., 1984; Woods and Clayworth, 1985; Picton et al., 1984).

-insert Figure 8 about here-

The steady state MLR recorded from binaural stimuli are larger than those recorded from monaural stimuli but smaller than the sum of the monaural responses. The binaural interaction component of the steady state MLR is periodic resembling two cycles of a sine wave. We have found these calculated responses have substantial intersubject variability. The BI component is smaller than the transient MLR BI and the latency of the waves is shorter.

SUBJECT PARAMETERS

(i) Maturation

Newborns have smaller transient MLR (Mendel et al., 1977; Mendelson and Salamy, 1981) and may have shorter peak latencies (Mendel et al., 1977). than adults. The later components Pb-Nc are not present and the early Pa component increases in amplitude in the first year of development. Shallop and Osterhammel (1983) found that the amplitude of the brainstem response and steady state MLR near threshold were equal in newborns. In contrast to the adult transient MLR, the ipsilateral recordings from newborns have more easily identifiable peaks than the contralateral peaks (Wolf and Goldstein, 1980). However this ipsilateral advantage has been contested by Mendel (1980). Therefore, transient MLR from newborns must be interpreted cautiously.

Kraus et al., (1985) performed an extensive study of the transient MLR in children between the ages of 6 days to 20 years. Components Na and Pa were visibly detected progressively easier with increasing age to 10 years. At 10 years of age the Na and Pa components were equivalent to the responses obtained from adults.

Suzuki et al., (1983) and Kileny (1983) report that the transient MLR in neonates and young children are particularly sensitive to filter settings. Suzuki et al. (1983) found that the main frequency component of the transient MLR was at 20 Hz for children and at 30-50 Hz for adults. The transient

MLRs of children recorded with a high pass filter setting of 30-40 Hz had attenuated Pa components. They also noted Pb was rarely observed in young children independent of filter settings. This observation was also reported by Okitzu (1984). When high-pass filter settings were below 20 Hz the responses were too variable. Digital filtering at 20 Hz "markedly reduces" the variablility. The use of high-pass analog filters set at 20 Hz using roll-off slopes of 24-48 Hz would therfore explain the variable reports on the transient MLR in the literature (Suzuki et al., 1983). Kileny (1983) reported that the distortion of the transient MLR when high-pass filter settings are changed from 5-30 Hz also occurs in neonates.

There are several reports in the literature suggesting that the transient MLR obtained from young adults are different from those obtained from elderly subjects (Pfefferbaum et al., 1979; Kelly-Ballweber and Dobie, 1984; Woods and Clayworth, 1985). The Pa component appears to be the only peak affected. It is larger in amplitude and longer in latency in elderly subjects. Woods and Clayworth (1985) proposed that age-related changes in Pa may be caused by neurochemical or structural alterations in the central nervous system. Aging causes a decrease in the production of GABA. Because the reticular thalamic nucleus has a high concentration of GABA projections and exerts an inhibitory influence on the thalamic relay nuclei therefore, decreased inhibitory input to the medial geniculate body may cause an enhanced amplitude of Pa.

Shallop and Osterhammel (1983) examined the 40 Hz steady state MLR from 36, non-medicated newborns using clicks and 500 Hz tonebursts using filter settings of 30-80 Hz (24 db/octave). They found reliable steady state MLR in newborns down to 20-30 dB (nHL). Davis et al., (1983) examined the steady state MLR from 19 sedated children recorded using filter settings of 30-80 Hz. The responses were rarely detectable at 30 db nHL. Suzuki et al., (1984) examined the effect of stimulus rate on the MLR recorded from 10 sleeping or sedated children. They found that the response amplitude decreased as stimulus rates were increased above 30/s. An amplitude enhancement for children was observed at presentation rates of 20/s. Fifer et al., (1984) reported similar results. Hence, if responses are recorded in children using presentation rates of 40/s and analog high-pass filters are set too low (0-20 Hz) or too high (greater than 20 Hz) these responses will be difficult to obtain. Klein (1984) compared the estimate of threshold using the steady state MLR to 500 Hz tonepips in 14 normal hearing adults and 40 normal infants (.5-4 months of age). The steady state MLR to 500 Hz tone pips were not significantly different between newborns and adults.

Stapells et al., (1985) examined the effects of stimulus rate and scalp distribution on the steady state responses from infants. They reported smaller amplitudes at all rates than responses to similar stimuli from adults. There was no amplitude enhanced response at 40/s as there is in responses from adults. Phase coherence was better at higher rates (54-59/s). Interestingly, the responses were recorded maximally at Oz which is in direct contrast to similar responses from adults.

(ii) Sleep

The transient MLRs have been studied extensively during sleep, but the literature is vague as to the exact effect of sleep upon these potentials. Mendel and Goldstein (1969b) reported that these potentials are "consistent" during sleep. In 1971, however, Mendel and Goldstein reported that the latencies of the transient MLR were slightly shorter during wakefulness than during sleep and remained constant across sleep stages. They reported that the amplitude was smaller during sleep and became smaller with deeper stages of sleep. Mendel and Kupperman (1974) reported no amplitude differences between responses obtained during REM (Rapid Eye Movement) and nonREM sleep. Pa and Nb were reported to have shorter latencies during REM sleep compared to responses obtained during nonREM sleep. Mendel (1974) compared the transient MLR obtained during light sleep (stage REM and 2) to responses obtained during deep sleep (stage 3 and 4). He reported little difference in response amplitude and latency between the two groups. Mendel et al., (1975) reported that in secobarbital induced sleep, thresholds for light sleep had a mean of 15 dB SL, for deep sleep had a mean of 21.5 dB SL and for wakefulness had a mean of 18.5 dB SL. They reported that during deep sleep thresholds were often indeterminate. The latency of Pa increased from wakefulness to light sleep and from light sleep to deep sleep. Brown and Shallop (1982) reported that during sleep Pb and Pc of the transient MLR are absent or very small. Osterhammel et al., (1985) found that the latency of the transient MLR, Nb component increased during sleep.

There is a conflict in the literature on the effect of sleep on the transient MLR recorded in young children. Engel (1971) reported that the transient MLR recorded from 24 sleeping neonates were absent or unstable. Mendel et al., (1977) examined the responses in 18 children who were less than 1 year old. The responses were reportedly easily elicited and similar to sleeping adults transient MLR. The latency was reported to be not affected by age and the amplitude of one component (Pa) was affected by age. Conflicting reports have proposed that the transient MLR are easily elicited in sleeping neonates and babies less than 1 year of age (McRandle et al., 1974; Mendel et al., 1977; Frye-Osier et al., 1977). However, Okitsu (1984) reported that the transient MLR recorded from young children during sleep were variable and not reproducible. The Na peak was less affected by sleep than the Pa peak. Therefore, in adults, the transient MLR may be recorded during sleep although they may be smaller in amplitude. Children, however, are difficult to obtain reliable responses from. An absence of a response may represent a hearing deficit or a maturation affect.

Galambos (1981) was the first to report on the effect of sleep on the steady state MLR. He found that the responses during sleep were half the size of the responses monitored during wakefulness. Brown and Shallop (1982) reported that the steady state MLR during sleep were one-third of the awake amplitude. They found the amplitude steadily decreased through stage 1 reached a minimum in stage 2 with no further decrements in stages 3 and 4. Their estimated thresholds were within 20-25 dB of the behavioural thresholds during sleep and within 10-15 dB during wakefulness. Klein (1983) reported that a decrease in the response amplitude and an increase of 5-20 dB in response threshold could occur during sleep. Shallop and Osterhammel (1983) reported the steady state MLR are smaller during sleep. Linden et al., (1985) reported that when measuring the responses at different rates, the maximum responses were obtained at stimulus presentation rates of 30-50/s during both wakefulness and sleep. They found the amplitude of the reponse was smaller during sleep than wakefulness but that the phase of the response was constant. Estimated thresholds on the basis of amplitude, phase and a standardized combination of amplitude and phase were not different between sleep and wakefulness (Figure 9). Jerger et al., (1985) examined the effects of sedated and natural sleep on the steady state MLR measured using a Fast Fourier Transform to measure the response. They proposed the use of phase incoherence to measure whether a response was present or not. This measurement did not differ between sleep and wakefulness. Szyfter et al., (1984) reported that the threshold of the steady state responses increased by 15 dB during sleep when measured using signal averaging. Makeig (1985) reported that the response amplitude decreased during sleep but that the response phase appeared to be unaffected. Interestingly, the steady state responses during sleep have been measured using magnetoencephalography (Romani et al., 1982). They reported that response amplitude decreased and response phase remained constant during sleep.

-insert Figure 9 about here-

(iii) Attention

The effect of attention on the transient MLR is unclear. Picton and Hillyard (1974) found that transient MLR recorded when subjects attended to incoming stimuli did not differ significantly from the responses obtained when subjects ignored the stimuli. McCallum et al., (1983) examined the transient MLR recorded in a target localization task and performed a principal component analysis (PCA) of the data. Examining the difference waveforms revealed that during target localization, attentional processing occurs as early as 15 ms. At 26 ms they found a component observable without subtraction techniques that differentiated between attended targets and irrevelant stimuli during a localization task. Kadobayashi et al., (1982) recorded transient MLR while subjects were viewing numbers presented to a screen, adding such numbers or multiplying them. They found the responses amplitude was larger during the more difficult task. Hillyard et al. (1985) recently reported an amplitude enhancement of the Na-Pa peak-to-peak amplitude to attended tones recorded at anterior and central scalp sites.

The steady state MLR examined in a monaural stimuli attention task and in a dichotic listening task recorded using both signal averaging and Fourier analysis were not affected by attention (Linden et al., 1985). Figure 10 illustrates this finding.

-insert Figure 10 about here-

The late responses (ERP) recorded in this dichotic listening task have an enhanced amplitude to attended targets which were slight increases in the frequency of the tone. High-pass filtering the late event related potentials at 10 Hz isolates the steady state response embedded in the late event related potentials. This embedded response has been termed the complex event related potential (CERP). The CERP is not affected by directed attention (Linden et al., 1985).

(iv) Adaptation and Habituation

Mendel and Goldstein (1969a) reported that the transient MLR latency and amplitude did not change over a 24 hr waking testing period. Goldstein et al., (1972), however, reported that the transient MLR decreased in size over the first few seconds of stimulation. Amplitude reduction was found to be complete within 1024 stimuli. Vivion et al., (1977) reported that there were no changes of the peak-to-peak amplitude or latency as stimulation progressed. Ozdamar and Kraus (1983) report that the transient MLR change over time. The Pb and Nb components sometimes disappeared. This may be explained by the fact that some of their subjects were sleeping during the recording.

Makeig (1985) reported that the steady state MLR do not habituate. Over a period of 30 minutes he found the mean response amplitude did not change. Interestingly, he reported that the response amplitude continually changes in amplitude and phase changing with periods of 20 to 120 seconds ("minute rhythms"). Linden et al., (1985) found that the steady state responses were stable during wakefulness. Responses obtained before bedtime were not significantly different from those compared to responses obtained immediately after the subjects were woken up after a night of stimuli. This supports Makeig's (1985) proposal that steady state responses do not habituate.

(v) Pharmacology

Secobarbital has been reported to have little effect upon the transient MLR (Mendel, 1974; Mendel et al., 1975). Ozdamar and Kraus (1983) reported that transient MLR are not affected by mild sedation (chloral hydrate and diazepam). However, some of the subjects that participated in the Ozdamar and Kraus study were sleeping while others were resting quietly. Therfore, because sleep affects the transient MLR the exact effect remains uncertain.

Bickford et al. (1964) reported that the transient MLR were myogenic. Harker et al., (1977) examined the transient MLR to 1000 Hz tone pips while a subject was resting, lightly sedated with diazepam and during complete succinylcholine induced muscle paralysis. They reported that the transient MLR appeared unchanged during the paralyzed state. Kileny (1983) recorded the transient MLR to 60 dB HL clicks from 12 patients during pancuronium (nondepolarized) induced muscle relaxation and fentanyl (narcotic analgesic) induced anesthesia. Response latencies were unchanged and peak detectability sometimes improved. Celesia and Puletti (1971) recorded the transient MLR from the transverse temporal gyri. They reported that with anesthesia (halothane and nitrous oxide) the latencies of the transient MLR increased and the response amplitude decreased. Goff et al., (1977) recorded the transient MLR to 60-70 dB SL clicks during sodium thiopental induced anesthesia. They reported that the components were suppressed by anesthesia. Kileny et al., (1984) suggested that the Goff et al., (1977) observations were different from their findings because of differences between levels of barbiturate dosage or recording parameters. Lee et al., (1984) recorded the transient MLR (subdurally) from the posterior banks of the sylvian fissure. They found that during barbiturate anesthesia the response amplitude decreased, the response latency shifted but the general morphology was consistent. Prosser and Arslan (1985) recorded the transient MLR from 9 children (1-4yrs) while under general anesthesia (fluothane). They reported component morphological instability and abnormal latency changes.

Davis et al., (1983) reported that the steady state MLR recorded from sedated children (secobarbital or chloral hydrate) is severely diminished. Suzuki and Kobayashi (1984) found that children, some of whom were sedated with triclofos, had longer peak latencies.

In summary, the transient MLR are not effected by muscle relaxants and decreased by sedative medication particularly if sleep is induced. The responses are severely reduced by anesthetic medication. The amount of sedative and anesthetic medication effects the response. Therefore you must be careful when you record these responses and take into consideration the pharmacological effects.

Clinical Uses

(i) Audiological

Goldstein and Rodman (1967) reported that in 20 normal hearing subjects, transient MLR to clicks were detectable in half their subjects as low as -5 dB SL. However caution was advocated because some subjects thresholds were not duplicated to within 5 dB of thresholds determined behaviorally. Several reports indicate that the transient MLR usually give an accurate estimation of threshold to within 10 dB of threshold (Picton et al., 1977; Mendel et al., 1984).

One of the objectives of electric response audiometry is to obtain frequency specific information. The ABR are reported to be only valid in testing the mid to high frequency ranges (Davis, 1976). The MLR have been suggested as a possible tool to analyze the low frequency range (Picton et al., 1977). Furthermore, there are known cases wherein audiological normal patients had no ABR (Worthington and Peters, 1980). The transient MLR can be elicited using tonebursts (Thornton et al., 1977) and tone pips (McFarland et al., (1977). Musiek and Geurkink (1981) compared thresholds elicited with ABR to those elicited with MLR. They reported that for eliciting near threshold responses, the MLR may be better than the ABR. However, Stapells (1984) demonstrated that the transient MLR are too variable and thresholds are too difficult to determine for threshold estimation. The transient MLR were only able to estimate threshold within 21 dB compared to 4-6 dB for the tone-ABR technique.

Galambos et al., (1981) first reported, that, because of the enhanced amplitude of the steady state MLR threshold estimation with these potentials may be superior. They reported responses to clicks and tones provided an estimate of threshold close to behavioral thresholds using these respones. This work stimulated research to examine this phenomena. Martin and Hayes (1982) performed an FFT on the steady state MLR to 500 Hz tone-pips and reported that the responses were able to estimate threshold to within 5 dB of the threshold determined behaviorally. Stapells et al., (1984) reported that the steady state MLR may be elicited with stimuli of magnitude similar to those stimuli required to obtain a behavioral response. In a comparison of several evoked potential techniques used to estimate threshold, Stapells (1984) reported that when using signal averaging, the steady state MLR is a better tool than the transient MLR but is not as good as the ABR technique to elicit threshold.

Stapells et al., (1984) demonstrated that the steady state MLR could be recorded with Fourier analysis and signal averaging and that these responses could be recorded close to behavioral threshold. This allowed threshold estimation techniques based on the amplitude and the phase of the response (Martin and Hayes, 1982; Stapells et al., 1984; Makeig and Galambos, 1983). Several statistical techniques have been developed such as linear regressions (Linden et al., 1985; Rodriguez et al., 1985), phase coherence (Makeig, 1985) and the Hotelling T^2 test (Rodriguez et al. 1985). Stapells et al., (1985) found that response threshold estimations for the steady state MLR to 500 Hz and 1000 Hz tones using phase coherence were within 6 dB of thresholds determined behaviorally. Kileny and Shea (1985) compared the sequential ABR and transient MLR to the steady state MLR as audiological tools. The difference between the behavioral threshold and threshold estimated with the steady state MLR were less than the differences between the behavioral threshold and estimated threshold from the transient MLR. The amplitude of the transient and steady state MLR at threshold were "virtually identical", yet the scorers found the steady state MLR easier to score.

The transient MLR have been examined in patients with hearing impairment. McFarland et al., (1977) reported that subjects with conductive, sensorineural and mixed hearing losses had transient MLR "essentially indistinguishiable" from normal subjects. Vivion et al., (1979) reported limited success when using the transient MLR to identify thresholds in a hearing impaired subject. Mendel (1980) published that the transient MLR are accurate in determining threshold compared to within 10-20 dB of behavioral data.

Lynn et al., (1984) reported that adult hearing impaired subjects had steady state MLR obtainable at levels close to behavioral threshold but may understimate thresholds for patients with low-frequency hearing loss. Dauman et al., (1984) found that steady state MLR are a good indicator of threshold in patients with high-frequency hearing loss. However, in one-third of their patients there were 20-30 dB discrepancies between thresholds determined behaviorally and electrophysiologically. Sturzebecher et al., (1985) obtained MLR at four different presentation rates in patients with sensorineural hearing loss. Response amplitude was greater at the 40/s presentation rate than at the 10/s, 20/s or 30/s rates. Rodriguez et al., (1985) reported that the steady state MLR are a good tool to estimate threshold in hearing impaired patients if there is sufficient time for recording and there is proper evaluation of the signal-to-noise ratio..

Threshold estimation using the transient MLR may have better results if the test is performed while the patient is sleeping. However, the tester must remember that the responses are different during sleep. The steady state MLR is a superior technique than the transient MLR to estimate threshold. Caution must be used when measuring these responses from children.

(ii) Neurological

Brainstem: The transient MLR have been suggested as a tool in the analysis of acoustic neuromas (Harker and Backoff, 1981) and in the diagnosis of multiple sclerosis (MS) and in the differentiation between dormant and active states of MS (Robinson and Rudge, 1977, 1978). The steady state MLR have been shown to be sensitive to lesions of the midbrain (Spydell et al., 1985). Caution must be used when measuring these responses in children. Age related nomograms must be constructed if these responses are to be used in children in an audiological or neurological setting (Kraus et al., 1985).

Cortical: Kileny et al., (1985) reported that the transient MLR may be a helpful tool to monitor recovery to injury to the temporal lobes. The transient MLR have been proposed as a valuable intraoperative monitoring tool. Kileny et al., (1983) recorded the transient MLR during open heart surgery with hypothermia. The responses were sensitive to changes in temperature and at a constant temperature were related to changes in blood pressure. Lee et al., (1984) proposed using the transient MLR to localize the primary auditory cortex.

Musiek and Donnelly (1983) found that children with cortical deafness had normal ABR and abnormal transient MLR and therefore suggested the MLR as a tool to measure central auditory dysfunction. Mason and Mellor (1984) compared the transient MLR in children with language or motor speech disorders and to responses obtained from normal children. A significantly larger amplitude of the early part of the waveform was recorded temporally and at the mastoids in the motor speech disordered children. Their working hypothesis was that the myogenic component of the MLR were specifically affected in the motor speech disordered children. However, Kraus et al., (1985) reported that there was no relationship between abnormal MLR and communicative disorders.

Conclusions

Audiometrically, you can expect to assess threshold to within 5-10 dB using the steady state MLR provided the subject is awake. However, this technique should not be used in children for the response characteristics are not yet known. The transient MLR may be too noisy to estimate threshold. It may be better to estimate the responses while the patients are sleeping. Neurologically, there is no present use because we do not know the source of these potentials. They may become helpful in the future in the assessing of central auditory dysfunction.

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FIGURE LEGENDS

Figure 1: Transient and steady state Middle Latency Responses (MLR) recorded from a single subject. The stimuli used to elicit the responses were 70 dB nHL, 500 Hz tones (4 ms rise-fall, 2 ms plateau duration) presented to the left ear (filled line) and right ear (dotted line). The tracings on the left were obtained using a presentation rate of 10/s. Wave V of the auditory brainstem response and the Na, Pa, and Nb components of the MLR are identified. The tracings on the right were obtained using a presentation rate of 40/s. The responses were recorded between the vertex and a balanced non-cephalic sterno-vertebral reference (Stephenson and Gibbs, 1951). Negativity at the vertex is represented as an upward deflection. Each waveform represents 4000 averaged responses. The steady state MLR is larger and resembles a 40 Hz sine wave.

Figure 2: Fourier analysis. This diagram shows the steps involved in evaluating the steady state evoked potentials using a Fourier analyzer (Regan, 1977). Sine and cosine reference signals are generated and the stimulus is time-locked to the frequency of these reference signals. The EEG recorded from the scalp contains (top line) a RESPONSE to the stimulus which has the same frequency as the rate of stimulation and a constant phase relationship to the stimulus. This is usually intermixed with EEG-NOISE (bottom line). When the recorded activity is multiplied by the reference sine and cosine signals, the activity in the EEG at the same frequency as the rate of stimulation generates a DC -offset signal whereas the EEG activity at other frequencies generates a mixture of high and low frequency AC components. Filtering out the high-frequency AC components makes the DC

offset easier to measure and the sine (X) and cosine (Y) offset values can be used to calculate the amplitude (A) and Phase (O) of the steady state evoked potential using the formula shown in the right-most section of the figure. The factor K is a calibration factor that depends upon the amplification of the EEG. From Picton et al., (1984).

Figure 3: The sweep technique. The computer sweeps or zooms a stimulus parameter--in this case, rate--and calculates the amplitude and phase of the EEG activity at the fundamental frequency (the repetition rate) as it sweeps the stimulus. Following this, the data is stored on disk to be averaged and plotted. The phase data are plotted such that values are reset to zero every 360° (eg. 540° is plotted as 180°). This technique has the computer carrying out most of the recording analysis functions, with little intervention required. From Stapells et al., (1984).

Figure 4: Scalp distribution of transient and steady state MLR. The waveforms are the grand means from 10 subjects, each representing 40,000 reponses (4000 per subject) to 70 dB nHL 500 Hz tones (4 ms rise-fall, 2 ms plateau duration) presented to the left ear. The responses were recorded using a non-cephalic chest reference (Stephenson and Gibbs, 1951). Negativity at the vertex was represented as an upward deflection. Electrodes were placed according to the International 10-20 system at Cz, C3, T3, C4, T4, M2 and M1. Negativity at the vertex is represented by an upward deflection. The tracings on the left represent the average responses when stimuli were presented at 10/s. The tracings on the right represent the average response when stimuli were presented at a rate of 40/s.

Figure 5: The postauricular muscle reflex. These recordings were taken between the vertex and the left mastoid area using a frequency bandpass of 25-3000Hz. Each tracing represents the average of 2000 individual responses with relative negativity at the vertex (or relative positivity at the mastoid) represented by an upward deflection. The stimulus was a 2 KHz 80 dB nHL tonepip with a total duration of 8 ms and rise and fall times of 4 ms. On the left is shown the habituation of the muscle reflex over four sequential averages when the stimulus was presented at a rate of 11/s. On the right are represented three simultaneous recordings taken using reference electrodes located at three different postitions on the mastoid process. The postauricular muscle reflex consisting of a mastoid-negative wave at 15 ms followed by a positive wave at 22 ms is very focal in distribution. From Picton and Fitzgerald (1983).

Figure 6: Grand mean (N=10) 500 Hz amplitude/rate and phase/rate functions. These functions were recorded using the sweep technique of Fourier analysis. A larger amplitude maxima is recorded at presentation rates of 30-50/s. The response phase increases as the stimulus presentation rate is increased. As the stimulus rate is increased above 30/s the phase/rate function becomes more linear.

Figure 7: Effects of the intensity sweeps on the amplitude and phase of the 40 Hz steady state potentials in response to 500 and 2000 Hz tonebursts. The results are grand means from 20 normal subjects (40 sweeps each). Mean psychoacoustic thresholds are indicated with arrows: for 500 Hz tones at 31 dB and for 2000 Hz at 24 dB peSPL. The amplitude increases and the phase decreases at higher intensities. The mean amplitude and phase slopes were 17

uV/dB and -1.3 /dB at 500 Hz, and 14uV/dB and -0.03/dB at 2000 Hz tones. From Rodriguez et al., (1985).

Figure 8: Binaural interaction of the transient and steady state MLR. The subject, stimulus and recording parameters are identical to those described in Figure 4. Tracings are from Cz. The top tracings are recorded from stimuli presented at 10/s. The lower tracings are recorded from stimuli presented at 40/s. The tracings on the left are recorded from stimuli presented binaurally. The middle tracings are the algebraically summed monaural responses (L+R). The tracings on the right illustrate the difference between the tracings in the middle subtracted from the tracings on the left. Four peaks (A,B,C,D) are identified in the difference waveform. The response waveform is smaller in the steady state MLR difference waveform.

Figure 9: The amplitude and phase intensity functions from a single subject during Wakefulness, Stage 2 and Slow Wave sleep. Each tracing is the vector-averaged sum of 20 sweeps of stimulus intensity. The amplitude data are plotted in the upper tracings and the phase data in the lower tracings. The subthreshold amplitude (background EEG noise), indicated by the line parallel to the abscissa in the upper tracings, is lower during sleep. The slope of the suprathreshold amplitude-intensity function is larger during wakefulness than during slepp. The phase of the response, random below threshold and decreasing linearly as the intensity is increased above threshold, does not change between wakefulness and sleep. The threshold, indicated by the vertical dashes, is -6 cB SL during Wakefulness, 3 dB SL during Stage 2, -9 dB SL during Slow Wave sleep. From Linden et al., (1985).

Figure 10: The grand mean data for the steady state evoked potentials (SSEP) measured using simultaneous signal averaging and Fourier analysis. The tracings represent the data from 7 subjects. The subjects attended (ATTEND) to targets in one ear and ignored (IGNORE) targets presented to the contralateral ear. The tracings on the left are the responses measured using signal averaging. There is no difference between the responses obtained while the subjects were attending or ignoring incoming stimuli. In the middle are the Fourier analysis data. The response phase for the SSEP is longer for the 41/s presentation rate and 500 Hz tone condition. There is no difference between the ATTEND and IGNORE codition in the responses measured with Fourier analysis. The late event related potentials (ERP) are on the right. They are larger for the ATTEND condtion than the IGNORE conditon therefore demonstrating selective attention. From Linden et al., (1985).

Figure 1

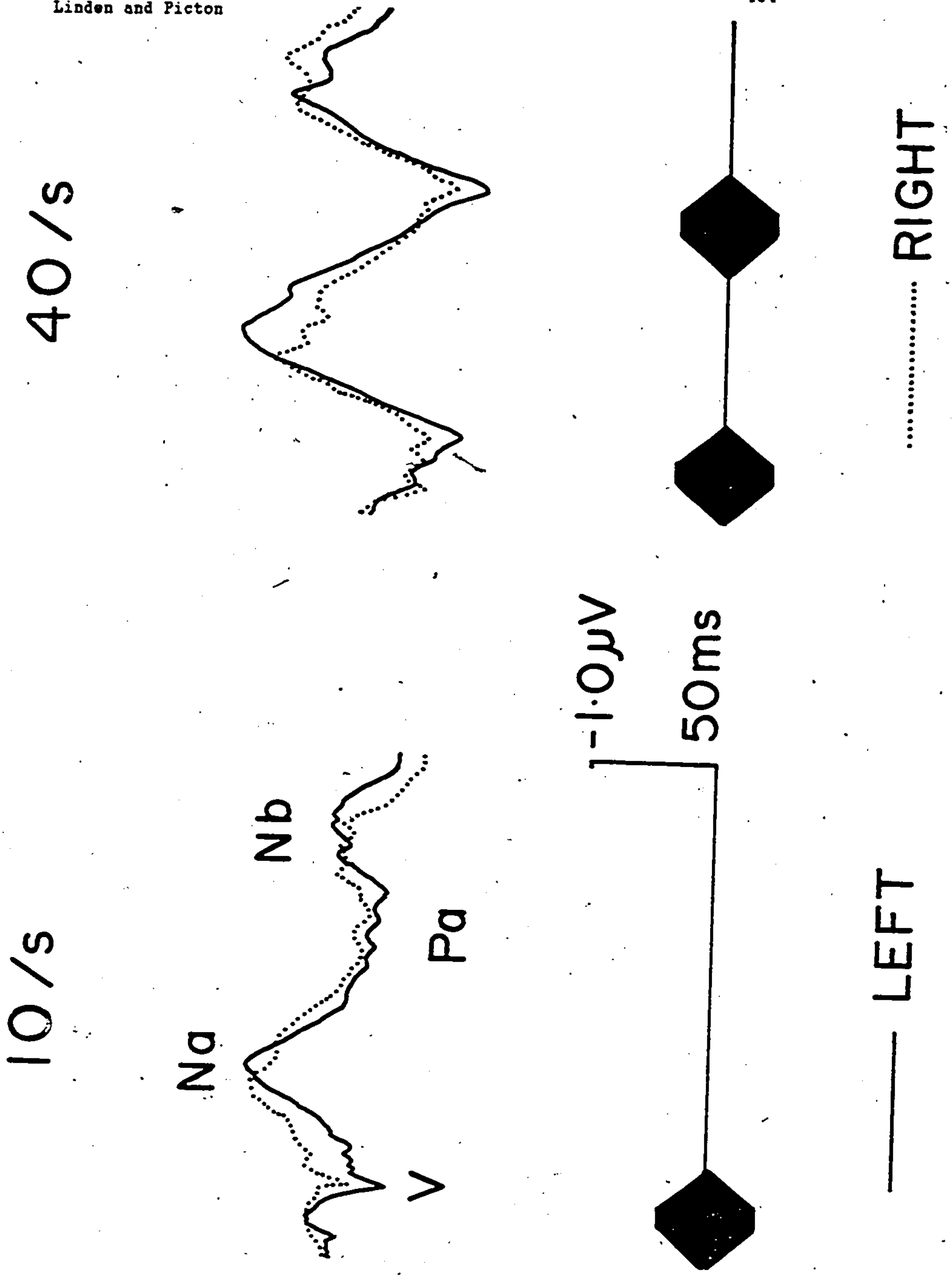


Figure 2

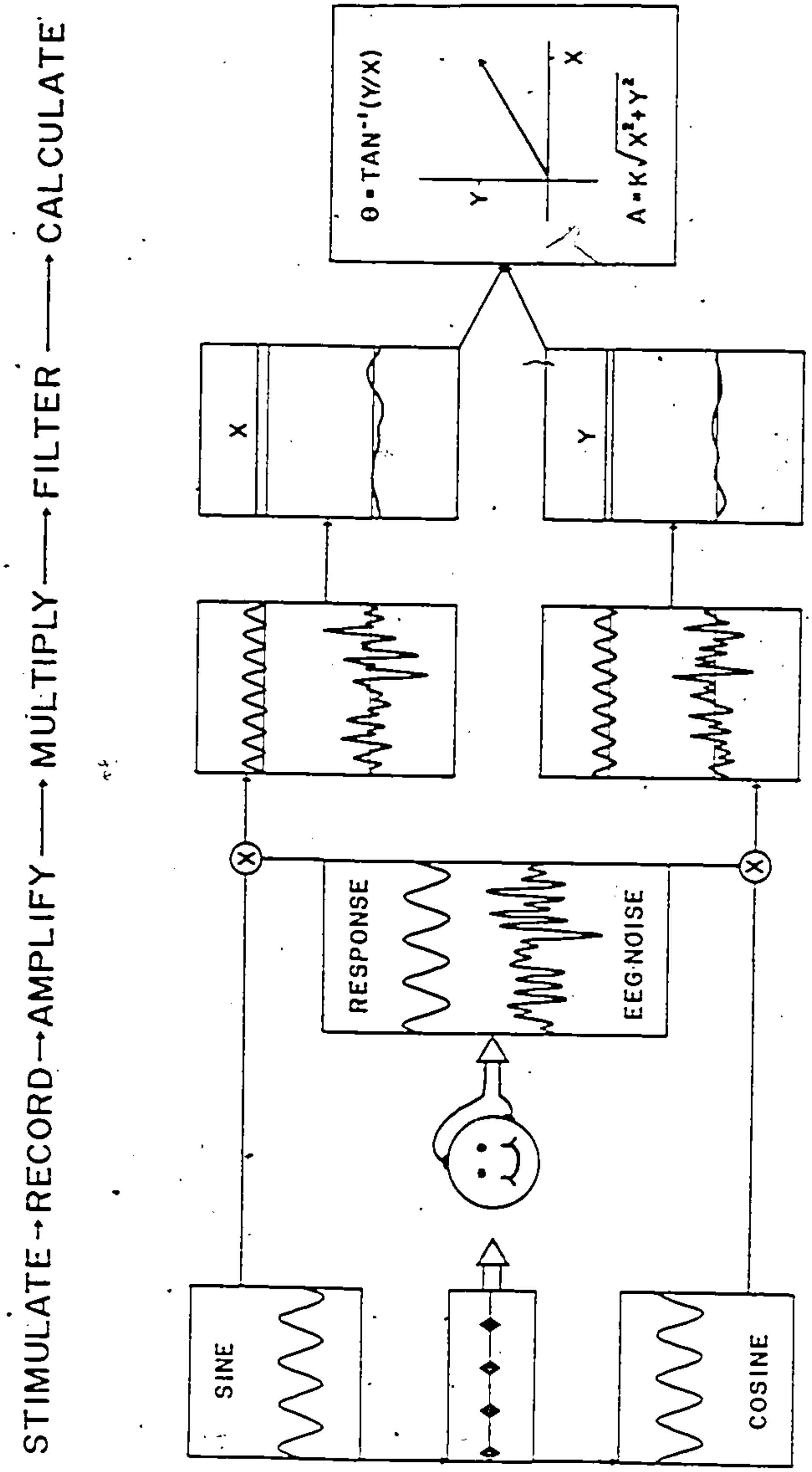

STIMULATE → RECORD → AMPLIFY → MULTIPLY → FILTER → CALCULATE
SINE
COSINE
RESPONSE
EEG NOISE
X
Y
θ = TAN⁻¹(Y/X)
A = K√(X² + Y²)
X
Y

Figure 3

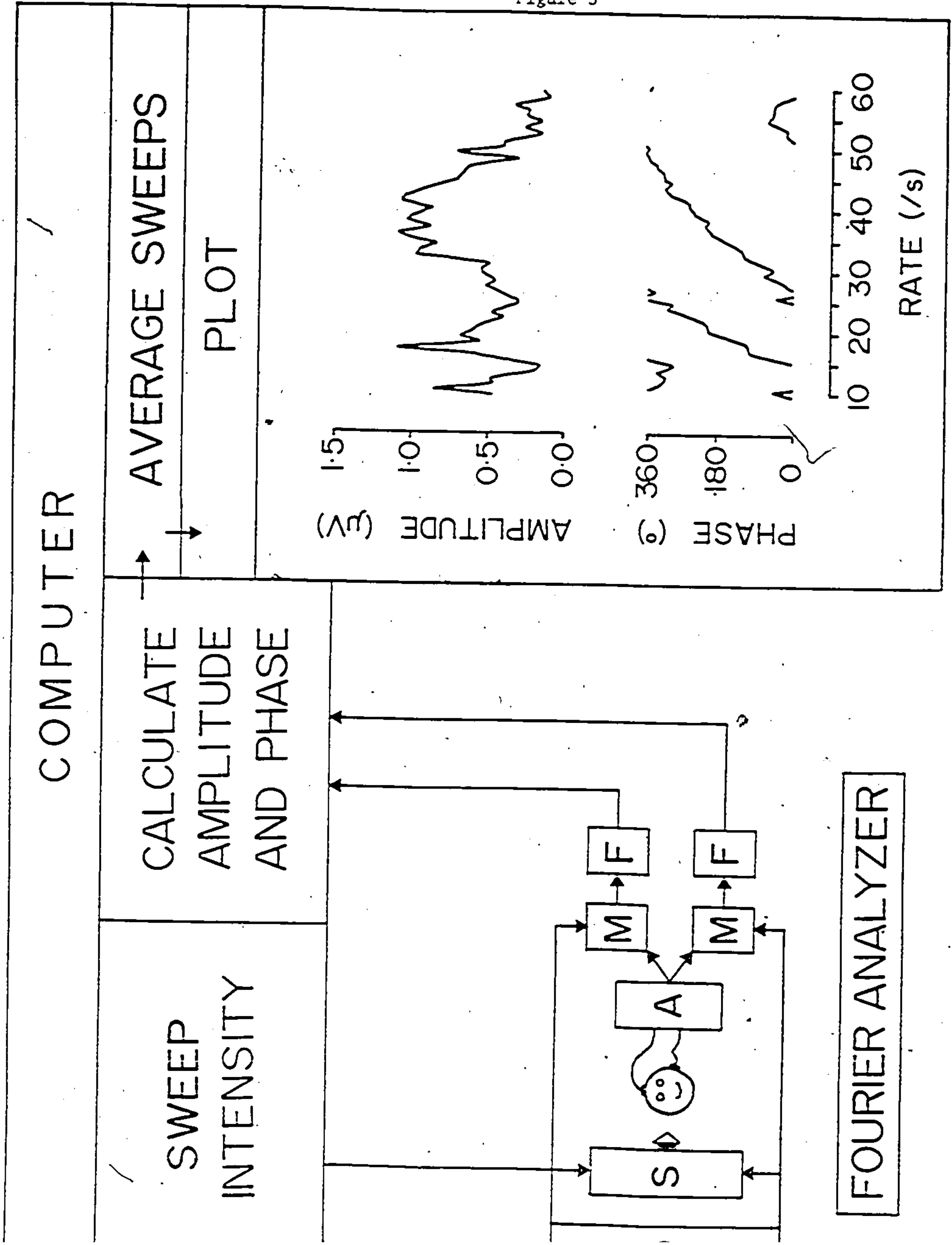

COMPUTER
SWEEP INTENSITY
CALCULATE AMPLITUDE AND PHASE
AVERAGE SWEEPS
PLOT
AMPLITUDE (µV)
1.5
1.0
0.5
0.0
PHASE (°)
360
180
0
10
20
30
40
50
60
RATE (/s)
S
A
M
M
F
F
FOURIER ANALYZER

Figure 4

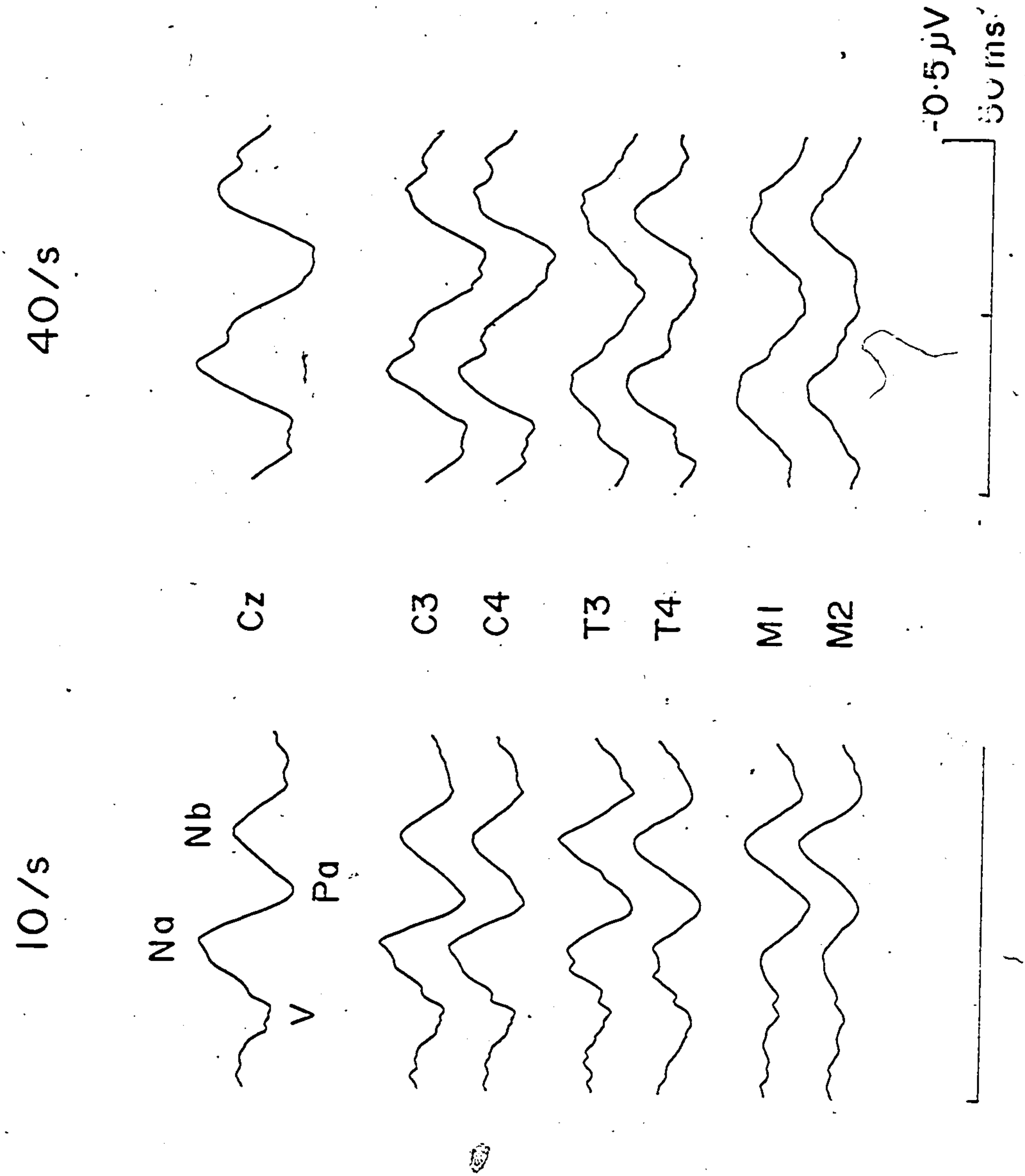


Figure 5

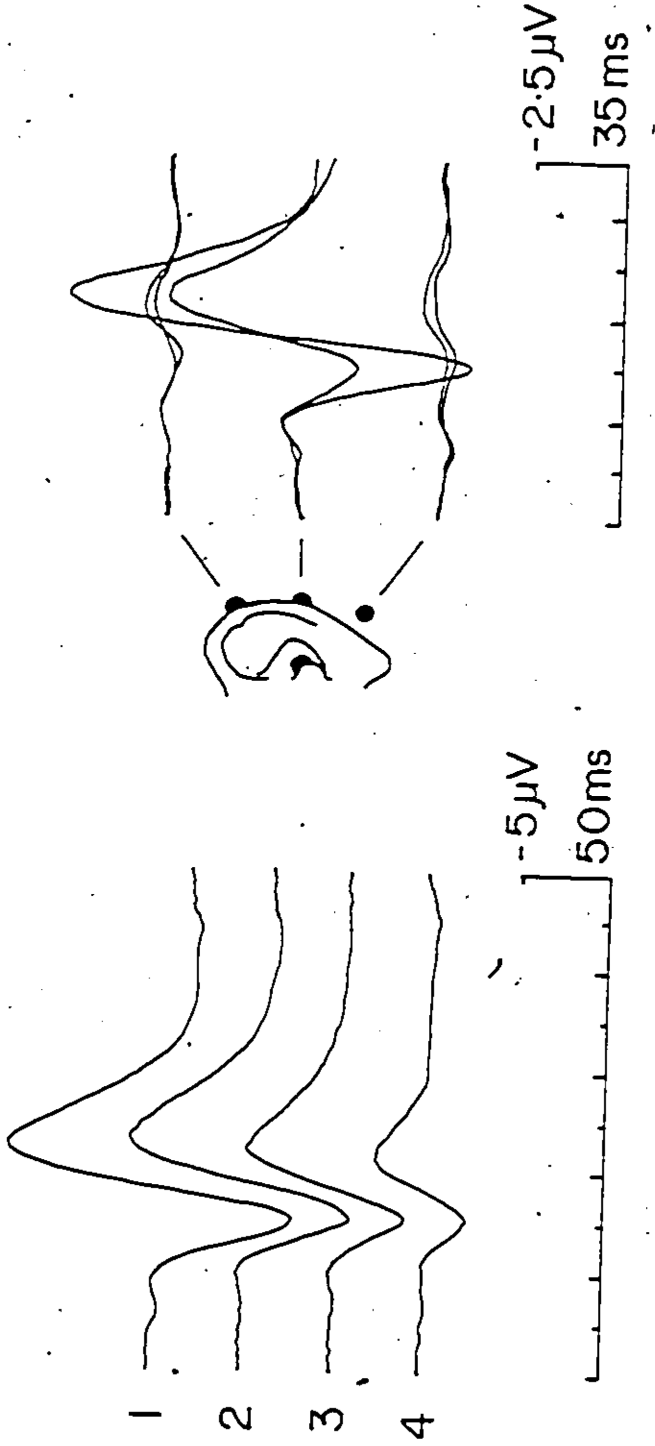


Figure 6

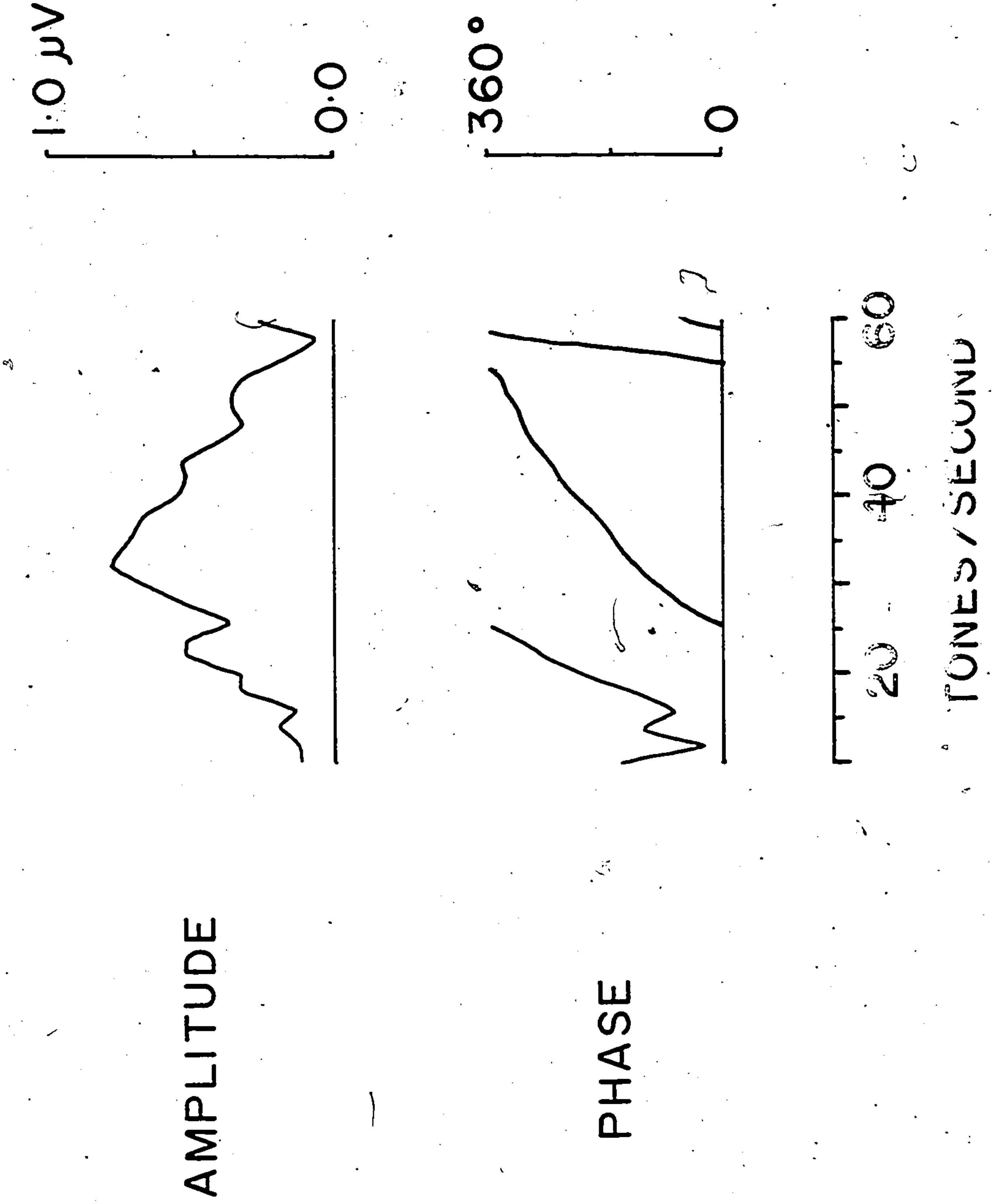


Figure 7

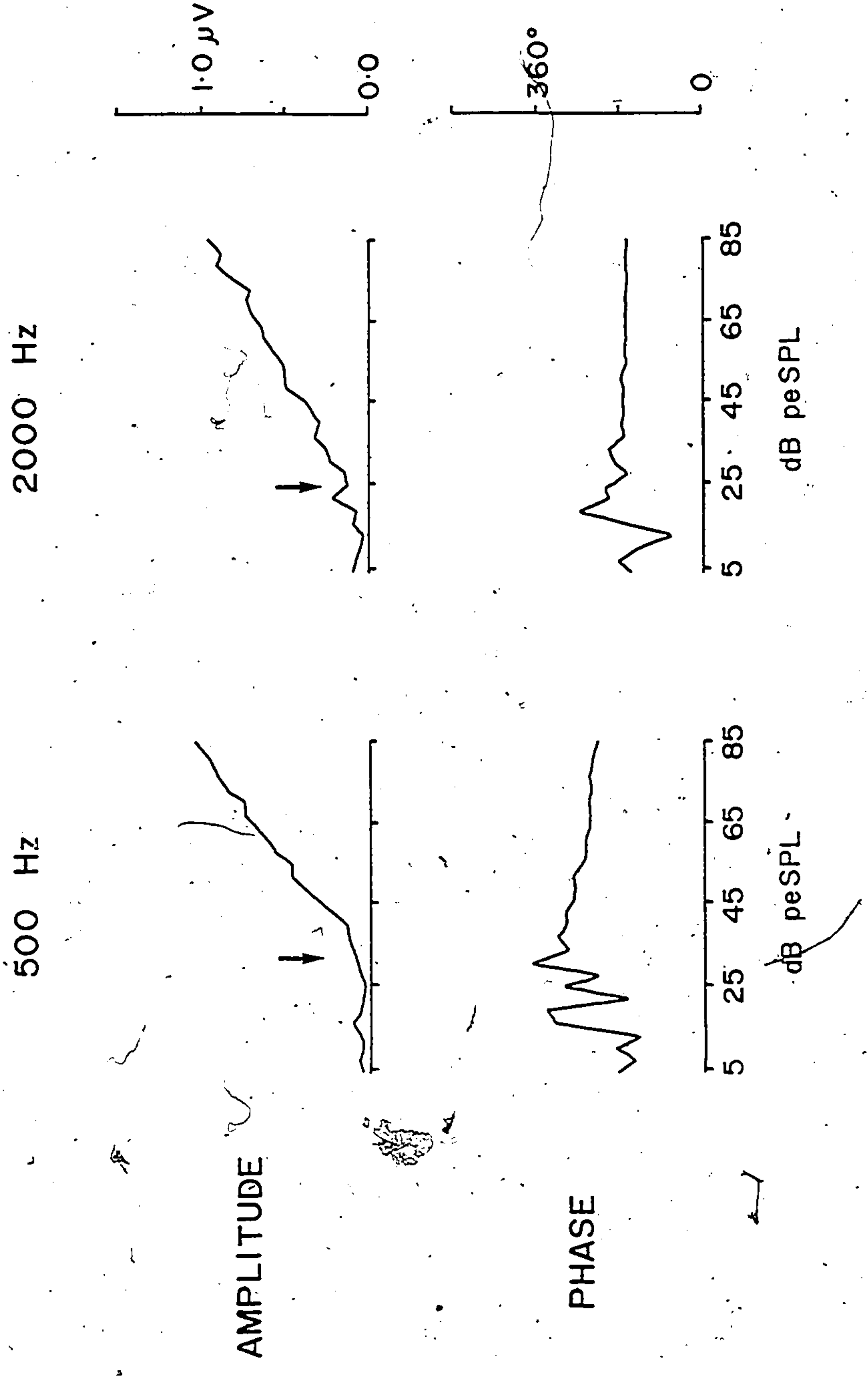

AMPLITUDE
PHASE
500 Hz
2000 Hz
1.0 μV
0.0
360°
0
5
25
45
65
85
dB peSPL

Figure 8

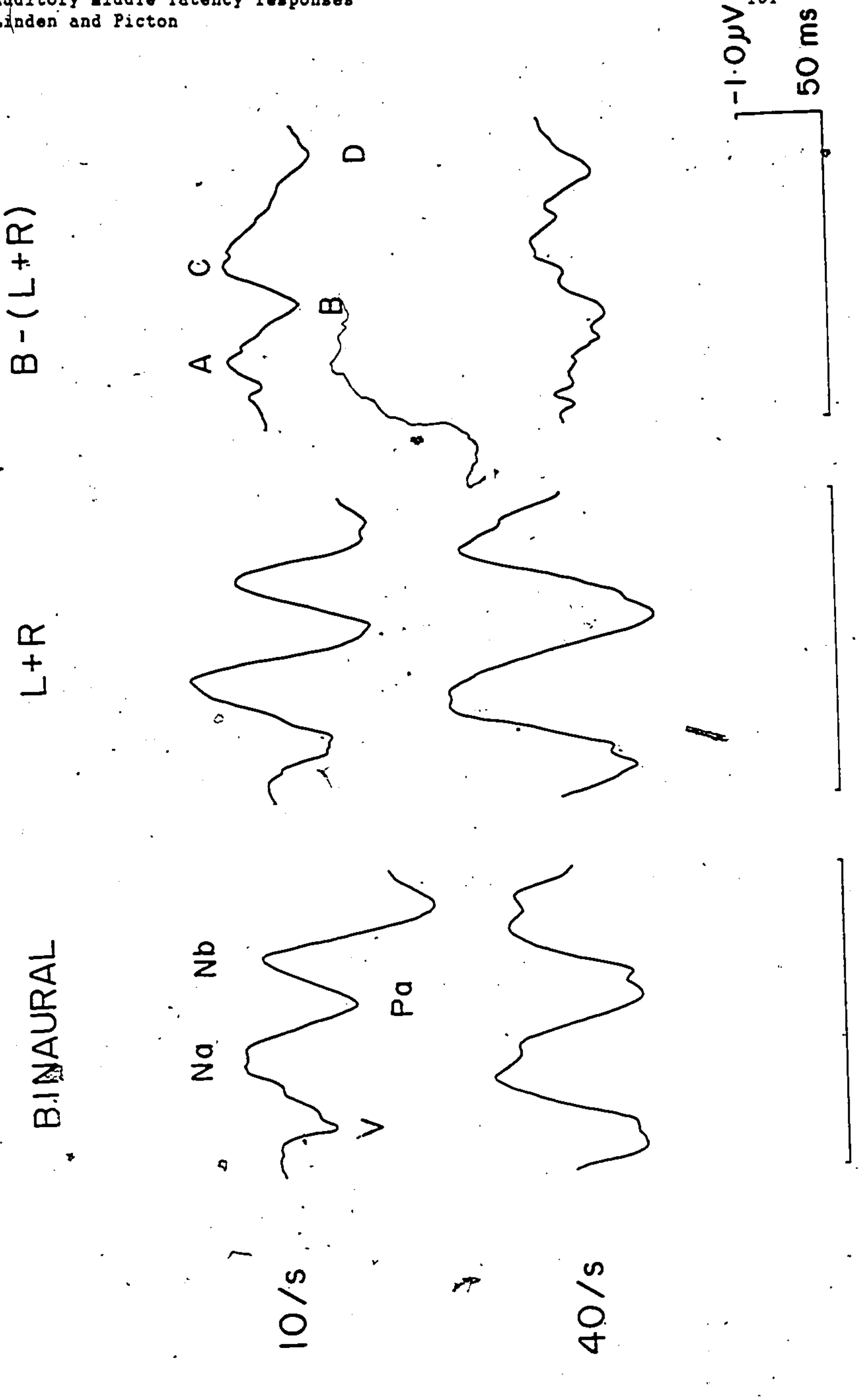


Figure 9

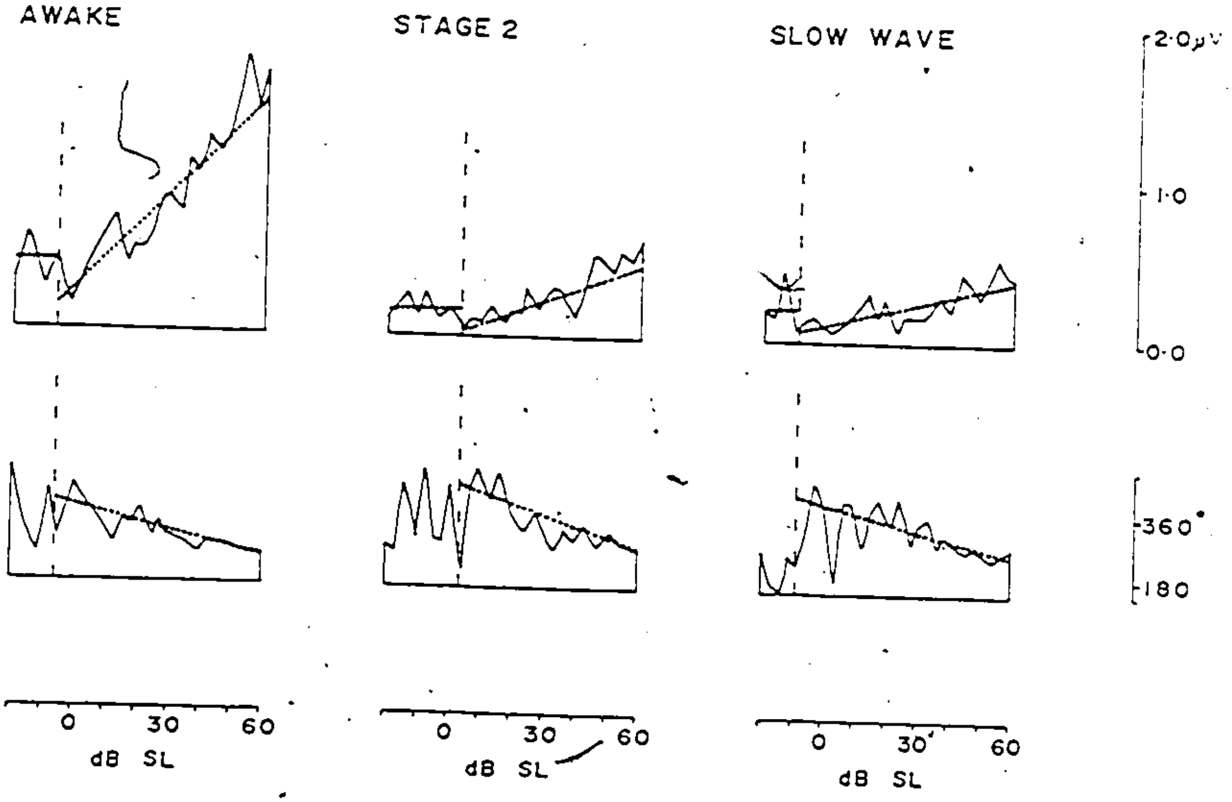
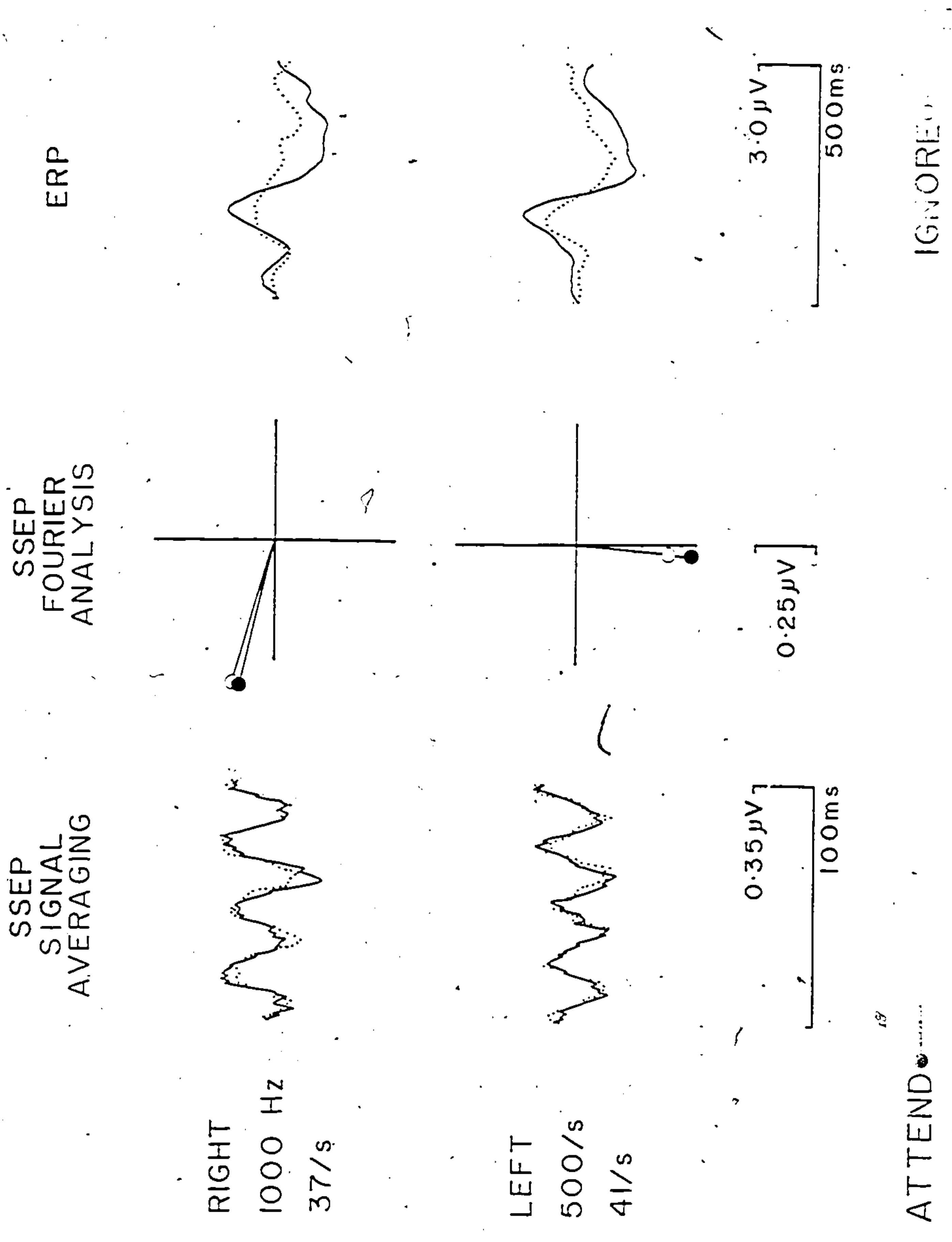

AWAKE
STAGE 2
SLOW WAVE
2.0μV
1.0
0.0
360°
180
0
30
60
dB SL
0
30
60
dB SL
0
30
60
dB SL

Figure 10


ERP
SSEP FOURIER ANALYSIS
SSEP SIGNAL AVERAGING
RIGHT
1000 Hz
37/s
LEFT
500/s
41/s
3·0μV
500ms
0·25μV
0·35μV
100ms
ATTEND
IGNORED

APPENDIX

THRESHOLDS FOR AUDITORY STEADY STATE EVOKED POTENTIALS DURING SLEEP

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Introduction

Human auditory evoked potentials can provide an objective evaluation of hearing in patients who are unable to respond to conventional testing techniques. Steady state evoked potentials are recorded when stimuli are presented at a sufficiently high rate such that the responses to the stimuli overlap [1,3]. One of the benefits of steady state evoked potentials is that the effects of stimulus intensity on the response amplitude and phase may be quickly and objectively assessed using Fourier analysis[4].

Because clinical patients are often tested while asleep, it is important to know the effect of sleep on the thresholds for these potentials. The main effect of sleep on the auditory steady state responses is a decrease in the response amplitude [1,2]. The phase of the response appears to be little affected by sleep [2]. This study compared thresholds for the auditory steady state response between wakefulness and the predominant stages of sleep: Stage 2 and Slow Wave.

Methods

Eight subjects (4 male, 4 female) were tested during a full night of natural sleep. The stimuli were 500 Hz tonebursts (4 ms rise-fall, 2 ms plateau duration) presented monaurally at 40/s at intensities that increased from -21 to 60 dB SL over 27 sec. The responses to the stimuli were recorded from vertex to mastoid and evaluated using a Fourier analyzer. The resultant amplitude and phase values were recorded during the sweeps of intensity and averaged over 20 sweeps.

Stage of sleep was monitored using a polygraphic recording of the Cz and Oz EEG, the EOG and submental EMG. Stage classification was done according to Rechtschaffen and Kales[3]. Stages were grouped into Awake, Stage 2 and Slow Wave sleep. The results were not analyzed if stage transitions were observed during the recording. REM stage recordings were not analyzed since many of the subjects did not have 20 sweeps during REM. Although more sweeps were often obtained the analysis was limited to 20 sweeps from each stage.

The data were modelled as having a random phase and a low amplitude (noise level) below threshold and a linear decrease in phase and a linear increase in amplitude with increasing intensity above threshold. This model was used to perform curve fitting and thresholds were postulated at all intensities from -15 dB SL to 51 dB SL. The intensity at which the data showed the least sum-of-squares deviation from the model was used to estimate the threshold.

The following measurements were compared statistically across stage: average amplitude below -9 dB SL; amplitude at 60 dB SL; slope of the amplitude-intensity regression above 21 dB SL; phase at 60 dB SL; slope of the phase-intensity regression above 21 dB SL. These measurements were analyzed using a repeated measures ANOVA. Post hoc analysis were based on the Tukey honestly significant differences (HSD). This analysis is different from an earlier interpretation of the data[2] in that only three stages were analyzed and a constant number of sweeps per subject and stage were analyzed.

Results

The figure represents the results from a typical subject and the table summarizes the results. The amplitude of the recording below threshold (reflecting EEG noise) was lower than above threshold. This subthreshold amplitude was significantly different across stage ($F=10.59$; $df=2,14$; $p<0.01$). Post hoc analysis revealed that the amplitude was lower during both sleep stages than during wakefulness. There was no significant difference between both sleep stages.

-insert Figure about here-

The amplitude of the response at 60 dB SL was significantly different across sleep stage ($F=18.4$; $df=2,14$; $p<0.001$). Post hoc analysis revealed the response amplitude at 60 dB SL was significantly larger during sleep with no significant difference between stage of sleep. Furthermore, the slope of the amplitude-intensity function (at intensities clearly above the steady state responses threshold) was statistically different across stage of sleep ($F=6.0$; $df=2,14$; $p<0.05$). Post hoc analysis revealed that the slope of the intensity-amplitude function was significantly lower during Slow Wave sleep than during wakefulness with no significant differences across sleep stages.

The phase of the response at 60 dB SL was not significantly different across sleep stage ($F=3.47$; $df=2,14$; $p>0.05$). The slope of the phase intensity function at values greater than 21 dB SL also did not differ significantly across stage of sleep ($F=0.19$).

The threshold, determined using an equally weighted combination of the amplitude and phase data, did not differ significantly during sleep (F=0.60).

-insert Table about here-

Discussion

The amplitude of auditory steady state responses decrease during sleep. However, response thresholds do not change from wakefulness to sleep. This may be explained by:

(1) the lower subthreshold amplitude during sleep (which makes the suprathreshold response easier to detect despite its lower amplitude).

(2) the consistency of the response phase between wakefulness and sleep.

The lack of any significant change in threshold means that the audiometric usefulness of the responses will be unaffected by whether the subject is asleep or awake. The standard deviation of the threshold estimates vary between 11 and 20 dB. This may be too broad a range for audiometry. The precision of the technique may, however, be improved by increasing the number of sweep recorded and/or by improving the model used to estimate thresholds.

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techniques, and scoring system for sleep stages of human subjects. (Institute of Health Publication no. 204) U. S. Government Printing Office, Washington D. C. (1968).

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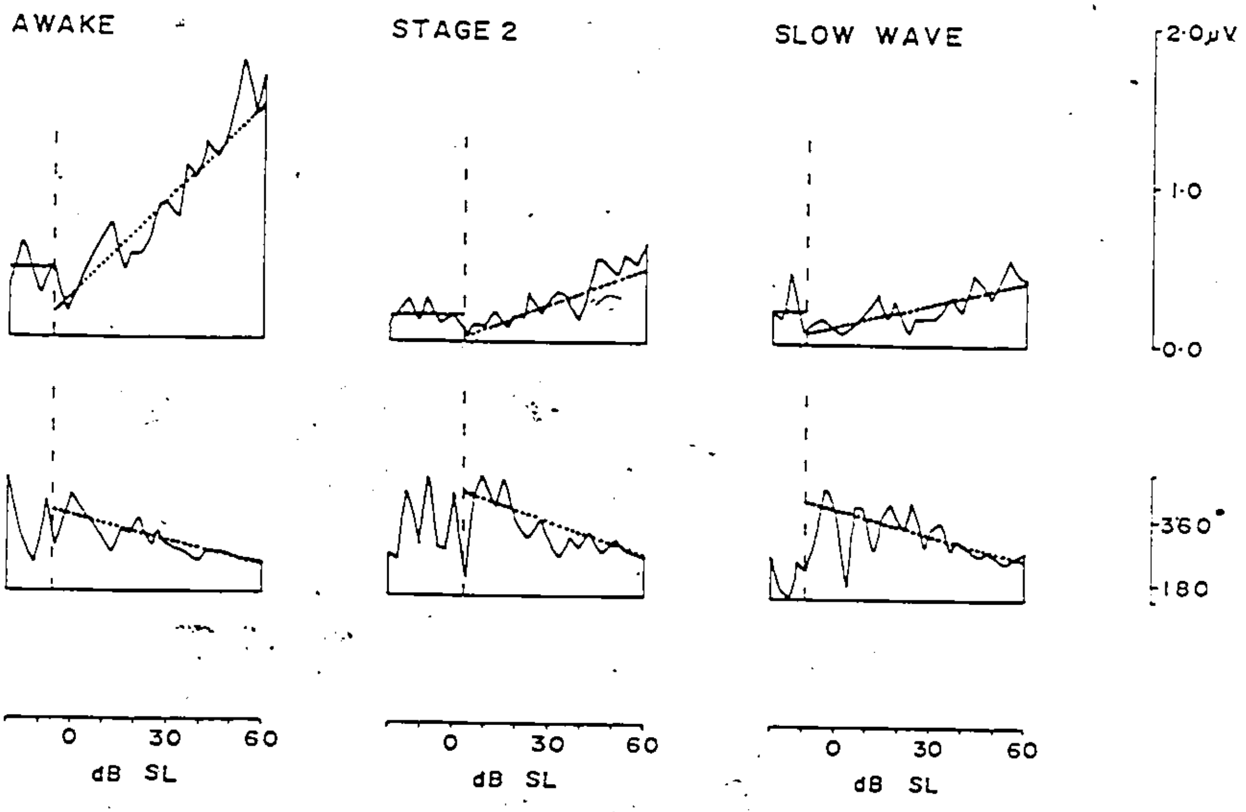
Figure

The amplitude and phase intensity functions from a single subject during Wakefulness, Stage 2 and Slow Wave sleep. Each tracing is the vector-averaged sum of 20 sweeps of stimulus intens[illegible]. The amplitude data are plotted in the upper tracings and the phase data in the lower tracings. The subthreshold amplitude (background EEG noise), indicated by the line parallel to the abscissa in the upper tracings, is lower during sleep. The slope of the suprathreshold amplitude-intensity function is larger during wakefulness than during sleep. The phase of the response, random below threshold and decreasing linearly as the intensity was increased above threshold, did not change between wakefulness and sleep. The threshold, indicated by the vertical dashes, is -6 dB SL during Wakefulness, 3 dB SL during Stage 2, -9 dB SL during Slow Wave sleep.

Effects of stimulus intensity and thresholds for recognizing the auditory steady state responses during sleep.

	AWAKE	STAGE 2	SLOW WAVE	
AMPLITUDE BELOW -9dB SL	.41 ± .06	.21 ± .04	.19 ± .07	p<0.01
AMPLITUDE AT 60 dB SL (uV)	.98 ± .40	.45 ± .21	.39 ± .19	p<0.01
AMPLITUDE SLOPE (nV/dB)	17 ± 15	7 ± 8	3 ± 5	p<0.05
PHASE AT 60 dB SL (°)	228 ± 47	295 ± 55	279 ± 78	ns
PHASE SLOPE (°/dB)	-1.5 ± 2.4	-2.0 ± 2.6	-2.1 ± 1.4	ns
THRESHOLD (dB SL)	11 ± 16	5 ± 11	6 ± 20	ns


AWAKE
STAGE 2
SLOW WAVE
2·0µV
1·0
0·0
360
180
0
30
60
dB SL
0
30
60
dB SL
0
30
60
dB SL

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