Parallels Between Timing of Onset Responses of Single Neurons in Cat and of Evoked Magnetic Fields in Human Auditory Cortex

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Biermann, Silke and Peter Heil. Parallels between timing of onset responses of single neurons in cat and of evoked magnetic fields in human auditory cortex. J Neurophysiol 84: 2426–2439, 2000. Sound onsets constitute particularly salient transients and evoke strong responses from neurons of the auditory system, but in the past, such onset responses have often been analyzed with respect to steady-state features of sounds, like the sound pressure level. Recent electrophysiological studies of single neurons from the auditory cortex of anesthetized cats have revealed that the timing and strength of onset responses are shaped by dynamic stimulus properties at their very onsets. Here we demonstrate with magnetoencephalography that stimulus-response relationships very similar to those of the single neurons are observed in two onset components, N100m and P50m, of auditory evoked magnetic fields (AEFs) from the auditory cortex of awake humans. In response to tones shaped with cosine-squared rise functions, N100m and P50m peak latencies vary systematically with tone level and rise time but form a rather invariant function of the acceleration of the envelope at tone onset. Hence N100m and P50m peak latencies, as well as peak amplitudes, are determined by dynamic properties of the stimuli within the first few milliseconds, though not necessarily by acceleration. The changes of N100m and P50m peak latencies with rise time and level are incompatible with a fixed-amplitude threshold model. The direct comparison of the neuromagnetic and single-neuron data shows that, on average, the variance of the neuromagnetic data is larger by one to two orders of magnitude, but that favorable measurements can yield variances as low as those derived from neurons with mediocre precision of response timing. The striking parallels between the response timing of single cortical neurons and of AEFs provides a stronger link between single neuron and population activity.

INTRODUCTION

Transients, i.e., rapid changes in spectral composition or amplitude of sounds, constitute important information-bearing elements in audition. Neurons of the auditory system, including auditory cortex, respond preferentially to acoustic transients, such as the onsets of sounds. Somewhat paradoxically, however, onset responses have usually been analyzed with respect to measures of the steady state of a stimulus, such as the sound pressure level (SPL) (see a review of studies using magnetoencephalography (MEG) or electroencephalography, see Näätänen and Picton 1987). And consequently changes in neuronal onset responses observed with changes in level have been interpreted to be significant for intensity coding (for electrophysiology, see e.g., Brugge and Merzenich 1973; Heil et al. 1994; Phillips et al. 1995; Schreiner et al. 1992; Suga 1977; for MEG, see Pantev et al. 1989). However, with variation of level, dynamic features of the stimulus are inevitably covaried, such as the time course of the envelope (peak pressure) at sound onset and the derivatives of that time course (see Fig. 1, top). Hence, such standard experimental paradigms are inherently ambiguous with respect to the stimulus variable(s) critical for shaping the ubiquitous onset responses.

Recently, Heil and Irvine (Heil 1997a,b; Heil and Irvine 1996, 1998) have addressed some of these ambiguities by studying the responses of auditory cortical neurons to tone onsets with parametric variation of level and rise time. With this two-dimensional design (Fig. 1), they could show that these onset responses are shaped by dynamic properties of such stimuli at their very onsets and not by steady-state level. Furthermore these data suggest a way in which such responses might track and encode the time-varying envelopes. The details of temporal envelopes provide critical information, e.g., in speech (Drullman et al. 1994; Shannon et al. 1995), and have perceptual correlates, such as timbre (e.g., Gray and Gordon 1978; Krumhansl and Iverson 1992; Pitt and Crowder 1992).

If the data of Heil and Irvine, which were collected in deeply anesthetized animals, and their interpretations have any significance for signal processing in the awake human brain, then similar stimulus-response relationships should be demonstrable in onset responses from the human auditory cortex. The present study examines this possibility in detail using MEG, a noninvasive technique now widely employed to study macroscopically cortical neuronal activity with high temporal resolution (Hari 1990, 1996; Hyde 1997; Jacobson 1994; Loukasmaa et al. 1996; Sams and Hari 1991). Auditory evoked magnetic fields (AEFs), which can be measured outside the head, are produced by intracellular currents flowing tangentially to the skull and simultaneously in thousands of pyramidal cells of the auditory cortex on the supratemporal gyrus (Häimäläinen et al. 1993; Papanicolaou 1995; Sato et al. 1991). We focus on two prominent components of AEFs, specifically the N100m and the P50m, as they are triggered by stimulus onset despite their long latencies of about 100 and 50 ms, respectively. This paper presents a direct comparison of the properties of these onset components of AEFs with those of single neurons of the auditory cortex of anesthetized cats have revealed that the timing and strength of onset responses are shaped by dynamic stimulus properties at their very onsets. Here we demonstrate with magnetoencephalography that stimulus-response relationships very similar to those of the single neurons are observed in two onset components, N100m and P50m, of auditory evoked magnetic fields (AEFs) from the auditory cortex of awake humans. In response to tones shaped with cosine-squared rise functions, N100m and P50m peak latencies vary systematically with tone level and rise time but form a rather invariant function of the acceleration of the envelope at tone onset. Hence N100m and P50m peak latencies, as well as peak amplitudes, are determined by dynamic properties of the stimuli within the first few milliseconds, though not necessarily by acceleration. The changes of N100m and P50m peak latencies with rise time and level are incompatible with a fixed-amplitude threshold model. The direct comparison of the neuromagnetic and single-neuron data shows that, on average, the variance of the neuromagnetic data is larger by one to two orders of magnitude, but that favorable measurements can yield variances as low as those derived from neurons with mediocre precision of response timing. The striking parallels between the response timing of single cortical neurons and of AEFs provides a stronger link between single neuron and population activity.

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auditory cortical neurons. This comparison provides an estimate to what extent temporal properties of single neurons are reflected in the global magnetic responses of neuronal populations as recorded with MEG.

METH ODS

Subjects

Eight subjects (7 males and 1 female), aged between 21 and 39 yr, contributed data to this study. All subjects had normal hearing in both ears as determined by standard clinical audiometry and were right-handed as established with a modified version of the handedness questionnaire by Annett (1967). Some subjects had previous experience with MEG. All subjects gave written informed consent.

Acoustic stimuli, experimental protocol, and apparatus

All stimuli used were tone bursts shaped with cosine-squared rise functions. Left: for 3 different stimuli, time courses of the peak pressure during the rise time are shown. Only the top halves of the symmetrical envelopes are illustrated. Middle and right: resulting time courses of the rate of change of peak pressure and of the acceleration of peak pressure, respectively. Signals in the rows from top to bottom have identical rise time, plateau peak pressure, and maximum acceleration of peak pressure, respectively. Note that signals that share the same maximum acceleration also share very similar initial time courses of the rate of change and of the peak pressure itself.

FIG. 1. Envelope characteristics of the onsets of tone bursts shaped with cosine-squared rise functions. Left: for 3 different stimuli, time courses of the peak pressure during the rise time are shown. Only the top halves of the symmetrical envelopes are illustrated. Middle and right: resulting time courses of the rate of change of peak pressure and of the acceleration of peak pressure, respectively. Signals in the rows from top to bottom have identical rise time, plateau peak pressure, and maximum acceleration of peak pressure, respectively. Note that signals that share the same maximum acceleration also share very similar initial time courses of the rate of change and of the peak pressure itself.

The maximum acceleration of peak pressure occurs at the beginning of the stimulus \( t = 0 \) and is given by

\[
APP(t = 0) = APP_{\text{max}} = \frac{PP_{\text{plateau}}}{2} \left( \pi \frac{t}{T_k} \right)^2
\]

Equation 4 reveals that a given \( APP_{\text{max}} \) can be obtained by different combinations of \( T_k \) and \( PP_{\text{plateau}} \). An increment of \( PP_{\text{plateau}} \) (in Pa) by a factor of two (equivalent to a 6-dB increase in SPL) will double \( APP_{\text{max}} \), while shortening the rise time by half will quadruple \( APP_{\text{max}} \). Figure 1 illustrates the time courses of \( PP(t) \), \( RCPP(t) \), and \( APP(t) \) for stimuli differing in \( T_k \) and \( PP_{\text{plateau}} \). Note that signals that share the same acceleration of peak pressure at onset also share similar or, for most practical purposes, identical initial time courses of the rate of change and of the peak pressure itself (Fig. 1, bottom).

Tones started with a positive zero crossing of the carrier. Within a given experimental session, all tones had the same frequency (200, 500, 1,000, or 2,000 Hz). Five different SPLs at 12-dB intervals, and thus covering a 48-dB range, and four to seven different rise times, differing by a factor of two or four and varying between 2 and 128 ms, were used. Most of the tone bursts had a plateau duration of 35 ms. This duration was chosen because it had been reported that the N100m as well as the N1-P2 amplitude of auditory evoked potentials (AEPs) summate over \( \sim 30 \) ms of a stimulus (Joutsiniemi et al. 1989; Onishi and Davis 1968), while, on the other hand, responses to stimulus onset decrease and those to offset increase with increasing stimulus duration and for a fixed interstimulus interval (ISI) or stimulus repetition rate (Hillyard and Picton 1978; Pantev et al. 1996). Because of the fixed plateau duration, the total stimulus duration and stimulus energy covaried with varying rise time. To test for the potential influence of these parameters on the responses, we included, in several experimental sessions, additional stimuli with 16-ms rise time but with a plateau duration of 135 ms. These stimuli were presented at the same five SPLs as the other stimuli in those sessions. Either 99 or 200 repetitions of each stimulus were presented, in three blocks of 33 stimuli or in randomized order, respectively, with an average ISI of 1 s (range 950–1,050 ms). In the block design, each block was followed by a block with a new stimulus until all different stimuli had been presented. The sequence was then repeated another two times. Stimulus presentation was either binaural or monaural to the right ear. Overall 27 experimental sessions, each lasting \( \sim 60–70 \) min, were run.

Neuromagnetic data were recorded continuously (at sampling rates of 508 or 1,017 Hz and with passbands of DC to 100 or to 400 Hz) using a 148-channel whole-head biomagnetometer (Magnes 2500, Biomagnetic Technologies, San Diego, CA). Measurements were carried out in a magnetically shielded, illuminated, and ventilated room. The homogeneous background magnetic field was suppressed by an on-line noise-reduction system, consisting of three reference sensors, oriented perpendicularly to each other and located \( \sim 10 \) cm from the measuring sensor array. For each of these 148 sensors, weighting factors were determined prior to an experiment such that the weighted sum of the magnetic field vectors in the reference system minus the field in the measuring sensor was minimized. The magnetically silent delivery of the acoustic stimuli required a system with speakers outside the magnetically shielded room. Acoustic stimuli were conducted to each ear via two plastic tubes of \( \sim 6 \) m length and of 16 mm ID connected to silicon ear pieces. This system produced acoustic delays of \( \sim 25 \) ms and attenuation of \( \geq 20 \) dB, depending on frequency. The frequency response of this system was flat (\( \pm 5 \) dB) within the range of 200–2,000 Hz, as checked by a microphone (Sennheiser KE4–211-2) sealed into the ear piece and connected to an oscilloscope.

Prior to each experiment, the subjects’ sensation levels (SLs) were determined for each ear with the 2-ms rise time tones under the proper...
experimental conditions. The level of the softest tone was then set to
16–35 dB SL, depending on subject and frequency, such that each
subject could tolerate the strongest stimulus, whose level was 48 dB
above that of the softest one, without discomfort or pain. Actual SPLs
were estimated from the SLs by taking each subject’s audiogram into
consideration. The lowest estimated SPLs varied between 22 and 47
dB. During the experimental sessions, subjects lay comfortably in a
deck chair. They were instructed to stay awake, to listen to the stimuli,
and to avoid head movements as far as possible. The position of a
subject’s head relative to the sensor array was measured with five
coils fixed at widely spaced positions on the subject’s head. Changes
in head position were quantified as the maximum difference in the
location of these coils prior to and after data acquisition. A monitoring
video camera offered additional control of head movements. The
maximum differences between pre- and postacquisition locations
ranged from 0.09 to 0.92 cm with a mean of 0.30 (18) cm.

Data analysis

Epochs of 1,300 ms, including 300-ms prestimulus intervals, were
extracted from the continuously recorded electromyographic signals. Off-
line noise reduction was carried out. Epochs with a signal deviation of
10 pT within 100 ms were considered to be contaminated by artifacts and
rejected. The averaged data were offset-corrected and digitally
filtered using a 0.1- to 40-Hz passband. Because of the large number
of different stimuli required in every experimental session (viz.,
20–40) and because the total duration of each session of ~1 h was
approaching the limit that subjects could endure without moving,
falling asleep, or feeling uncomfortable, the number of repetitions of
each stimulus was limited (to 99 or 200; see preceding text). Hence for
many stimuli, the signal-to-noise ratios were suboptimal. To improve
those ratios, we selected from the 148 channels those four neighboring
channels over each hemisphere which yielded the strongest signals of
the same polarity (see Fig. 2) for averaging. The averaged signal
amplitudes were then offset-corrected using a 100-ms prestimulus
baseline. For a given subject, the same eight channels were selected
for data collected in different experimental sessions.

The two relatively prominent deflections of opposite polarity that
occurred in most data sets ~50 and 100 ms after stimulus onset (see
Fig. 3) are termed here P50m and N100m, in analogy to the corre-
spanding components of AEPs. The peak latency and peak amplitude
of these two deflections were measured for each stimulus and hemi-
sphere whenever they could be identified. Because the channels had
been selected to yield favorable N100m signals and because the
sources of P50m are slightly more anterior than those of N100m (e.g.,
Pellizone et al. 1987), the signal-to-noise ratios for P50m were likely
even smaller than they could have been had the channel selection been
optimized for this deflection. Analysis of peak values seemed to be
more reliable than those of the center of gravity or, for latency, the
initial zero crossing. The 108 data sets (27 sessions by 2 hemispheres
by 2 deflections) yielded 2,300 measures of response latency and
amplitude each, i.e., ~80% of the maximum number possible. Aver-
aging over a large number of channels would have reduced signal
amplitudes and broadened the signals in the time domain, because
peak latencies vary across different sensors, due to moving sources or
multiple sources with different response time courses (e.g., Lü et al.
1992; McEvoy et al. 1997; Sams et al. 1993). All measures of latency
described in the following text are corrected for acoustic delays of the
sound-delivery system.

RESULTS

Wavesforms

Figure 2 illustrates electromyographic signals recorded simulta-
neously at 148 sensor positions over both hemispheres from a
single subject. The strongest deflections of the signals, each of
which is the average of ~200 epochs, occur at ~100 ms after
stimulus onset (N100m) in the lateral sensors over each hemi-
sphere. The reversals of signal polarity from more anterior to
more posterior sources correspond to pronounced dipolar mag-
netic field distributions that are consistent with a source in the
auditory cortex on the superior temporal plane of each hemi-
sphere (e.g., Hari 1990; Lütkenhöner and Steinsträter 1998).
The details of the spatial distribution and time course of AEFs
depend on subject, hemisphere, and stimulus.

The 4 neighboring channels of a given polarity over each hemi-
sphere selected for averaging and data analysis are indicated (*).

FIG. 2. Auditory evoked magnetic field of a single subject. Signals re-
corded simultaneously from 148 sensors arranged around the head of one
subject (PeHa) during a 200-ms time window starting at stimulus onset are
shown as if viewed from above and flattened onto a single plane. The ordinates
represent ±150 fT. Stimuli were 500-Hz tone bursts with 2-ms rise time
presented binaurally at 68 dB SL. Note the polarity reversal of the N100m
deflection within each hemisphere. The dipolar distributions are consistent
with a source in the auditory cortex on the superior temporal plane of each
hemisphere. The 4 neighboring channels of a given polarity over each hemi-
sphere selected for averaging and data analysis are indicated (*).

Effects of stimulus level, rise time, and acceleration of
pressure on N100m and P50m latency

We have reported previously that the first-spike latency of
different conditions from the primary (AI) and posterior fields of the
auditory cortex of barbiturate-anesthetized cats varies system-
atically with rise time and with level. However, for cosine-
squared rise functions, latency forms a rather invariant function
of the acceleration of peak pressure at tone onset (APP_max)
which covaries with rise time and level (Heil 1997a; Heil and
Irvine 1996–1998). Data from one AI neuron (95-
98-11) are shown in Fig. 4, left. Figure 4A shows that latency increases monotonically with rise time for any given level and that the increase is most pronounced for low levels. It is also obvious that the increase in latency with rise time is compressively nonlinear. In Fig. 4B, the data are replotted as functions of level with rise time as the parameter. For any given rise time, latency decreases monotonically and nonlinearly with increasing level. Latencies are longest and the decreases are steepest for long rise times and low levels. In Fig. 4C, the data of B are plotted against APP_{max}. It is obvious that all latency functions are now in very close register.

Very similar observations are made here for N100m peak latency. Figure 3 shows that for a given rise time (32 ms in A; 4 ms in C), N100m peak latency decreases with increasing level and, for a given level increases with increasing rise time (Fig. 3, B and D). P50m peak latency also varies with level, and rise time, though not as systematically as N100m peak latency. The systematic nature of the dependencies of N100m latency on level and rise time are shown for a complete data set in Fig. 4, D and E (subject PeHa). Figure 4D shows that, apart from some irregularities, N100m peak latency increases monotonically with rise time for a given level and that the increase is most pronounced for low levels. Also the increase of latency with rise time seems to be compressively nonlinear at least at low tone levels. In Fig. 4E, the data are replotted as functions of level with rise time as the parameter, latency consequently decreases monotonically and nonlinearly with increasing level for a given rise time. Latencies are longest and the decreases are steepest for long rise times and low levels. Also note that latency functions obtained with tones of 16-ms rise time and plateaus of short versus long duration (ld16 ms) are very similar. Thus variation in total duration and stimulus energy with variation in rise time and level has minor, if any, effects on N100m peak latency (see also following text). In Fig. 4F, where the data of E are plotted against APP_{max}, it can be seen that all latency functions are now in close register.

Figure 5 illustrates four additional examples from another four subjects, for four different frequencies, both hemispheres, monaural and binaural stimulation, and for N100m as well as for P50m. In the left column, latency is plotted against level with rise time as the parameter. In the right column, the same data are plotted against APP_{max}. Note that in each case the different latency functions tend to be more aligned and be in closer register when plotted against APP_{max} as compared with level.

The closer alignment of the N100m and P50m peak latency functions, when plotted against APP_{max} rather than level, was not always as obvious as for the examples shown in Figs. 4 and 5 or as obvious as for the single-neuron data from cat auditory cortex (cf. Fig. 4, C with F). To quantify the improvement in alignment of latency functions by the transformation from level to APP_{max}, we first fitted the following simple power function to each data set

\[ L = L_{\text{min}} + k \cdot (X/X_0)^{-c} \]  

(5)

The equation contains three free parameters, viz. \(L_{\text{min}}\), \(X_0\), and \(c\). \(L_{\text{min}}\) (in milliseconds) represents the minimum against which the latency \(L\) converges asymptotically at high values of \(X\). In other words, \(L_{\text{min}}\) represents the transmission delay of the system. \(X\) either represents stimulus level (in dB SPL) or
APP_{max} (in Pa/s²), and X₀ a reference SPL or reference APP_{max}, respectively. When X = X₀, then the difference between L and L_{min} is k = 1 ms. A small X₀ describes a latency function in a more leftward position and a large X₀ a function in a more rightward position along the abscissa. Therefore X₀ can be thought of as an inverse measure of sensitivity of the AEF source or the neuron. The exponent c quantifies the degree of curvature of the latency function. The fits obtained for the N100m and P50m peak latency versus APP_{max} relationships of the neuromagnetic measurements shown in Figs. 4 and 5 are indicated by - - - in Figs. 4F and 5, B, D, F, and H and for the first-spike latency of the single neuron in Fig. 4C.

The fits describe the data well, as reflected in the high nonlinear coefficients of determination r_{nl}² also given in those panels. We also calculated the variance of each fit. The improvement in alignment of latency functions by the transformation from SPL to APP_{max} was then quantified as the ratio of the variances of fits of latency against SPL and against APP_{max}. Ratios >1 thus identify data sets that do bring about an improvement in alignment of latency measures by this transformation. And, the larger that ratio, the greater the improvement. Figure 6 shows a scatterplot of these improvement ratios against the variance of latency fits against APP_{max}, separately for N100m and P50m. For N100m, 47 of 53 ratios were > 1.
with ratios ranging from ~0.5 to 14 and with a geometric mean of 2.1. For P50m, 33 of 43 ratios were >1 with ratios ranging from ~0.5 to 7 and with a geometric mean of 1.3. The higher improvement ratios for N100m are probably due to the larger signal-to-noise ratios for N100m than for P50m. For each of the neuromagnetic signals and for the two combined, the improvement effect was highly significant (i.e., the null-hypothesis that improvement ratios are equal to 1 has a probability \( P < 0.0004 \); Wilcoxon). For comparison, the single-neuron data from cat AI are also shown in Fig. 6. For these data, all 90 ratios were >1, ranging from 2.7 to 690, with a geometric mean of 46.

Figure 6 also shows that the improvement ratios are the higher, the lower the variance of the fit of the latency against \( \text{APP}_{\max} \) function, even for the neuromagnetic data alone. Because of error along both axes, the Bartlett-procedure (Sachs 1997) was used to quantify the slope of the log-transformed data. The negative estimate of \(-0.26\) (\( n = 98; r^2 = 0.151 \)) for the neuromagnetic data thus confirms the impression that the better the quality of the data, the clearer is the improvement.
effect. Hence it is likely that the lack of improvement in the minority of cases (6 of 53 for N100m and 10 of 43 for P50m) is caused by too large a variance. The ratios for the single neurons seem to constitute a continuation of those for N100m and P50m, i.e., the variance of the fit of latency against \( \text{APP}_{\text{max}} \) is much smaller and the improvement larger than for the neuromagnetic signals. However, differences in the number and range of rise times tested for a given neuron and differences in extent of latency functions (see Heil 1997a; Heil and Irvine 1997) also contributed to the variation in improvement ratios. It is likely that the larger variance of the neuromagnetic data is due to the fact that a large number of neurons with different properties contribute to the signal (see following text). Also note in Fig. 6 that favorable neuromagnetic measurements can yield variances as low as, and improvement ratios as high as, those derived from some single neurons. This is reflected in the histograms in Fig. 6 as overlap between neuromagnetic and single-neuron data.

It can also be tested for each individual data set whether there is a significant improvement effect, for example, by a pairwise comparison of the squared deviations of fits of latency against level versus those of fits of latency against \( \text{APP}_{\text{max}} \). For the examples shown in Figs. 4 and 5, there was a significant effect (Wilcoxon, Fig. 4, E and F: \( P < 0.001 \); Fig. 5, A–D: \( P < 0.01 \); Fig. 5, E–H: \( P < 0.05 \)). Similar results were obtained with the absolute deviations.

In summary, these analyses reveal that, much like the first-spike latencies of single auditory cortical neurons, the peak latencies of both N100m and P50m are better described as functions of the acceleration of peak pressure at stimulus onset than of level, i.e., plateau peak pressure, even though the neuromagnetic data are noisier than the single-neuron data.

**Shape of latency versus acceleration functions**

It was observed previously that the latency versus acceleration functions of different neurons were of very similar shape (Heil 1997a; Heil and Irvine 1997, 1998). Much the same applies to the latency versus acceleration functions derived from the neuromagnetic signals. N100m and P50m peak latency versus acceleration functions obtained in the same and in different experimental sessions, under different protocols (binaural and monaural), with different frequencies, and from different subjects, appeared to be of similar shape. This qualitative impression was quantified by the results of the fits of Eq. 5 to the data, with \( X \) and \( X_0 \) representing \( \text{APP}_{\text{max}} \) and the reference \( \text{APP}_{\text{max}}(0) \), respectively. Specifically the values of the exponent \( c \) are informative because that parameter quantifies the degree of curvature of the latency versus acceleration function, while \( L_{\text{min}} \) and \( \text{APP}_{\text{max}(0)} \) characterize the position of the function along the ordinate and abscissa, respectively.

Figure 7A illustrates the distribution of the exponent \( c \) for the single-neuron data. That distribution is very narrow with a mean of 0.40(08). Figure 7B shows, stacked on top of each other, the distributions for the 53 and 43 sets of N100m and P50m peak latency data, respectively, which could be fitted with Eq. 5. The histograms show the relative frequencies of the exponent \( c \), after each estimate had been weighted with the root number of latency measures having contributed to the fit and with the reciprocal of the variance of the fit. In this way, estimates of \( c \) derived from only few latency measures or from
noisy data are weighted less. The distributions for N100m and for P50m are both relatively narrow and not different from one another: for N100m the mean $c$ equals 0.13(18) and for P50m 0.14(22). Therefore the two distributions were combined and yielded a mean of 0.14(16). As this exponent is smaller than that of the single-neuron data, the latency versus acceleration functions of single neurons from the cat auditory cortex are more steeply curved than those of N100m and P50m.

The narrow distributions of the exponent $c$ confirm quantitatively the visual impression of rather similar shapes of latency versus acceleration functions across neurons and stimulus conditions for the single-neuron data on the one hand and across subjects and stimulus conditions for the neuromagnetic data on the other. Next all data sets were fitted once again, now with the exponent $c$ fixed at the mean of 0.40 of the single-neuron data and at 0.14, the mean of the combined distributions, for the neuromagnetic data. In this way, a function with a fixed shape is fitted to each single-neuron and neuromagnetic data set, and estimates of $L_{\text{min}}$ and $\text{APP}_{\max(0)}$, i.e., of the function’s position within the coordinate system, can be compared across data sets. This procedure yielded physiologically plausible estimates of the transmission delay, i.e., $L_{\text{min}} > 0 \text{ ms}$, for 49 of 53 data sets for N100m and for 42 of 43 data sets for P50m.

It was observed previously for the single-neuron data that the transmission delay decreased with increasing stimulus frequency (Heil 1997a; Heil and Irvine 1997). This is shown in Fig. 8A where $L_{\text{min}}$, obtained from fits of Eq. 5 with $c = 0.4$, is plotted against stimulus frequency. For all data points shown that frequency is identical to the frequency to which each neuron is most sensitive, i.e., its characteristic frequency. While there is considerable scatter of $L_{\text{min}}$ at a given frequency, an overall trend for $L_{\text{min}}$ to decrease with increasing frequency is indicated. Such a decrease is consistent with the frequency-dependent delays in the cochlea. Figure 8B shows the transmission delays, estimated from fits of Eq. 5 with $c = 0.14$, for...
the neuromagnetic data, separately for N100m and for P50m. Medians are also shown and connected by lines. Despite considerable scatter of points for both deflections and at all frequencies, medians of $L_{\text{min}}$ for N100m and P50m are $\sim 40 – 45$ ms apart, independent of frequency. However, there is no clear indication for $L_{\text{min}}$ to decrease with increasing frequency. This may be due to the fact that, partly, or even largely, overlapping neuronal populations would contribute to the neuromagnetic signals recorded with different stimulus frequencies. Note that the estimates of transmission delays for the neuromagnetic signals, particularly for N100m, are much longer than those for the vast majority of single neurons, recorded mostly from middle layers of cat AI. However, a few single AI neurons have minimum latencies of $30 – 40$ ms, i.e., near the estimates of transmission delays for P50m. Hence, these data are compatible with the suggestion that P50m originates in the human primary auditory cortex, though likely not in the input layers, and N100m in the planum temporale (Hashimoto et al. 1995; Pantev et al. 1990; Pellizone et al. 1987).

Figure 8C shows for the single-neuron data a plot of $\text{APP}_{\text{max}(0)}$, resulting from the same fits, against stimulus/characteristic frequency. As explained in the preceding text, this parameter can be thought of as an inverse measure of the neuron’s sensitivity to the tones’ onsets and will therefore be referred to as transient sensitivity. As noted earlier (Heil 1997a), the transient sensitivity varies with frequency in a manner somewhat similar to the cat’s audiogram. A corresponding plot for the neuromagnetic data is shown in Fig. 8D. In addition, medians are shown and connected by lines. For N100m, $\text{APP}_{\text{max}(0)}$ ranged from $10^7$ to $10^{14}$ Pa s$^{-2}$ and for P50m from $10^{-7}$ to $10^{12}$ Pa s$^{-2}$. There is no uniform dependence of $\text{APP}_{\text{max}(0)}$ on frequency, although for both N100m and P50m, medians are lowest, i.e., sensitivity is highest, at 1 kHz, where humans have the lowest threshold when tested with ear phones, which bypass the frequency-dependent amplification of the pinna (Han and Poulson 1998).

The fits of latency versus acceleration functions with Eq. 5 and a common exponent $c$ allow superimposition of all fitted functions, which in turn allows examination of the residuals more systematically. Figure 9A shows, for the single neurons, a plot of $(L - L_{\text{min}})$ against $\text{APP}_{\text{max}}/\text{APP}_{\text{max}(0)}$, i.e., of the difference between measured first-spike latency and estimated transmission delay against the stimulus $\text{APP}_{\text{max}}$ normalized for each neuron’s estimate of transient sensitivity $\text{APP}_{\text{max}(0)}$. In this way, the functions fitted to each data set (with $c$ fixed at 0.4) are all superimposed. The 2,288 data points in this plot form a very narrow band (Fig. 9A), emphasizing once again the similarity in the shape of latency versus acceleration functions of different neurons and stimulus conditions (Heil 1997a). A renewed fit of these data with Eq. 5 (Fig. 9A, —) yielded the low variance of 1.9 ms$^2$. Figure 9B shows the residuals of this renewed fit. Note that the residuals scatter unsystematically and relatively closely around the horizontal zero line. Most data points fall within a band of 1 or 2 ms from that line of best fit. An error estimation for $c$, provided by the functions that would fit 70% of measured points, reveals that 0.35 $< c < 0.48$ is compatible with variance.

Corresponding plots for N100m and P50m peak latency are shown in Fig. 9, D and E. The 2,187 data points from the 93 data sets (51 for N100m and 42 for P50m) are in rather close register, confirming the similarity in the shape of latency versus acceleration functions derived from the neuromagnetic data. A renewed fit yielded a variance of 39 ms$^2$, $\sim 20$ times that of the single-neuron data. This is compatible with the suggestion that neurons with different transient sensitivities and transmission delays (Fig. 8, A and C) contribute to the neuromagnetic signals (see also Fig. 3 in Heil 1997a). The larger variance is also reflected in a larger scatter of the neuromagnetic residuals in Fig. 9E (cf. with Fig. 9B). Nevertheless, the residuals scatter unsystematically, emphasizing the quality of the fit. An error analysis analogous to those for the single-neuron data reveals a range of $0 < c < 0.33$. These results confirm that the curvature of the latency versus acceleration functions for N100m or P50m is less steep than that of the functions for the single neurons.

**Effects of stimulus duration on shape of latency versus acceleration functions**

Only data points from stimuli with a plateau duration of 35 ms contributed to the parameter fitting. Because, in several experimental sessions, control stimuli with a plateau duration of 135 ms were also presented (see METHODS), the 140 latency measures obtained from these stimuli could post hoc be compared with the global fit. In a plot of the residuals of $(L - L_{\text{min}})$ against $\text{APP}_{\text{max}}/\text{APP}_{\text{max}(0)}$ of the global fit with $c = 0.14$, data points also scattered randomly around the horizontal zero line (not shown). Hence the changes in latency with rise time, described in the preceding text, are not due to the concomitant changes in total stimulus duration and energy (see also Figs. 4, E and F, and 5, G and H).

**Test of the fixed-amplitude threshold model**

It has been proposed that the changes in response latency associated with changes in stimulus level or rise time can be explained by changes in the time needed for the stimulus to reach some fixed-amplitude threshold (e.g., Ruhm and Jansen 1969). Our data allow us to test this model directly. It follows from Eq. 1 that the time $t_{\text{thr}}$ needed to reach some fixed threshold pressure $\text{PP}_{\text{thr}}$ is given by

$$t_{\text{thr}} = 2T_{\text{thr}}/\pi^* \arcsin \left(\frac{\text{PP}_{\text{thr}}}{\text{PP}_{\text{plateau}}}\right)^{0.5}$$

Thus this model predicts a linear relationship between latency and rise time for any given level with a slope of $2/\pi^* \arcsin \left(\frac{\text{PP}_{\text{thr}}}{\text{PP}_{\text{plateau}}}\right)^{0.5}$. Because $\arcsin (x) \sim x$ for very small $x$, a condition met when $\text{PP}_{\text{thr}}$ is very small relative to $\text{PP}_{\text{plateau}}$ (note that these are measures of amplitude on a linear scale), the model also predicts an exponent $c$ of 0.5 for the relationship between latency and $\text{APP}_{\text{max}}$ or between $(L - L_{\text{min}})$ and $\text{APP}_{\text{max}}/\text{APP}_{\text{max}(0)}$ for that matter. Figure 4D suggests that the growth of latency with rise time is compressively nonlinear, and re-inspection of Fig. 7B shows that the vast majority of values obtained from the fits of the N100m and P50m peak latency versus acceleration functions are smaller than 0.5 ($\cdot \cdot \cdot$). Much the same holds for the single-neuron data (see Figs. 4A and 7A). Figure 9 also demonstrates the inadequacy of this model. The dashed lines in A and D represent the best fits of this model to the data, and panels C and F show the residuals for this model. Note that the residuals are large, highly systematic, and of similar nature for neuromagnetic signals and single neurons. Hence, the changes in N100m and P50m peak latency with stimulus parameters are incompatible
with a fixed-amplitude threshold model, as noted earlier for first-spike latency of single neurons (Heil and Irvine 1996).

Effects of stimulus level and rise time on N100m amplitude

The peak amplitude of the neuromagnetic deflections tended to increase with increasing tone level for a given rise time and to decrease with increasing rise time for a given level (see Fig. 3). However, most individual amplitude data sets, even of N100m, were very noisy, in agreement with previous reports (Hyde 1997; Rogers et al. 1990). Thus to obtain a clearer picture, at least for N100m, data sets were averaged. However, two facts needed to be considered. First, there was considerable variability in absolute N100m amplitudes across subjects (see Fig. 3). Second, for binaural stimulation, N100m amplitudes, averaged across all stimuli presented in a given session, were similar in the left and right hemisphere (n = 18; Wilcoxon, P = 0.468 > 0.3), but for monaural stimulation were considerably larger in the left hemisphere, contralateral to the stimulated ear (n = 9; Wilcoxon, P < 0.01; not shown). Hence to highlight the average changes in N100m amplitude with tone level and rise time, each data set was first normalized with respect to the N100m peak amplitude averaged across the five levels of the tones of 500 Hz and 2-ms rise time and recorded in a given subject and hemisphere. Then these normalized amplitudes from different subjects and hemispheres were averaged.

Figure 10 shows these average normalized N100m ampli-
ties at their very onsets. That not only the peak latency but also the peak amplitude, at those on the spike counts of single neurons therefore suggests effects of level and rise time on N100m peak amplitude with tone onset to that instant. The correspondences of the average function of the integral of rate of change of amplitude from delay between the measured latency and the estimated transmission instant of response generation is given by the difference between plateau amplitude reached at the end of the rise time. The generation, instead of level, a measure of the steady-state or a function of the stimulus amplitude at the instant of response given neuron with tones of different rise time can be brought the spike count versus tone level functions obtained from a time. As shown previously (Heil 1997b; Heil and Irvine 1998), the dynamic range increase systematically with increasing rise time. It is shorter rise times so that at high levels, N100m amplitudes tended to decrease most steeply with increasing rise time. It is also obvious, at least for short-rise-time tones, that the increase of N100m amplitude with tone level is steepest at 500 Hz, intermediate at 1,000 Hz, and shallowest at 2,000 Hz.

The systematic effects of level and rise time on N100m peak amplitude, described in the preceding text, are qualitatively similar to those seen in the spike count versus tone level functions of many cortical neurons, viz. those where such functions are monotonic (Heil 1997b). Here threshold level and dynamic range increase systematically with increasing rise time. As shown previously (Heil 1997b; Heil and Irvine 1998), the spike count versus tone level functions obtained from a given neuron with tones of different rise time can be brought into close register. This is achieved by plotting the responses as a function of the stimulus amplitude at the instant of response generation, instead of level, a measure of the steady-state or plateau amplitude reached at the end of the rise time. The instant of response generation is given by the difference between the measured latency and the estimated transmission delay $L_{\text{min}}$. Hence response magnitude can be considered as a function of the integral of rate of change of amplitude from tone onset to that instant. The correspondences of the average effects of level and rise time on N100m peak amplitude with those on the spike counts of single neurons therefore suggests that not only the peak latency but also the peak amplitude, at least of N100m, are determined by dynamic stimulus properties at their very onsets.

**FIG. 10.** Effects of tone level, rise time, and carrier frequency on N100m peak amplitude. For each subject and hemisphere, data points were first normalized with respect to the mean amplitude across all 5 levels of the 500-Hz tones of 2-ms rise time and then averaged across subjects and hemispheres. N100m peak amplitude tends to increase with increasing level (in dB SL) and to decrease with increasing rise time. The effects are most prominent at 500 Hz.

**Comparison with previous studies**

Several previous studies have demonstrated systematic influences of rise time, or rise time and level, on latencies and amplitudes of various components of AEPs (Barth and Burkard 1993; Brinkmann and Scherg 1979; Folsom and Aurich 1987; Hecox and Deegan 1983; Hecox et al. 1976; Kodera et al. 1979; Milner 1969; Onishi and Davis 1968; Pardo et al. 1999; Ruhm and Jansen 1969; Suzuki and Horiuichi 1981; but for contrasting results, see Liegeois-Chauvel et al. 1994). A few studies have also looked at the effects of these parameters on brain stem evoked potentials in anesthetized (e.g., Burkard 1991; Starr and Farley 1983) and awake animals (Phillips and Burkard 1999). While there is some disagreement with respect to details, the major findings of these studies are consistent with ours in that peak latencies decrease with increasing level and increase with increasing rise time and peak amplitudes increase with level and decrease with rise time (for review, see Hyde 1997). Furthermore consistent with previous results, we found that tone duration (plateaus of 35 vs. 135 ms) has no effect on N100m latency (Joutsiniemi et al. 1989), that monaural stimulation elicits larger N100m peak amplitudes in the contralateral than in the ipsilateral hemisphere (Mäkelä et al. 1993; Pantev et al. 1998; Reite et al. 1981), and that the average growth of N100m amplitude with stimulus level is steeper for lower than for higher frequencies, a fact attributed to deeper source locations for higher frequencies (tonotopic organization) (Antinoro et al. 1969; Pantev et al. 1995; for review, see Hyde 1997).

We have used our data to show that for tones shaped with cosine-squared rise functions, N100m and P50m peak latency form a rather invariant function of the acceleration of peak pressure at tone onset, a parameter that covaries with level and rise time. This is not to say that latency is mechanistically determined by that acceleration because stimuli which share a common acceleration at onset also share common initial time courses of the rate of change and of the peak pressure itself (Fig. 1). Latency may therefore also be determined by these stimulus parameters or a combination thereof. Nevertheless it can be safely concluded that N100m and P50m peak latencies are largely determined by dynamic stimulus properties at their very onsets. This must consequently also apply to peak amplitudes. Indeed, as shown here, the N100m peak amplitude varies systematically with stimulus level but also with rise time.

Hari and Mäkelä (1986, 1988) have conjectured that the synchrony of postsynaptic potentials, evoked by afferent input to the cortex, would depend on the speed of modulation (of frequency or amplitude) and would so affect N100m latency. Our data from auditory-nerve fibers (Heil and Irvine 1997) and auditory cortical neurons (Heil 1997a; Heil and Irvine 1998) show that the first-spike latencies of individual fibers/neurons decrease with increasing acceleration. Because of their curved nature, functions from different fibers/neurons will converge with increasing acceleration, thus leading to higher synchronization of first spikes, and probably also of postsynaptic potentials, across the neuronal population. Thus increased synchrony is a consequence of the increased rapidity of the transient but is likely not the cause, or at least not the sole cause, of decreasing N100m latency.
Latency versus acceleration functions obtained under different stimulus conditions and from different subjects are of rather similar shape as reflected in a similar exponent of the functions fitted to the latency versus acceleration functions. The functions are, however, displaced along the latency axis, reflecting differences in transmission delay $L_{min}$, and displaced along the acceleration axis, reflecting differences in transient sensitivity $AEP_{max(0)}$. The transient sensitivity was highest at 1 kHz, both for P50m and for N100m, i.e., latency versus acceleration functions obtained with that frequency are in a most leftward position, while those obtained with lower and higher frequencies would be in more rightward positions within the coordinate system. Thus for tones of any given acceleration (i.e., of fixed level and rise time), latency would be shortest for 1 kHz and would increase for lower and higher frequencies. In addition, because latency versus acceleration functions are curved and not straight, different functions converge with increasing acceleration. Therefore those latency increases with frequency distance from 1 kHz would be the steeper the lower the acceleration, i.e., the lower the level when rise time is fixed. Exactly such results have recently been observed for N100m (Roberts and Poeppel 1996; Stufflebeam et al. 1998).

Rejection of the fixed threshold model and functional implications

Because signals of cosine-squared rise function have practically identical initial time courses of the peak pressure when they share the same acceleration at their onsets (Fig. 1), one may argue that latency could be determined by the instant at which tones of identical acceleration at onset reach some low but common and fixed-amplitude threshold. Hence changes in latency with changes in level or rise time would then be brought about by changes in the time needed to reach that fixed-amplitude threshold. This fixed-amplitude threshold model has been proposed directly (e.g., Ruhm and Jansen 1969) or is implied indirectly (e.g., Brinkmann and Scherg 1979; Ross et al. 1999), although Onishi and Davies (1968) have pointed out one observation incompatible with it. Our data clearly show that this model is inadequate. The deviations of the measured N100m and P50m peak latencies from those predicted by the model are quite pronounced and systematic (Fig. 9F). In other words, the stimulus amplitude at which the N100m or P50m peak amplitudes are triggered is not constant, even for a given frequency, but varies systematically with the dynamics of the increase in stimulus amplitude, i.e., with rise time, with level, and likely with rise function. Furthermore the deviations of the measured latencies from the fixed threshold model are unlike those that would be expected if accommodation would operate. Accommodation would effectively raise the trigger amplitude when the pressure increases slowly so that latency versus rise time functions should be curved upward. Instead they are compressively nonlinear (Fig. 4, A and D). Hence the faster the increase in stimulus amplitude (peak pressure), the higher the trigger amplitude.

These phenomena are not restricted to cosine-squared rise functions or AEFs. A re-analysis (Heil, unpublished) of published data from suitable studies (Barth and Burkard 1993; Folsom and Aurich 1987; Hecox et al. 1976; Milner 1969; Onishi and Davis 1968; Ruhm and Jansen 1969; Suzuki and Horiuchi 1981) shows that for linear rise functions, latency of AEPs (Jewett’s wave V and N100) is an invariant function of the rate of change of peak pressure. Hence for these stimuli, latency is also determined by stimulus events at their very onset (see also Onishi and Davis 1968; Suzuki and Horiuchi 1981). And second, the deviations of the shape of the latency functions from the shape predicted by a fixed-amplitude threshold model are much the same as those described in the preceding text for cosine-squared rise functions.

There appear to be quite parallel phenomena in the visual system. Jaskowski (1993) has presented stimuli shaped with linear luminance increases of various rise times to human subjects whose task was to press a response button as soon as they detected the stimulus. He observed that the reaction time increased with increasing rise time when the peak luminance was held constant, while reaction time was constant for stimuli with the same rate of change of luminance. Jaskowski also suggested a model where reaction time behaves as onset latency, i.e., as the time interval from stimulus onset to the moment that an internal response crosses a critical value and where the internal response is directly proportional to luminance. However, the data illustrated are too noisy and too few to clearly decide whether that fixed-luminance threshold model is really appropriate.

The failure of a fixed-amplitude threshold model is noteworthy because in audiology AEPs such as the N100 are used, or promoted, as tools to estimate the pure-tone audiogram for a large and diverse target population, including medicolegal and industrial hearing-loss compensation claimants (Hyde 1997; see also Ross et al. 1999). Hyde has suggested that rise function is irrelevant and that rise times are important only in so far as they affect spectral splatter. It is therefore important to stress that our data show that the dynamics of the stimulus at tone onset, determined by level but also by rise time and by rise function, are absolutely critical for shaping N100m and P50m and likely other AEFs or AEPs. It should be kept in mind that such components are triggered by the increase in stimulus amplitude at tone onset, i.e., by a transient. Hence such components may be more useful as estimates of sensitivity to transients rather than of absolute threshold.

The potential integration times underlying P50m and N100m are given by the difference between measured latency and transmission delay and can be directly read from the ordinate of Fig. 9D. Depending on the rapidity of the amplitude increase, here on the acceleration at tone onset, integration times vary between near 0 ms and ~50–70 ms. In our data, 92% were shorter than 30 ms and 48% still shorter than 10 ms. While for short-rise-time tones most integration times were longer than the rise times, that percentage dropped to about half for 16-ms rise-time tones and to zero for 64- and 128-ms rise-time tones. Overall the integration times were shorter than the rise times for 62% of our combinations of rise times and levels. Therefore the peak amplitudes of N100m and P50m were triggered before these tones reached their steady-state levels. This raises doubts as to the validity of the concept of an amplitopic organization of the human auditory cortex. Such an organization has been suggested based on systematic changes in the position of the N100m equivalent current dipole with the level of tones shaped with 15-ms rise times (Pantev et al. 1989).
Comparison with single-neuron data and implications for envelope coding

As demonstrated in this paper, essentially all observations made on N100m and P50m are very similar to those made previously on the onset responses of single neurons from the auditory cortex of barbiturate-anesthetized cats (Heil 1997a,b; Heil and Irvine 1997, 1998). As expected, the data obtained from spikes of single neurons are much cleaner than those from AEFs: on average, variances of single-neuron data are one to two orders of magnitude smaller. Still, some favorable MEG measurements can yield variances as low as those from single neurons with rather sloppy timing precision (Fig. 6). The major difference between the human and the cat data is that the latency versus acceleration functions of the former are less steeply curved. However, the fact that in MEG thousands of neurons, many of which have characteristic frequencies different from the frequency of the tonal stimulus, contribute to the signal is unlikely to account for the difference in curvature. This is so because latency versus acceleration functions obtained from a given neuron with tones of different frequencies are displaced along the acceleration axis but have the same curvature (Heil 1997a). And a compound latency versus acceleration function, obtained by averaging such functions, would have the same curvature as that of each individual function. Nevertheless it is conceivable that the difference in curvature is due to differences in measuring methods and their underlying signals (dendritic currents in large populations of neurons vs. spikes of single neurons), or due to differences in state (awake vs. anesthetized), or in species.

The correspondences suggest that the observed properties of single neurons from the cat’s auditory cortex per se are not artifacts of anesthesia. As shown here, similar relationships exist in the human auditory cortex and involve thousands of neurons simultaneously. As detailed elsewhere (Heil 1997b; Heil and Irvine 1997, 1998), the single-neuron properties seem ideal not for coding steady-state SPL, but for tracking, in real time and with high fidelity, rapidly varying envelopes, such as, but not limited to, those occurring at tone onset. The present study suggests that much the same mechanisms operate in the auditory cortex of awake humans where they might be most useful to encode the rapidly varying envelopes characteristic of many sounds, including speech.

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REFERENCES


PARALLELS OF SINGLE-NEURON BEHAVIOR AND MEG SIGNALS


