Azimuth Coding in Primary Auditory Cortex of the Cat. II. Relative Latency and Interspike Interval Representation

JOS J. EGGERMONT
Departments of Physiology and Biophysics, and Psychology, The University of Calgary, Calgary, Alberta T2N 1N4, Canada

Eggermont, Jos J. Azimuth coding in primary auditory cortex of the cat. II. Relative latency and interspike interval representation. J. Neurophysiol. 80: 2151–2161, 1998. This study was designed to explore a potential representation of sound azimuth in the primary auditory cortex (AI) of the cat by the relative latencies of a population of neurons. An analysis of interspike intervals (ISI) was done to assess azimuth information in the firings of the neurons after the first spike. Thus latencies of simultaneously recorded single-unit (SU) spikes and local field potentials (LFP) in AI of cats were evaluated for sound presented from nine speakers arranged horizontally in the frontal half field in a semicircular array with a radius of 55 cm and the cat’s head in the center. SU poststimulus time histograms (PSTH) were made for each speaker location for a 100-ms window after noise-burst onset using 1-ms bins. PSTH peak response latencies for SUIs and LFPs decreased monotonically with intensity, and most of the change occurred within 15 dB of the threshold at that particular azimuth. After correction for threshold differences, all latency-intensity functions had roughly the same shape, independent of sound azimuth. Differences with the minimum spike latency observed in an animal at each intensity were calculated for all azimuth-intensity combinations. This relative latency showed a weakly sigmoidal dependence on azimuth that was independent of intensity level >40 dB SPL. SU latency differences also were measured with respect to the latencies of the LFP triggers, simultaneously recorded on the same electrode. This difference was independent of stimulus intensity and showed a nearly linear dependence on sound azimuth. The mean differences across animals for both measures, however, were only significant between contralateral azimuths on one hand and frontal and ipsilateral azimuths on the other hand. Mean unit-LFP latency differences showed a monotonic dependence on azimuth with nearly constant variance and may provide the potential for an unbiased conversion of azimuth into neural firing times. The general trend for the modal ISI was the same as for relative spike latency: the shortest ISIs were found for contralateral azimuths (ISIs usually 3 ms) and the longer ones for ipsilateral azimuths (the most frequent ISI was 4 ms, occasionally 5 ms was found). This trend was also independent of intensity level. This suggests that there is little extra information in the timing of extra spikes in addition to that found in the peak PSTH latency.

INTRODUCTION

Temporal response measures such as latency and interspike intervals have not attracted much attention as a potential cortical neural code for sound azimuth until recently (Brugge et al. 1996; Middlebrooks et al. 1994). First spike latencies of cortical neurons for stimuli with linear rise times largely reflect the rate of change of peak sound pressure at stimulus onset, whereas for stimuli with a cosine, squared rise time the latency reflects the acceleration of sound pressure. Latency-intensity functions become virtually identical when plotted as a function of the rate of change of SPL or as acceleration of SPL, suggesting a peripheral origin of this dependence (Heil 1997a,b). This description likely applies only to monaural stimulation and ignores the effects of interaural differences, which are the main determinants of an azimuth-dependent relative latency. Thus although an accurate code for this stimulus aspect seems provided in first spike latency, this measure or alternatively the poststimulus time histogram (PSTH) peak latency is defined by the experimenter with respect to stimulus onset, and this time reference is unknown to the animal. In general, one of the conditions for identifying certain response parameters as a useful code for the CNS is that such a code cannot in any way make use of features of the external stimulus such as time of presentation, frequency content, or position in space. Thus one cannot use latency as part of the stimulus-response features used in a panoramic code, but one may use interspike intervals, latency differences between neurons across a population, or time-dependent differences in firing probability (Middlebrooks et al. 1994). Alternatively one may use firing times of neurons relative to an internally available global time marker. Global membrane potential oscillations may potentially serve as such a clock. Hopfield (1995) proposed that analogue stimulus information can be represented by using the timing of action potentials with respect to an ongoing collective oscillatory pattern of activity. The computation in this representation is done by combining information through pathways with different delays. The analysis requires a coherence of the oscillation across a localized set of neurons, but such coherence in cortex is common at frequencies in a wide range from 1 to 100 Hz (Buzsáki and Chrobak 1995). The first spike in a burst will carry information in its timing, whereas additional stimulus information also will be carried in the number of action potentials that occur within a cycle of the reference oscillation. In Hopfield’s model, it is the relative timing between cortical units that conveys information about the stimulus components.

In the auditory cortex of the lightly ketamine anesthetized cat, the most dominant oscillation is in the 7- to 14-Hz frequency band. This oscillation can be synchronized easily with stimulus presentation and affects the firing times of the single units (Eggermont 1992; Eggermont and Smith 1995). Because the frequency and temporal characteristics of the spontaneous “spindle” oscillations and the click-induced
local field potential is generally considered to result from a phase reorganization of ongoing field activity (Lopes da Silva 1987; Sayers et al. 1974). The timing of these LFPs represent many of the stimulus properties in the same way as single-unit firings do. For instance, temporal modulation transfer functions, which represent the capacity of neurons to follow AM of various frequency or clicks with varying repetition rates, are the same for single-unit firings and for LFPs (Eggermont and Smith 1995). Under these conditions, unit latencies in response to clicks are always longer than LFP latencies. For tone bursts, the response can consist of two components, one with a latency shorter than the LFP and the other with a somewhat longer latency (Eggermont 1996). LFPs are largely an expression of excitatory synaptic activity (Mitzdorf 1985) but single-unit activity in addition may be dependent on inhibitory effects that determine if and when a spike will be initiated. We previously have demonstrated that LFPs predict thresholds and characteristic frequencies (CFs) of recording sites quite accurately and that they are reasonably localized in their response properties (Eggermont 1996). However, LFPs represent a more general phenomenon than the single-unit firings because they include postsynaptic activity from cells that remain subthreshold and thus may serve as an internal time reference for a large number of neurons. Thus LFPs will indicate in what time frame a cell potentially can fire, but this is a necessary but not sufficient condition for the cell to actually fire in response to a stimulus.

Spike times resulting from interaural stimulus differences likely provide the dominant coding information for sound localization up to the level of the inferior and superior colliculi. For instance, interaural latency differences to transient sound and those derived from interaural phase differences for low-frequency continuous tones are converted into place information in the medial superior olive (Carr 1993; Yin and Chan 1990). It also can be argued that interaural intensity differences (IIDs), which are processed in the lateral superior olive (LSO), cause temporal differences in the spike trains from both ears because of the systematic changes in first spike latency with intensity (Hirsch et al. 1985; Irvine 1986; Yin et al. 1985). Therefore an IIID will give rise to ipsi- and contralateral spike patterns that differ systematically in the timing of the spikes. It recently has been demonstrated in vitro (Wu and Kelly 1992) that LSO neurons are sensitive to physiologically plausible time-of-arrival differences of spikes induced by electric stimuli applied ipsi- and contralaterally to the trapezoid body. This corroborates the idea that IIDs also may be processed on the basis of spike time differences. Similarly, interaural phase differences, either in the low-frequency carrier or in the AM waveform of a high-frequency carrier or in any other complex sound, are transformed into interaural time differences by the precise phase-locking of the auditory nerve fibers (Joris and Yin 1992) and the enhancement in this accuracy provided by certain populations of neurons in the cochlear nucleus (Frisina et al. 1985). Combining phase differences for different frequencies (components of a complex signal) allows the auditory system to reconstruct interaural delays without ambiguity (Yin and Kuwada 1984). Thus both interaural timing (ITD) and intensity differences likely are evaluated on basis of a spike timing information.

In primary auditory cortex, cell responses show dependencies on ITD and IID similar to those found in the brain stem and midbrain (Brugge 1988; Irvine et al. 1996). For primary auditory cortex (AI), Reale and Kettner (1986) showed that the mean response latency was affected by both contralateral and ipsilateral ear sound pressure level (SPL). In most neurons, latencies decreased with increasing contralateral as well as ipsilateral intensity level, but in some neurons, ipsilateral sound level had hardly any effect on latency. This was echoed by Semple and Kitzes (1993) who found that under binaural stimulus conditions, the response latency of neurons in AI largely reflected the contralateral ear SPL. They also noted that, for nonmonotonic units, latency continued to decrease even if the number of discharges was reduced with increasing SPL. For virtual acoustic space stimulation, Brugge et al. (1996) also reported a monotonic decrease of latency with intensity. Using a virtual space auditory source, Brugge et al. (1996) found that response latency varied across the receptive field by 3–5 ms and occasionally up to 20 ms. The shortest latencies tended to occupy the “the effective receptive field” area in the contralateral field, close to the acoustic axis.

In the exploration of a panoramic code of azimuth in anterior ectosylvian sulcus (AES) (Middlebrooks et al. 1994), the timing of the spikes in addition to the onset spike played an important role in the performance of the neural network prediction. In the present paper, I also explore the specific directional information that may be present in interspike intervals as additional to those present in mean spike latency.

In the present paper, I show that relative latencies, especially with reference to the simultaneously recorded LFPs, may allow the construction of a level tolerant code for azimuth in primary auditory cortex.

**METHODS**

The care and the use of animals reported on in this study was approved (No. P88095) by the Life and Environmental Sciences Animal Care Committee of the University of Calgary.

The methods are identical to those reported in the companion paper (Eggermont and Mossop 1998). Briefly, cats were kept under light anesthesia with intramuscular injections of 2–5 mg·kg⁻¹·h⁻¹ of ketamine so as to keep them in an areflexive state. Light anesthesia refers to an areflexive state with light breathing and good spontaneous activity. Noise bursts were presented from an array of nine loudspeakers, separated by 22.5°, placed in a semicircle around the cat’s head with radius of 55 cm in the horizontal plane. Calibration and monitoring of the sound field was done using a B&K (type 4134) microphone placed directly above the animal’s head, facing the loudspeakers. Using tonal stimuli, CF and tuning curve of the individual neurons were determined. After the CF was determined, 100-ms pseudorandom noise bursts with 5-ms linear rise-fall time were presented once per second from a randomly selected speaker. The pseudorandom noise itself was further randomized by drawing from 10 different seed numbers for the noise generation. For each azimuth, 50 noise bursts were presented, thus including five repetitions each of the 10 different random sequences, and the entire stimulus ensemble for one intensity level lasted 450 s. At each azimuth the same set of 10 random
RELATIVE LATENCY REPRESENTATION OF SOUND AZIMUTH

noise bursts was presented. Intensity levels were presented interleaved usually starting at 75 dB SPL, then 55, 35, and 15 dB and subsequently at the intermediate intensities. Around threshold, 5-dB steps were made. The speakers at −90, −67.5, and −45° will be referred to as contralateral, those at −22.5, 0, and 22.5° as frontal, and those at 45, 67.5, and 90° as ipsilateral. Consequently, contralateral units were defined as those having a best azimuth (at threshold) or preferred azimuth (at 25 dB above threshold) for speakers at −90, −67.5, and −45°. Frontal units had a best or preferred azimuth at −22.5, 0, and 22.5°. Ipsilateral units had best or preferred azimuths at 45, 67.5, and 90°. Omnidirectional units were defined as having a bandwidth at 25 dB above threshold of ±180°, i.e., a 50% response criterion was obtained for all speaker positions. Multipeaked units had more than one well-defined peak within the response area, and the highest peak at 25 dB above the lowest threshold was used for the assignment of preferred azimuth.

For each azimuth, 50 noise bursts were presented. Intensity levels were presented interleaved usually starting at 75 dB SPL, then 55, 35, and 15 dB and subsequently the intermediate intensities. Around threshold, 5-dB steps were made. Threshold levels were estimated as the highest stimulus level that did not produce visible noise-burst locked activation as judged from the PSTH. Best azimuth was defined as that azimuth that resulted in the lowest threshold.

In general, the recorded signal on each electrode contained activity of more than one neural unit. The responses of different units were separated with a spike-sorting algorithm. The electrode signals were also band-pass filtered between 10 and 100 Hz to obtain spike-free signals of ongoing LFPs. These signals were passed through Schmitt triggers set at ±2 SD below the mean value (at about −1 μV) of the ongoing signal during silence. The spikes of these signals were processed in the same way as single-unit spike data. We have shown previously (Eggermont and Smith 1995) that these level crossings faithfully represent most of the temporal response properties of the single units recorded at the same electrode. Recordings were generally made between 300 and 1,000 μm below the cortex surface.

Poststimulus time histograms (PSTHs) were made for neural activity in response to noise bursts from each speaker location for a 100-ms window using 1-ms bins. PSTHs were smoothed with a rectangular 5-bin window to facilitate peak latency readings. Latency differences were computed from the PSTHs for single units and LFP triggers. Both response latencies include a 1.5-ms acoustic delay. The response latencies for the digitally low-pass filtered LFPs were corrected for a 5-ms filter delay.

All calculations were performed using MATLAB 5 on a Macintosh Power PC. Statistical analyses were performed using Statview 4.5 and additional data plotting was done with Horizon and Powerpoint software.

RESULTS

Recordings were obtained in 13 juvenile (>33 days) and 13 adult cats (>70 days). In only five of the juvenile cats was a complete intensity series obtained, so the data from 58 MU recordings and 36 LFP recordings, comprising 102 isolated single units, presented here are for 18 cats. Except for minor differences in absolute latencies the two age groups showed similar results. The groups are the same as used in the companion paper (Eggermont and Mossop 1998). At 25 dB above threshold, 40 single units (SU) were tuned to contralateral azimuths (−90 to −45°), 18 were tuned to frontal azimuths (−22.5 to +22.5°), and 22 to ipsilateral azimuths (45–90°). The remaining 22 units were not tuned to azimuth, i.e., had a 50% bandwidth of 180°.

CFs obtained were uniformly distributed from 3 to 25 kHz. LFP latencies, independent of azimuth, showed a negative correlation with CF with slopes of the regression lines between −0.3 and −0.5 (CF in kHz). In contrast, SU latencies were independent of CF (r² < 0.003) for all azimuths. As a result, the latency differences with LFPs, again independent of azimuth, showed a positive correlation with CF with slopes of the regression lines between 0.3 and 0.53 (CF in kHz).

Figure 1 shows SU dot displays and LFP-trigger displays and the corresponding multiunit (MU; i.e., all the isolated SUs combined) and LFP-trigger PSTHs for two simultaneous recordings ~1 mm apart in a 75-day-old cat at a depth of 990 μm below the surface in the 9-kHz iso-frequency strip. Only LFP triggers for electrode 1 are shown, those for electrode 2 were similar. The intensity range used was from 5 to 75 dB SPL. At the lowest stimulation levels (5 and 15 dB), notable spontaneous activity is seen for the SUs on both electrodes; high stimulus levels produce a nearly complete suppression of spontaneous activity after the 20-ms duration on-response. For electrode 1 (Fig. 1, A and E) no obvious directionality is seen at high stimulus levels, albeit that there are systematic latency differences. From 35 dB SPL down, the response to sound from the frontal speaker locations becomes clearly longer in latency and less robust: this holds for the SU (dot display), MU (PSTH), and LFP triggers. Note that the SU- and MU-response duration at near threshold values, which is 25 dB for the frontal speaker and 15 dB for the contralateral speakers, is prolonged compared with that at suprathreshold levels. This tendency of longer duration bursting and/or more latency jitter close to threshold values was a general finding for the type of stimulus we used. It corresponds likely with a reduced postactivation suppression, which at higher levels terminates the response after ~10–20 ms. Response latencies, best seen in the PSTH (Fig. 1E), appear to be shortest for contralateral stimulus locations across the intensity range. For electrode 2 (Fig. 1, B, C, and F), the response at high-intensity levels has a dominant omnidirectional late component with latency ~80 ms and a PSTH peak at 90–95 ms, whereas there is a weak short-latency (~35 ms) component that tends to be dominantly ipsilateral for unit 2.3. For lower intensities, the short-latency response increases in strength, becomes maximal at 25 dB SPL for both SUs and splits up in two activity areas at 15 dB. The LFP triggers (Fig. 1, D and G) at levels >25 dB SPL show secondary responses (at 60–70 ms latency) that do not have a correlate in the MU response, whereas the short latency LFP triggers correlate very well with the onset spike activity on electrode 1. The LFP triggers show a basic change from an omnidirectional response at high levels to a contralateral response at 15 dB SPL.

Peak response latencies for SUs and LFPs change monotonically as a function of intensity and do so especially within 15 dB of the threshold at that particular azimuth. The latency changes for the MU activity on electrode 1 (as shown in Fig. 1E) are larger than those for the LFP triggers (Fig. 1G). Figure 2, A and B, shows this dependency; azimuths for ipsilateral sites are indicated with positive angles, for contralateral sites with negative angles and the frontal speaker is at 0°. Note that all latency-intensity functions have
RELATIVE LATENCY REPRESENTATION OF SOUND AZIMUTH

FIG. 1. Single-unit firing and local field potentials (LFP)-trigger dot displays as a function of stimulus azimuth and sound intensity. A: activity of a single unit on electrode 1. B and C: activity of 2 single units on the 2nd electrode. D: LFP triggers from electrode 1. Individual intensity plots are for a time window of 100 ms after stimulus onset and the activity for 9 speaker locations separated by 22.5° from far contralateral (−90°) to far ipsilateral (90°) are presented. E–G: poststimulus time histograms (PSTHs) with 1-ms bins for the spike activity represented in 1. A 5-point smoothing was applied. MU activity for electrodes 1 and 2 is shown in E and F and LFP-trigger activity in F. Bimodal PSTHs at higher intensity levels in E are not the result of different latencies for the individual units but rather present 2 favored firing times, as also visible for the single unit in A.

FIG. 2. Latency-intensity relations for multiunit and LFP triggers for the recordings shown on Fig. 1, E and G. Peak latency readings were taken, this explains the different latencies at high intensities for ipsilateral, where the bimodal PSTH has its maximum for the 2nd peak, compared with contralateral sound locations where the PSTH is maximum for the 1st peak.

roughly the same shape (as also shown by Heil 1997a,b for other stimulus conditions).

For each animal, the azimuth-intensity combinations for which the minimum latencies occurred were calculated. Per intensity, the average speaker positions, rounded to the nearest speaker azimuth, that produced the shortest PSTH peak response latencies are shown in Fig. 3. Data are presented for all cats combined and also for those cats that only had contralaterally sensitive units, based on their threshold azimuth preference for firing rate (Eggermont and Mossop 1998). Across all cats, minimum latencies were found on average for stimuli presented in the contralateral hemifield. The sound position for which minimum latencies were found was independent of stimulus intensity. One observes that contralateral units (best azimuths at −90, −67.5, and −45°, 66/102 units in 10/18 cats) on average had their minimum latencies at the same azimuths as all cats combined, except for the two lowest intensities where the minimum latency azimuth was more contralateral.

Because the shape of the functions was rather similar across animals, it was assumed that, after correction for average minimum latency differences, the pooled data across cats would be representative for the behavior of the neural population in a single animal. The minimum latencies per azimuth/intensity combination could serve as global reference points for extracting the spatial information contained in SU response latencies. Latencies for individual SUs were calculated relative to the minimum latency values per azimuth/intensity combination observed for the particular animal from which the units were recorded. For each azimuth/intensity combination, there was always at least five units that showed the minimum latency for that intensity. Thus at each azimuth/intensity combination, relative latencies can be calculated with respect to that minimum. Figure 4A shows the average relative latency and standard errors for all units combined as a function of stimulus azimuth for stimulus levels below and above 40 dB SPL. Above 40 dB SPL no significant effect of intensity on relative latency was found. For this high-intensity group, the relative latencies for azimuths ranging from +22.5° to +90° were not significantly different from each other and neither were those for azimuths −67.5° to 0° (paired t-test, P > 0.05). For low intensities, a strong azimuth dependence is evident. The relative latencies for frontal azimuths were not significantly different from...
those for ipsilateral azimuths but were significantly (paired t-test, $P < 0.05$) larger than those for contralateral azimuths. Figure 4B shows, across all intensities, the average relative latencies for the three groups of directionally sensitive units. At contralateral sound azimuths, relative latencies for units with ipsilateral best azimuth were significantly longer (analysis of variance, post hoc Scheffe test, $P < 0.05$) than for units with contralateral and frontal best azimuth.

An alternative evaluation of relative latencies may be based on a comparison of spike latencies with the latencies of the LFPs simultaneously recorded on the same electrode. In this particular study, we used the latency of the LFP triggers (which were shown to capture much of the time-dependent properties of the LFPs) (Eggermont and Smith 1995) as the reference. For all units at each of the nine azimuth positions and across all intensities, the spike latencies are correlated with the latency of the LFP triggers. Figure 5 shows three examples for speaker locations at $-45^\circ$, $0^\circ$, and $+45^\circ$. The range of unit latencies was generally larger than that for the LFP triggers. The $r$’s ranged from 0.3 (frontal speaker, Fig. 5B) to 0.46 (ipsilateral speaker, Fig. 5A), and the slopes of the regression lines were all close to and not significantly different from 1 (range 0.885–1.115).

The latency difference with the LFPs is, as might be expected, largely independent of stimulus intensity. For the
three speaker locations at 45, 0, and −45°, this is illustrated in Fig. 6, A–C. Linear regression analysis for all azimuths showed that slopes of the regression lines were not significantly different from 0 (range 0.00015–0.039) with r²'s in the range of 10−7−6.10−3. This intensity independence is important because a code based on this latency difference thus would be level tolerant.

Because of the intensity independence, latency differences (mean and standard errors) between units and LFP triggers were collapsed across intensity and displayed as a function of azimuth for the three groups of azimuth-sensitive units (Fig. 7). Contralateral units showed the smallest latency difference of ~5–6 ms, with a modest sigmoidal dependence on azimuth. Minimum latency differences for contralateral units were found for contralateral azimuths. The latency differences for ipsilateral azimuths (speakers at 45, 67.5, and 90°) did not differ significantly (P = 0.54) from the frontal azimuths (speakers at −22.5, 0, and 22.5°) but were significantly smaller (P = 0.006) than for contralateral speaker positions (−90, −67.5, and −45°). For contralateral units, the latency differences for frontal speakers were significantly longer than for contralateral sound positions (P = 0.02).

For units with a frontal best azimuth, the overall latency differences were larger and in the range of 7–10 ms, with minimum values found for frontal azimuths, but these differences were not significant. Ipsilateral units showed much larger latency differences, between 15 and 22 ms, with minimum values in the ipsilateral field. Pooling across all units, where the number of contralateral units dominated, the latency difference at −90° was significantly larger (paired t-test, P < 0.05) than those for frontal and ipsilateral azimuths (−22.5° to +90°). No other pairwise comparisons showed a significant difference.

FIG. 7. Mean and SE of the latency difference with LFP triggers for 3 groups of azimuth-sensitive units. Minimum latency differences for each group are found for speaker locations for which that group is most sensitive.

FIG. 8. Azimuth dependence of latency differences relative to to minimum population latencies and to LFP triggers. Regression lines calculated through the individual data points also are drawn in. For the latency difference with LFP triggers, the linear approximation fits the mean data curve quite well. For the relative latency difference to population minima, the linear dependence does not hold for ipsilateral azimuths.
A comparison between relative unit latencies (reference point is minimum latency per intensity and azimuth) and unit-LFP latency differences is shown in Fig. 8. One observes that the dependence on azimuth is, except for an azimuth-independent shift of 3 ms, largely similar for relative unit latency (○) and unit-LFP latency difference (■). The unit-LFP latency differences and the relative latencies were correlated positively with azimuth. The linear regression lines calculated for all the individual data points (drawn in for comparison) show a slightly steeper (not significant) slope for the relative latency data. The relative latencies were positively correlated with the unit-LFP latency difference for all azimuths (r²s ranging from 0.18 at +67.5° to 0.48 at −45°).

**Interspike intervals**

Most responses to a 100-ms noise burst consist of isolated spikes or spike pairs. Rarely were more than four spikes observed. One of the more responsive recordings served as the example in Fig. 1, yet for SU records, the number of interspike intervals (ISI) <50 ms was very small and not concentrated on a particular interval and did not allow a comprehensive analysis. Most responses consisted of isolated spikes. The recording shown in the example of Fig. 1A of the companion paper (Eggermont and Mossop 1998) gave a sufficient number of intervals especially for two of the three units to allow a detailed description of the azimuth dependence. ISI histograms and autocorrelograms were computed separately for these two SU units and appeared to be very similar to each other across intensity and azimuth. Therefore the ISI histograms and autocorrelograms of the individual units were superimposed and both are shown as a function of azimuth and intensity in Fig. 9. For each intensity, the ISI histograms (□) are scaled to the maximum of the correlograms (■) for the most responsive of the nine sound azimuths. For most of the data, the correlogram is very similar to the ISI histogram, suggesting that within the 50-ms analysis window the vast majority of the responses are either isolated spikes (which are not represented in this analysis) or spike pairs. The most frequent ISI is 3 or 4 ms, and across all intensities the ISIs for contralateral azimuths are the shorter ones. At low-intensity levels, most of the spike pairs occur for contralateral azimuths; at 20 and 25 dB, the units also start to respond with spike pairs for the far ipsilateral azimuths until at 45 and 55 dB SPL, there is a fairly homogenous response across all azimuths. The ISI histograms appear to be somewhat more selective than firing rate at low-intensity levels largely because frontal

![Fig. 9](https://example.com/fig9.png)

*Fig. 9*. Interspike-interval (ISI) histograms as a function of sound azimuth for a series of stimulus intensities. At low-intensity levels the dominant activity is for contralateral azimuths. For each intensity, the ISI histograms (□) are scaled to the maximum of the correlograms (■) for the most responsive of the 9 sound azimuths.
azimuths do not produce spike pairs until levels of 45 dB are reached but do produce isolated spikes (Figs. 1A and 2A in Eggermont and Mossop 1998).

Ten of the 53 recordings gave acceptable ISI histograms for one or two of the constituent SUs, the behavior was generally predictable from the firing rate of the units: the higher the firing rate, the larger the number of ISIs. The general trend for the modal ISI was the same as for absolute and relative spike latency: the shortest interspike intervals were found for contralateral azimuths (usually 3 ms) and the longer ones for ipsilateral azimuths (most frequent ISI 4 ms, occasionally 5 ms).

**Discussion**

The results have shown that relative latency, either within a global pool of units or between units and the LFPs recorded on the same electrode, shows a linear to weakly sigmoidal dependence on azimuth, especially for units with contralateral best azimuth. The amount of change in latency with azimuth and the finding of shortest latencies in the contralateral field both confirm those described by Brugge et al. (1996). In ~20% of the recordings, firing activity was sufficiently strong to produce spike pairs and allow the calculation of ISI histograms. The distribution of relative latency and ISI across azimuth was less dependent on intensity than for the corresponding firing rates (Eggermont and Mossop 1998), but otherwise showed the same azimuth preference at 25 dB above threshold.

**LFPs and unit firing**

I have used the peak latency of the PSTH instead of first-spike latency used in Hopfield’s (1995) computation scheme. In situations without spontaneous activity, as is usually the case under barbiturate anesthesia, unit responses to noise bursts are crisp and first spike latency is defined readily. Under ketamine anesthesia, as used in the present study, considerable spontaneous activity exists, and defining first-spike latency is impossible without exactly defining the window where it could happen. Because this is unknown, the results will be extremely biased. Peak PSTH latency is easy to measure and uniquely defined. Bin height in the PSTH results from both first-spike latency and any subsequent ISIs. This ambiguity means that peak latency may be less sensitive to stimulus azimuth than first spike latency. However, the nervous system cannot reliably estimate first-spike latency when stimulus onset is not known! The only thing that works under such conditions is a reliable coincident (or synchronous) firing of a small group of units to distinguish spontaneous activity from activity resulting from a stimulus. This is a mechanism that will result in an estimate similar to the PSTH of a SU or MU.

The latency-intensity functions in Fig. 2 show two different features, one is the parallel upward shift with azimuth at higher intensities and the other is a shift along the SPL axis mostly visible at low intensities. The shift along the intensity axis is likely related to the azimuth-dependent threshold and may be related to the rate of change of the SPL at those levels (Heil 1997a), and the functions can be made to overlap by shifting them in relation to their threshold difference with the 67.5° curve. The remaining upward shift in azimuth-dependent latency is likely the result of interaural intensity differences (IID) and is much larger for the MU latencies than for the LFP latencies. Because the negative LFP components are compound, excitatory postsynaptic potentials from a large number of cells (Mitzdorf 1985), longer azimuth-dependent latencies for MUs compared with LFPs are likely the result of inhibition. Thus both peripheral factors, dominant near threshold, and central factors (related to IID) will play a role in determining latency.

**Comparison with other studies**

Latency-place representations, based on the relative time-of-arrival of action potentials at different cortical positions, are a potential code for azimuth (Brugge et al. 1996; Middlebrooks et al. 1994). Such codes may use a competition of excitation and inhibition that depends both on latency mean and variance (Cariani 1995). Shorter latency activity may excite cells, whereas longer latency spikes may be subject to inhibition (both lateral inhibition and postactivation suppression) resulting from the activity of the short-latency spikes. In a hypothetical situation where two types of units exist, one with shortest latencies to contralateral sound and one with shortest latencies to ipsilateral sound, a simple decision rule for sound location could be based on the shortest latency activity. Unfortunately, latencies for ipsilateral units in our study were always longer than those for contralateral units especially for ipsilateral azimuths. This makes a decision rule as suggested earlier and based on intracortical activity comparison nearly impossible. In individual auditory cortical hemispheres, the shortest latencies are likely those for contralaterally sensitive units. Thus comparisons of the type suggested above could only rely on converging activity from both hemispheres where each hemisphere’s contralaterally “tuned” neurons may act in complementary fashion. The shortest latency would indicate unambiguously from which hemisphere the sound originated. A scheme of this sort would not need the ipsilateral, frontal, or omnidirectional units but could rely exclusively on the contralateral units, which are more sensitive because of the amplification by the pinna resonance.

Given that callosal fibers originating from contralaterally sensitive cells in for instance the right AI may terminate on noncontralaterally tuned cells in the left AI (Imig and Brugge 1978; Imig et al. 1982; Innocenti 1986), a comparison between the latencies of contralateral units in each hemisphere is unlikely to happen in primary auditory cortex. What the callosal fibers in fact might do is increase the latency of frontal and ipsilateral units by providing a short-latency (2–4 ms) but long-lasting inhibition (Kitzes and Doherty 1994). A latency difference of this magnitude was in fact observed for the frontal units in this study, whereas the ipsilateral units had on average a 10–15 ms longer latency than the contralateral units.

The lesion experiments of Jenkins and Merzenich (1984) have suggested that binaural sound localization does not require the connections of AI with other auditory fields in the same hemisphere, the connections to contra-
lateral cortical fields, and the descending connections to the IC. This would suggest that the only cells needed for a frequency-specific representation of the contralateral hemifield in AI are the contralateral cells. Potential evidence for an, albeit weak, projection from AI to the superior colliculus (Winer 1992) together with a more potent one from AES (Stein and Meredith 1993) have been demonstrated. It has also been shown that activity from AES is required for multimodal cells in the superior colliculus to respond to sound (Stein and Meredith 1993). However, the longer latencies of firings in AI compared with those in the superior colliculus, seem to make a simple gating process of activity in the superior colliculus unlikely. In awake monkeys, very long latencies in superior colliculus were reported (Jay and Sparks 1984) that potentially allow AI activity to interact with this activity.

Decoding relative latencies

Membrane potential oscillations, specifically the 40-Hz gamma band oscillation, have been proposed as an internal reference for the measurement of relative latencies (Hopfield 1995). In this study, we have used the LFPs that are generated by cortical pyramidal cells and are related to the oscillations in the 7- to 14-Hz band. Previously we had shown that the LFPs possess similar, but not identical, temporal properties as SUs in AI (Eggermont and Smith 1995). Both LFP latencies and spike latencies show a similar intensity dependence. As shown, the latency difference between the two measures is intensity independent and thus can serve as a level tolerant code. Across all units the relation between average unit-LFP latency difference is weakly sigmoidal, but significant differences were restricted to those between far contralateral (-90°) and frontal and ipsilateral azimuths (-22.5 to +90°).

The decoding stage that I propose makes use of the fact that the neurons have a subthreshold membrane potential oscillation that is synchronized with the one for the encoding neurons. Afferent spikes will fire the cell most efficiently if they are present at the phase of the oscillation that is closest to threshold. Because the spikes are delayed with respect to the local field potentials, a detector of such delays would require either advancing spikes (through faster conducting axons) or alternatively delaying field potentials. The LFP phase-delays, demonstrated for the alpha-rhythm, can amount to 1–2 ms per 0.3 mm within a cortical area (Golomb 1998; Lopes da Silva 1987). Thus in this decoding model, the neural correlator between the LFP and spikes is the receiving cell itself by virtue of the fact that its subthreshold membrane potential oscillation evoked by the stimulus is globally available and shows a “delay map.”

ISI-interval coding

ISIs generally showed the same azimuth preference as overall firing rate (Eggermont and Mossop 1998). The paucity of ISIs in the majority of units shows that for many neurons in the sample the response consists of a single spike. Only in 20% of the recordings were firing rates high enough to result in a sufficient number of spike pairs to make construction of ISI histograms meaningful. In these cases the most frequent ISIs were either 3 or 4 (occasionally 5) ms, with at most 1–2 ms difference between contralateral and ipsilateral azimuths. This suggests that azimuth-specific ISI patterns are likely not common in the cat’s AI under light ketamine anesthesia. It also indicates that PSTH peak latencies largely reflect the average first spike latency. This also suggests that there is little extra information in the timing of spikes after the first spike for our data. Neural network based decoding of the activity patterns in the AES as a function of azimuth has suggested that the probability of firing within a 40-ms window after first spike latency contributes to the accuracy of the prediction of sound azimuth (Middlebrooks et al. 1994). This can mean two things; either that only the probability of firing matters and consequently that poststimulus firing times are largely independent or that specific patterns in SU firing are important as an azimuth code. For primary auditory cortex, no support for the latter possibility was obtained in the present study.

Conclusions

In summary, relative latency values referenced to population minima or to the local field potential show a level tolerant representation of stimulus azimuth especially at level >40 dB SPL. The differences across azimuth, however, are only significant between contralateral (-90, -67.5, and -45°) and other azimuths for relative latency in reference to a population minimum and between far contralateral (-90°) and azimuths between -22.5 and +90° for latency differences with the LFP. Compared with firing rate and synchrony measures (Eggermont and Mossop 1998), relative latency codes performed worse in the discrimination of frontal azimuths (between -22.5 and +22.5°) at intensity levels >40 dB SPL. On the other hand, mean unit-LFP latency differences show a monotonic dependence on azimuth with nearly constant variance and provide the potential for an unbiased conversion of azimuth into neural firing times.

G. Smith provided valuable suggestions throughout the experiment. D. Bowman, K. Ochi, and M. Kenmochi assisted with the data collection. J. Mossop and J. Schnupp commented on an earlier version of the manuscript.

This investigation was supported by grants from the Alberta Heritage Foundation for Medical Research and the Natural Sciences and Engineering Research Council of Canada.

Address for reprint requests: Dept. of Psychology, The University of Calgary, 2500 University Dr. N.W., Calgary, Alberta T2N 1N4, Canada.

Received 16 October 1997; accepted in final form 8 July 1998.

REFERENCES


Cariani, P. As if time really mattered: temporal strategies for neural coding