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# Neuromagnetic steady-state responses to auditory stimuli

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Steady-state magnetic responses to clicks presented at rates between 10 and 70 Hz have been recorded in healthy humans. The responses were highest in amplitude around 40 Hz. This amplitude enhancement is satisfactorily explained by summation of responses evoked by single clicks. The field maps suggest activation of the auditory cortex at all stimulus frequencies. Similar responses were obtained with gated noise bursts and by pauses in a series of clicks. The mean "apparent latency," determined from the phase lag at rates 30–70 Hz, was 54 ms. The physiological relevance of this quantity is shown to be questionable.

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## INTRODUCTION

It is customary to classify cerebral evoked responses as transient or steady-state responses. The former are elicited by stimuli presented at slow repetition rates, typically below 3 Hz. When the interstimulus interval (ISI) is shortened, steady-state responses are formed. If the system under study is nonlinear, steady-state and transient responses can give complementary information.

Galambos and co-workers (1981, 1982, 1988) described a sinusoidal auditory steady-state scalp potential phase locked to periodically presented clicks and short tone bursts. Maximum amplitude was obtained at stimulus repetition rates around 40 Hz; hence, the term "40-Hz response." Because tactile stimuli elicited similar responses, a subcortical source was suggested. Unfortunately, no scalp distributions were presented to test this hypothesis. The authors, however, felt that the commonly observed decrease of cortical responses when the ISI decreases supports their interpretation about a subcortical source. Thereafter, discussion about the sources of the steady-state responses has continued and both cortical and subcortical generator areas have been proposed (see Mäkelä and Hari, 1987, for references).

Magnetoencephalography (MEG) is well suited for studies of the human auditory cortex (for a recent review, see Hari, 1989). The main sources of cerebral magnetic fields are currents tangential to the skull, arising in the parallelly oriented pyramidal cells in the walls of cortical fissures. Studies of the auditory cortices have demonstrated in humans some functional features earlier observed in animals and have also given new information about the functional organization of and feature extraction in the human auditory cortex. Furthermore, recordings of both electric evoked potentials and magnetic fields under identical conditions have been important in identifying neural sources of auditory-evoked responses.

A clear 40-Hz response has been detected in the magnetic recordings by using trains of clicks (Mäkelä and Hari, 1987; Tiihonen *et al.*, 1988). During this response, the magnetic field component normal to the skull has two extrema, one at the anterior and the other at the posterior end of the

Sylvian fissure, indicating a source at the supratemporal auditory cortex, 20–35 mm beneath the scalp.

In the present work, we scrutinized the magnetic steady-state responses, evoked by continuous click stimulation, by studying their dependence on stimulus repetition rate and by mapping their topographic distribution.

## I. METHODS

### A. Subjects and experimental situation

Ten healthy adults (four females, six males) with no histories of hearing disorders were studied in the magnetically shielded room of the Helsinki University of Technology. During the experiment, the subject was lying on a bed with his head supported by a vacuum cast.

The stimuli were 0.5-ms clicks led to a TDH-49 earphone, situated outside the shielded room. The earphone was connected with a 3.3-m plastic tube (i.d. 15 mm) to a nonmagnetic earpiece inside the room. The sound pressure was measured with a Brüel and Kjaer ear simulator (B&K 4157), including a microphone (B&K 4134) and a preamplifier (B&K 2639), with an adaptor (DP 0530) connected to the earphone. Third-octave analysis was made using an HP 3561A dynamic signal analyzer, which employs synthesized filters (passband 12–20000 Hz) meeting the ANSI standards for bandwidth and filter shape. The analyzer was calibrated according to the sound-pressure level (SPL). The intensity of the clicks was 70-dB SPL rms when measured from the stimulation at 40 Hz; the approximate hearing threshold, determined for two subjects, was 32–35 dB SPL.

The stimulus repetition rates were 10.1, 20.1, 30.1, 35.1, 37.6, 39.7, 40.1, 42.6, 45.1, 55.1, 60.1, and 70.1 Hz presented in random order; all frequencies were not tested on every subject. Repeated measurements were made at some frequencies. Except for a few control experiments, subjects were instructed to ignore the stimuli and read a novel.

In order to learn more about the generation mechanism of the responses, several additional experiments were made with a few subjects by using, for example, chopped broadband (0–5 kHz) noise. The frequency spectrum of the periodically gated white noise is flat, in contrast to the spectrum

of the clicks presented at 40 Hz, where peaks of about equal amplitudes occur at 40 Hz and at its harmonics.

## B. Recordings and data analysis

The magnetic field over the right hemisphere was measured with a seven-sensor first-order gradiometer SQUID (superconducting quantum interference device) system of 5- to 6-fT/(Hz)<sup>1/2</sup> intrinsic noise level (Knuutila *et al.*, 1987). The pickup coils, separated by 36.5 mm, formed a hexagonal array on a spherical surface (radius 125 mm), 18–20 mm above the scalp. The orientations of the coil axes were close to the normal of the head. The exact location and orientation of the sensor array, with respect to the head, was determined by measuring the magnetic field produced by a set of small coils fixed to known locations on the scalp.

The bandpass-filtered signals (3-dB points at 0.05 and 100 Hz, roll-off for the high-pass filter 35 dB/decade, and over 80 dB/decade for the low-pass filter) were digitized at 2 kHz. The analysis period was two cycles, and about 1000 artifact-free responses were averaged on-line. In all experiments, the vertical electrooculogram was recorded, and magnetic responses coinciding with blinks or eye movements were discarded from the average. In a few experiments, a wider passband (0.05–250 Hz or 0.05–500 Hz) was used to detect details of the response waveform.

In all subjects, recordings were obtained from several locations (one position of the seven-channel instrument) at the posterior extremum of the magnetic field pattern, in two subjects also at the anterior extremum. Furthermore, responses were measured over the right hemisphere of two subjects at 35 and 49 sensor locations, respectively. Equivalent current dipoles were found using a spherically symmetric conductor model with the center of symmetry estimated on the basis of the shape of the head in the measurement area. The confidence limits for dipole locations were calculated using the noise estimates obtained from signals recorded in the absence of stimuli.

The fitting algorithm was informed about the measured sensor locations and orientations, so that the field point and the component of the measured magnetic field was precisely known for each sensor. Since some confusion exists about measurements of field components that are not exactly normal to the skull, we want to emphasize that simple analytical expressions exist for all components of the magnetic field outside a spherically symmetric conductor (cf. Sarvas, 1987), and, therefore, nonradial measurements cause no fundamental nor practical problems in dipole fitting, provided that the exact sensor locations are known.

The signal channel with maximum amplitudes from the posterior extremum was chosen for further analysis in every subject. The amplitude ( $A$ ) and the phase lag ( $\varphi$ ) of the response at the stimulation rate  $f_0$  were computed as  $A(f_0) = \sqrt{a^2 + b^2}$ , and  $\varphi(f_0) = \arctan(a/b)$ , where  $a$  and  $b$  are the Fourier coefficients:

$$a = \frac{2}{T} \int_0^T r(t) \sin(2\pi f_0 t) dt,$$

and

$$b = \frac{2}{T} \int_0^T r(t) \cos(2\pi f_0 t) dt.$$

Here,  $r(t)$  is the response waveform and  $T = n/f_0$  is the analysis period of  $n$  cycles at  $f_0$ . Note that because  $A$  gives the amplitude of a sine wave at  $f_0$ , the peak-to-peak amplitude of the steady-state response equals  $2A$ . Below, we always refer to  $A$  when discussing response amplitudes. Assuming that  $\varphi(f)$  is a linear function of  $f$ , the “group delay”

$$\tau = \frac{1}{2\pi} \frac{\partial \varphi}{\partial f}$$

is constant, independent of  $f$ , and can be estimated as the slope of the regression line between  $\varphi$  and  $f$ . Under this assumption,  $\tau$  is often called the apparent latency (Regan, 1972). The significance of this quantity will be critically discussed in this paper. In order to keep  $\varphi(f)$  monotonically increasing for the analysis,  $2\pi$  was added to it when needed.

## II. RESULTS

Figure 1 illustrates responses of subject 1 from one measurement location at four different stimulus repetition rates. The responses closely resemble a sinusoid and are highest in amplitude at the rate of 39.7 Hz. Qualitatively similar responses were obtained from all subjects with maximum amplitudes varying from 10 to 37 fT; the mean ( $\pm$  S.E.M.) of all ten subjects was 21.3 ( $\pm$  2.6) fT. Figure 1 also shows the dependence of response amplitudes of all subjects on the stimulus repetition rate. In one subject the highest amplitude was obtained at 20.1 Hz, in another at 35.1 Hz, and in all others around 40 Hz. The mean amplitude was highest at 40 Hz, being 2.7 times that at 30.1 Hz and 1.8 times that at 60.1 Hz; both differences are statistically highly significant ( $p < 0.001$ , two-tailed  $t$  test for group means).

The phase lag increased with the stimulus repetition rate, being very similar in all subjects (Fig. 2). The increase was linear between rates of 30.1 and 70.1 Hz. The mean ( $\pm$  S.E.M.) apparent latency, estimated from the slopes of the regression curves, was 53.9 ( $\pm$  1.6) ms, ranging from 46 to 63 ms in different subjects.

Figure 3 illustrates the responses under different conditions. Clear signals were obtained down to intensities close to the hearing threshold. Responses were similar in amplitude and latency when the subject was either ignoring the stimuli by concentrating in reading or when he was attentively listening to the sounds (shown for the 70-dB clicks). Furthermore, the responses evoked by gated noise bursts were similar in form and amplitude to those evoked by clicks, in spite of the striking differences between the frequency spectra of these stimuli (see Sec. I). Similar responses were also evoked by 40-Hz “click omissions” (not shown in the figure), when every 25th click was omitted in a continuous presentation of clicks at 1 kHz.

Figure 4 shows responses of two subjects with a passband up to 250 Hz. Clicks presented at 10.1 Hz evoked replicable “middle-latency” deflections at 32, 39, and 47 ms (down-up-down in the figure) in subject 1, and at 32, 40, and 52 ms in subject 2. The 40-ms peak was seen in responses at all repetition rates. The apparent latencies, determined from the steady-state responses, were significantly longer in

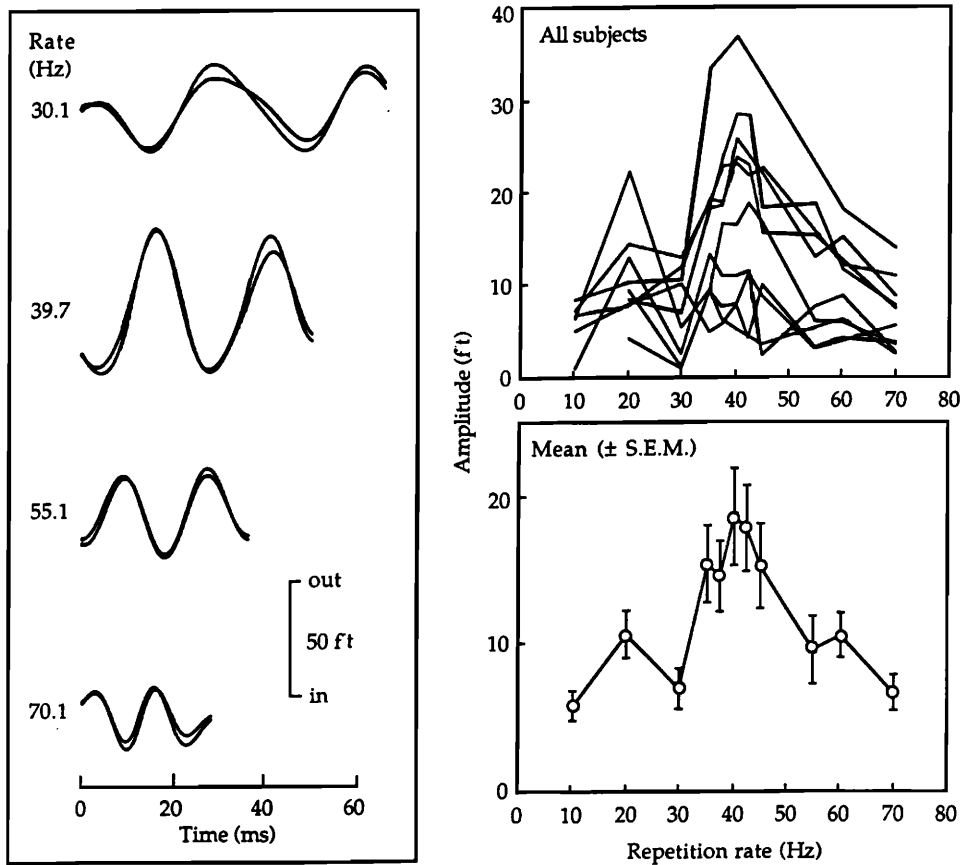


FIG. 1. Left: Responses of subject 1 at four different stimulus repetition rates. Responses have been averaged during two cycles of the stimulation and the experiment was repeated once (superimposed curves). Upper right: Response amplitudes of all subjects as a function of the stimulus repetition rate. Every subject was not presented with all repetition rates. Lower right: Mean ( $\pm$  S.E.M.) amplitudes of all ten subjects at different frequencies.

both subjects, 56 and 53 ms, respectively. The synthetic response, calculated from the 10.1-Hz responses by assuming that each click evokes a similar response at all repetition rates and that the responses to individual clicks simply add up, closely resembles the measured signal. Therefore, the amplitude enhancement at 40 Hz can be satisfactorily explained by superposition of successive responses.

Figure 5 shows field maps of one subject to clicks pre-

sented at 40.1 and 70.1 Hz. The patterns display two extrema of opposite polarities, and can be accounted for by a single-dipole model, which explains up to 93%–96% of the field variance. The strongest dipole moments were 5–6 nAm for subject 1, and 3 nAm for subject 2 during the 40-Hz response, and 2–3 nAm during the 70-Hz response. The sources were on average 35 mm beneath the scalp; source locations did not differ at the 95% confidence level for the 40- and 70-Hz responses. For subject 2, the location of the dipole changed systematically in the sagittal plane during 7–8 ms around all four peaks (two for each cycle) of the 40-Hz response: both the  $x$  and  $y$  coordinates of the dipole location increased by about 10 mm ( $x$  and  $y$  directions are equal to the horizontal and vertical directions, respectively, in the maps of Fig. 5). Although this movement of the equivalent dipole occurred within 1 cm<sup>2</sup>, we consider it significant because of its reproducibility during all peaks of the response. This type of behavior strongly suggests the existence of at least two sources, for example two closely located dipoles, both showing biphasic activity but with a phase lag. In subject 2, the source locations did not change in any systematic way during the response.

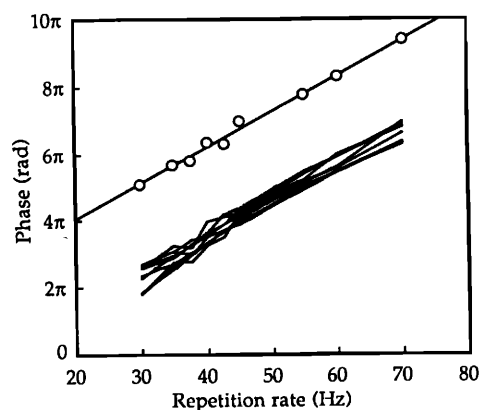


FIG. 2. Phase lags as functions of stimulus repetition rate (30.1–70.1 Hz) in ten subjects. The circles show the mean values of all subjects; for clarity,  $2\pi$  has been added to these values. The linear regression line  $\varphi = 2\pi(0.953 + f \cdot 0.053 \text{ s})$  is also illustrated.

### III. DISCUSSION

We have recorded magnetic steady-state responses at several stimulus repetition rates. Individual variability in the response amplitudes was considerable, as has been observed earlier for the magnetic 40-Hz response (Mäkelä and Hari,

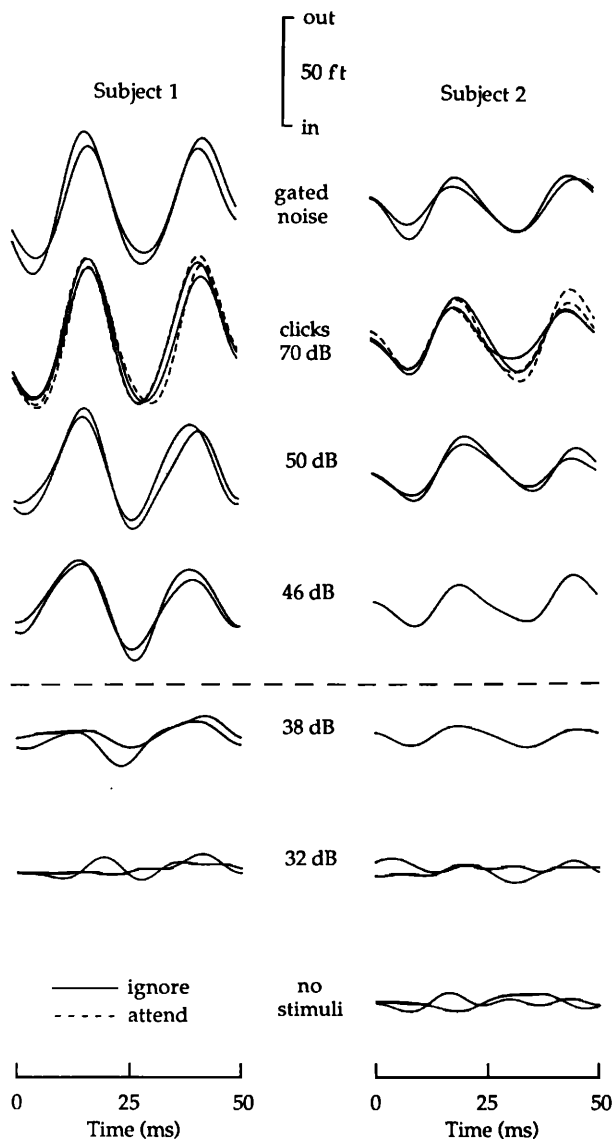


FIG. 3. Effects of attention and of stimulus quality and intensity on steady-state responses to stimuli presented at 39.7 Hz for two subjects. The superimposed curves illustrate repetitions of the same condition. The uppermost waveforms show responses to gated 0.5-ms noise bursts, and the other curves responses to clicks presented at different intensities. For the 70-dB clicks, continuous lines show responses when the subject was reading and ignoring the stimuli, while the dashed lines are responses when the subject was attentively listening to the clicks. The hearing threshold is marked by the horizontal dashed line.

1987). Like the electric evoked potentials (Galambos *et al.*, 1981; Lee *et al.*, 1984; Stapells *et al.*, 1984), the responses disappeared close to the hearing threshold. The insensitivity of the responses to the attentional state, in our easy task, also agrees with electric recordings (Linden *et al.*, 1987).

### A. Generation site of steady-state responses

The observed field patterns were satisfactorily explained by an equivalent dipole located at the supratemporal auditory cortex. In comparison with the source of the largest auditory-evoked response, N100m (cf. Hari, 1989), the sources of the steady-state responses were slightly posterior

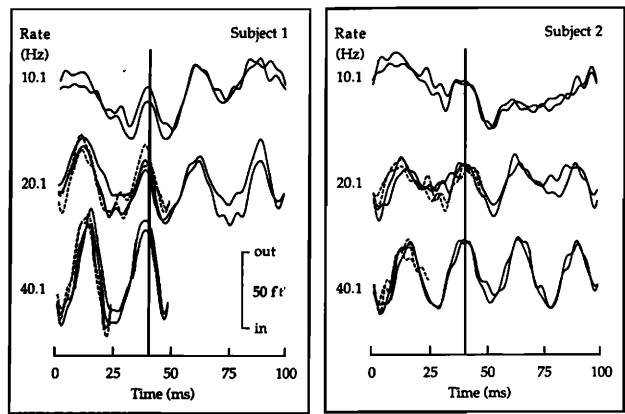


FIG. 4. Responses of two subjects to clicks presented at 10.1, 20.1, and 40.1 Hz. The recordings are from the posterior field extremum over the right hemisphere. The passband is 0.05–250 Hz; 1500–1800 responses were averaged for each curve. Continuous lines show the measured responses, and the dashed lines illustrate "synthetic responses." The latter were calculated by adding two or four 10.1-Hz responses together, shifted by a half-cycle or a quarter-cycle, thus generating simulated 20.2- and 40.4-Hz responses, respectively. The vertical line is at 40 ms.

and deeper, suggesting different source configurations for these two signals. Different binaural interaction in the magnetic 40-Hz response and in the transient N100m (Tiihonen *et al.*, 1989) also suggests different neuronal populations underlying these responses. The depths of the sources, 35 mm on average, suggest that the responses might be generated close to the primary auditory cortex, in the area supratemporalis granulosa (Braak, 1980), deep within the Sylvian fissure.

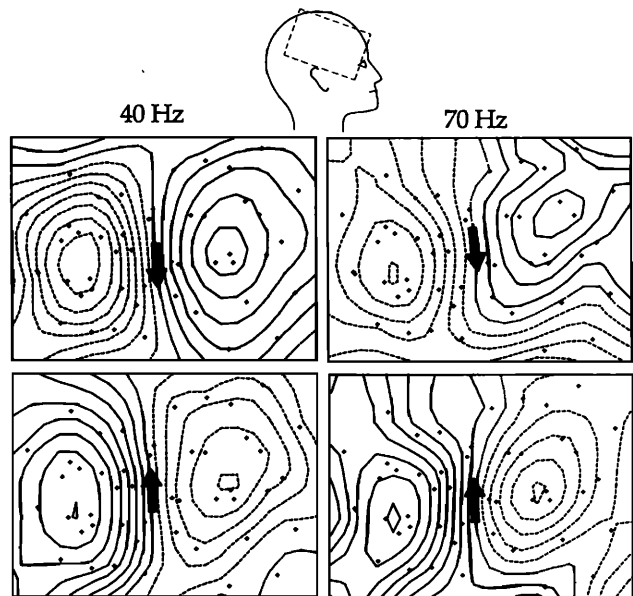


FIG. 5. Field maps of subject 1 for responses to clicks presented at 40 and 70 Hz. The dots show the measurement locations. Continuous lines indicate magnetic flux out of the skull and dashed lines into the skull. The arrows show the sites and orientations of the equivalent dipoles. The location of the map area with respect to the head is shown above. The maps have been drawn for two opposite peaks of the sinusoidal steady-state response. Iso-contour lines are separated by 5 fT for the 40-Hz response and by 1.5 fT for the 70-Hz response.

Although subcortical generators have been frequently suggested for the auditory steady-state responses (cf. Spydell *et al.*, 1985), our magnetic field mappings, like those reported earlier for the 40-Hz response (Mäkelä and Hari, 1987; Tiihonen *et al.*, 1988), strongly support cortical origin for these responses. Simulation in a four-layer sphere model (Hari and Mäkelä, 1987) shows that the strengths of the sources at the auditory cortex are sufficient to explain the electric potentials measured on the scalp. The cortical origin for the human steady-state responses is also supported by subdural recordings (Lee *et al.*, 1984). The ability of the auditory cortex to follow stimulation frequencies up to 100 Hz has been observed in multiple unit recordings of alert monkeys and cats (Goldstein *et al.*, 1959; Ribaupierre *et al.*, 1972; Steinschneider *et al.*, 1982; Mäkelä *et al.*, 1989).

### B. Generation mechanism of steady-state responses

The observed response maximum around the stimulus repetition rates of 40 Hz agrees with earlier electric recordings (Galambos *et al.*, 1981; Stapells *et al.*, 1984). Two explanations can be presented for this type of amplitude enhancement. First, the 40-Hz response may result from the consolidation or superposition of successive middle-latency responses (Galambos *et al.*, 1981). The other possibility is that the neural network displays an intrinsic rhythm and, when receiving periodic input, behaves like a tuned oscillator with a resonance around 40 Hz. Resonant modes of neu-

ral networks have been suggested to help to optimize signal transfer between various brain structures (Basar, 1988), and 40-Hz rhythms have been found in several species and at several brain sites (Bressler and Freeman, 1980).

Our successful reconstruction of the 20- and 40-Hz responses from the 10-Hz response (Fig. 4) strongly suggests that the main factor in the amplitude enhancement at 40 Hz is the superposition of responses evoked by single clicks. Therefore, no resonance properties of the network are needed to explain the amplitude enhancement. A tendency of the cerebral network to react in the 40-Hz range can, however, be considered the impetus of the enhancement because it affects the frequency content of the single responses and thereby determines the stimulus repetition rate at which response enhancement may be observed. This superposition implies that the equivalent sources of the 40-Hz responses may reflect activity of several areas. Evidence to support this hypothesis was obtained in our subject 2.

The apparent latency  $\tau$ , determined from the linear phase-rate dependence, is commonly used to characterize a latency of the steady-state response (Regan, 1972). Very different values have been observed, but our mean  $\tau$  of 54 ms is similar to the 49 ms of Romani *et al.* (1982) for magnetic steady-state responses to amplitude modulation (AM) of a continuous tone. Both these values are, however, clearly longer than the 37–38 ms reported by Picton *et al.* (1987) for electric steady-state responses to AM and frequency modulation (FM) of a continuous tone and the 33–34 ms reported

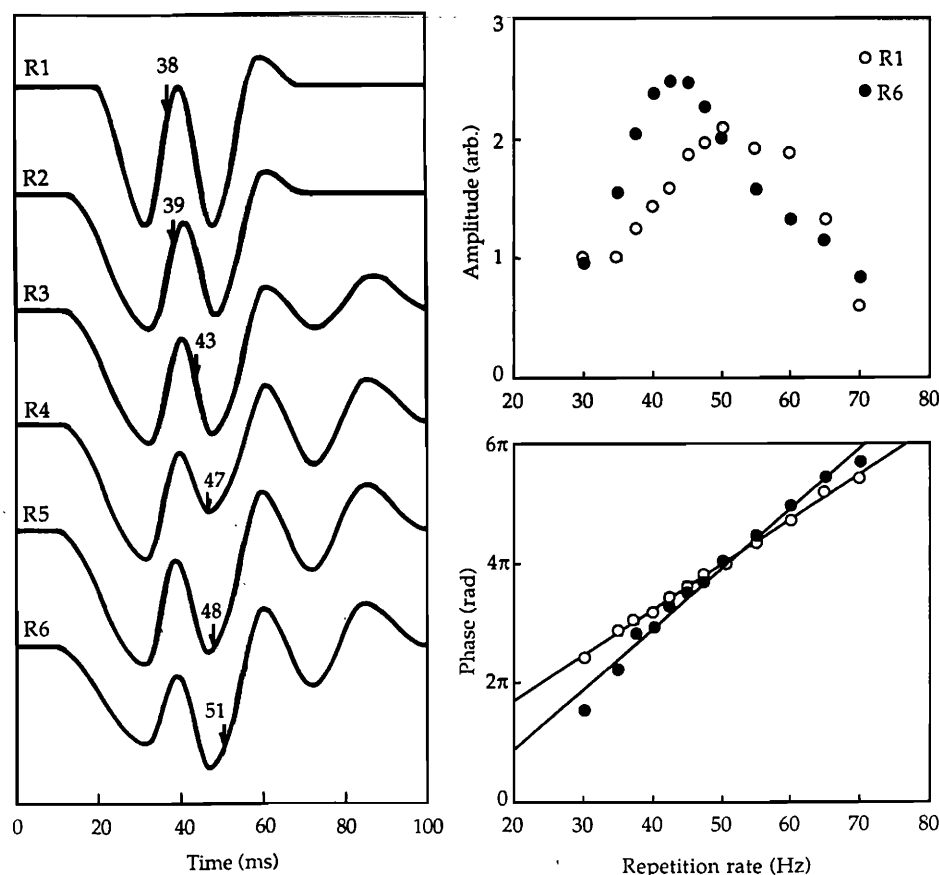


FIG. 6. Effect of response waveform on apparent latencies and on amplitude/rate functions of the synthetic steady-state responses. The latter were calculated from the single responses by "repeating" them at different rates and adding overlapping parts (cf. legend of Fig. 4). Left: The six synthetic single responses (*R* 1–*R* 6). The waveforms resemble the measured 10.1-Hz responses of subject 1 in Fig. 4, with variable weights on different deflections. The arrows indicate the apparent latencies (in ms), obtained from the phase lags of the calculated steady-state responses. Right: Amplitudes and phases of the steady-state responses, calculated for *R* 1 and *R* 6, as a function of the stimulus repetition rate. For the phase plots, the linear regression lines are also shown.

by Stapells *et al.* (1984) for the electric responses to 10-ms tone bursts. All these values are significantly longer than the delay for impulse transfer from cochlea to the auditory cortex. Because the neural events determining  $\tau$  are not known, it is difficult to decide which factors in the experimental set-up might explain the observed differences.

To assess this question, we made simulations by constructing a steady-state response as a sum of single responses with fixed shape (Fig. 6): The basic waveforms resemble the 10.1-Hz response in Fig. 4. The synthetic steady-state response behaves like the measured one showing, for example, amplitude enhancement at 42 and 50 Hz, for responses R6 and R1, respectively. The phases increase linearly as a function of the stimulus repetition rate, in agreement with the measured data. As shown in the figure, the apparent latencies of the synthetic steady-state responses vary from 38 to 51 ms depending on the waveform and they do not coincide with any peak in the response. The obtained value of  $\tau$ , therefore, seems to be a complex result of the amplitude and frequency content of the response. Even in the case of linear superposition, which is a simplification for the auditory system,  $\tau$  cannot be considered as reflecting the delay from periphery to the cortical area where the response is generated. The term "latency" is, therefore, misleading: different  $\tau$  values mainly illustrate differences in response waveforms.

### C. Steady-state responses and periodicity pitch

Spectral analysis occurring in the cochlea is considered the main basis of pitch sensations, whereas the coding of the nonspectral "periodicity pitch" is still partly unknown. The fibers in the auditory nerve reflect temporal aspects of low-frequency stimuli, including complex tones, and the human auditory system is able to extract frequencies from the temporally coded information at frequencies below 800 Hz (Javel and Mott, 1988). Our findings with chopped noise confirm that the steady-state responses reflect temporal aspects of the stimuli because the flat spectrum does not provide any cue for the periodicity. The site of origin of the steady-state response can, however, be specific to stimulus features depending, for example, on the carrier frequency of an AM tone (Romani *et al.*, 1982). Periodically chopped noise bursts activate in the cat auditory cortex "locker cells," which fire timelocked to the stimuli up to repetition rates of 1 kHz (Goldstein *et al.*, 1959; Ribaupierre *et al.*, 1972). The locker cells have been considered to have response characteristics appropriate for the coding of periodicity pitch.

The steady-state responses might be related to neural mechanisms involved in periodicity pitch. Our observation that click omissions evoke clear steady-state responses do not support the hypothesis that the auditory system, in extracting the periodicity pitch, "monitors high amplitude peaks in the temporal fine structure of the stimulus waveform" (for references, see Javel and Mott, 1988); rather, simply the existence of a temporal periodic structure seems necessary. In monkey, utilization of periodicity cues demands integrity of cortical areas (Symmes, 1966): Bilateral ablation of the primary auditory cortex disables discrimination of chopped noise bursts presented at frequencies of 10 or

300 Hz. Recordings of steady-state responses with the neuromagnetic technique, which provides good spatial resolution for cortical sources, could therefore be applied to studies of human neural mechanisms involved in coding of periodicity pitch at low frequencies.

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