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Temporal Nonlinearity During Recovery From Sequential Inhibition by Neurons in the Cat Primary Auditory Cortex

Kyle T. Nakamoto,[2] Jiping Zhang,[1,3] and Leonard M. Kitzes[1,2]
[1]*Departments of Anatomy and Neurobiology and* [2] *Cognitive Science, University of California, Irvine, California; and* [3]*Department of Biology, School of Life Science, East China Normal University, Shanghai, People's Republic of China*

Nakamoto, Kyle T., Jiping Zhang, and Leonard M. Kitzes. Temporal nonlinearity during recovery from sequential inhibition by neurons in the cat primary auditory cortex. *J Neurophysiol* 95: 1897–1907, 2006. First published December 7, 2005; doi:10.1152/jn.00625.2005. Auditory stimuli occur most often in sequences rather than in isolation. It is therefore necessary to understand how responses to sounds occurring in sequences differ from responses to isolated sounds. Cells in primary auditory cortex (AI) respond to a large set of binaural stimuli when presented in isolation. The set of responses to such stimuli presented at one frequency comprises a level response area. A preceding binaural stimulus can reduce the size and magnitude of level response areas of AI cells. The present study focuses on the effects of the time interval between a preceding stimulus and the stimuli of a level response area in pentobarbital-anesthetized cats. After the offset of a preceding stimulus, the ability of AI cells to respond to succeeding stimuli varies dynamically in time. At short interstimulus intervals (ISI), a preceding stimulus can completely inhibit responses to succeeding stimuli. With increasing ISIs, AI cells respond first to binaural stimuli that evoke the largest responses in the control condition, i.e., not preceded by a stimulus. Recovery rate is nonlinear across the level response area; responses to these most-effective stimuli recover to 70% of control on average 187 ms before responses to other stimuli recover to 70% of their control sizes. During the tens to hundreds of milliseconds that a level response area is reduced in size and magnitude, the selectivity of AI cells is increased for stimuli that evoke the largest responses. This increased selectivity results from a temporal nonlinearity in the recovery of the level response area which protects responses to the most effective binaural stimuli. Thus in a sequence of effective stimuli, a given cell will respond selectively to only those stimuli that evoke a strong response when presented alone.

INTRODUCTION

In a natural environment, stimuli rarely arrive in isolation; they tend to consist of sequences of sounds such as speech and the gurgling of water in a stream. Psychophysical studies have demonstrated that the perception of a sound can be altered by a preceding sound. For example, a complex set of perceptual phenomena, the precedence effect, occurs when sounds are separated by interstimulus intervals (ISIs) <10 ms, although interactions among stimuli can occur over a longer time period for stimuli of longer duration (Blauert 1997; Gilkey and Anderson 1997; Litovsky et al. 1999; Zurek 1987). Psychophysical studies have demonstrated that successive sounds occurring at longer intervals can also influence perception (Grantham and Wightman 1978; Perrott 1982). These psychophysical studies demonstrate that auditory perception can be altered by sequences of sounds separated by tens to hundreds of millisec-

onds. The purpose of the present study was to examine the effect of ISI on responses of units in primary auditory cortex (AI) to the second stimulus of pairs of binaural stimuli.

More than 90% of AI cells are sensitive to the interaction of level at the two ears (Kelly and Judge 1994; Semple and Kitzes 1993a; Zhang et al. 2004). AI neurons respond to a wide range of binaural stimuli presented in isolation (Clarey et al. 1994; Imig et al. 1990; Irvine et al. 1996; Nakamoto et al. 2004; Semple and Kitzes 1993a,b; Zhang et al. 2004). Stimuli at either ear can be excitatory, inhibitory, or evoke a level-dependent combination of excitation and inhibition. A level response area consists of responses evoked by stimuli of the same frequency that differ systematically in inter-aural level (ILD) and average binaural level (ABL). A general feature of these level response areas is a contiguous set of preferred binaural combinations (PBC) of levels at the two ears that evokes the largest responses from an AI cell. A change in level at either ear that moves the stimulus out of the PBC results in a reduced response (Semple and Kitzes 1993a,b; Zhang et al. 2004).

The occurrence of a preceding stimulus can reduce the entire level response area (Reale and Brugge 2000; Zhang et al. 2005). The magnitude of such sequential inhibition varies systematically in a nonlinear manner across the level response area. (We use the phrase "sequential inhibition" to refer to the impact of a preceding stimulus on the response to a succeeding stimulus and the term "inhibition" to refer to the reduction of a response with no implication of a mechanism causing the reduction.) For a given preceding stimulus, the inhibition of responses to stimuli within the PBC is least; the inhibition increases progressively for stimuli that are progressively more remote from the PBC (Zhang et al. 2005). The ability of a preceding binaural stimulus to inhibit the response to a succeeding binaural stimulus depends on its proximity to the PBC rather than on its absolute binaural levels (Zhang et al. 2005). PBC stimuli exert the strongest sequential inhibition, and the strength of inhibition decreases as the stimulus parameters depart from the PBC, either in the ILD or ABL dimension. Thus for stimuli of the same frequency, the organization of the binaural stimuli that induce the most sequential inhibition is similar to the organization of the excitatory level response area.

Stimuli that evoke strong responses evoke stronger sequential inhibition than stimuli that elicit weak responses. The relationship between the strength of the preceding response and the degree of sequential inhibition has been demonstrated in AI

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using monaural tones (Brosch and Schreiner 1997; Calford and Semple 1995), binaural tones (Brosch and Schreiner 1997; Zhang et al. 2005), and narrowband and broadband stimuli generated in virtual acoustic space (Reale and Brugge 2000). In virtual acoustic space (Reale and Brugge 2000), stimuli arising from a cell's preferred spatial direction induced longer sequential inhibition than stimuli arising from other, distant directions. AI cells with nonmonotonic monaural (Calford and Semple 1995) and nonmonotonic binaural level response functions (Zhang et al. 2005) tend to exhibit nonmonotonic sequential inhibition, i.e., preceding stimuli at moderate levels near those of the most effective stimuli evoke greater sequential inhibition than stimuli at higher or lower levels.

A response to the preceding stimulus is not necessary for sequential inhibition (Brosch and Schreiner 1997; Calford and Semple 1995; Reale and Brugge 2000). For example, stimuli outside of the response area, both in frequency and level, can still sequentially inhibit responses to subsequent stimuli within the response area. The excitatory level response area and the effect of sequential interaction are related, but responses to the preceding tone do not determine the degree of suppression of the response to the succeeding tone (Zhang et al. 2005). The lack of a relationship between the change in response to a subsequent stimulus and the magnitude of the response to a preceding stimulus has recently been confirmed in the cortex of the unanesthetized marmoset (Bartlett and Wang 2005).

The present paper is a continuation of our study of the effect of a preceding stimulus on the binaural level response area of AI cells in the cat. We examined the time course of recovery from the sequential inhibition exerted by a preceding sound. The recovery time was shortest for stimuli with binaural levels within the PBC and systematically increased as the levels of the stimulus were moved away from the PBC. These data confirm and augment previous observations (Zhang et al. 2005) that stimuli within the PBC of AI cells are the most resistant to sequential inhibition and that this differential sensitivity to sequential inhibition increases the selectivity of AI cells for particular stimuli within their level response areas for tens to hundreds of milliseconds.

METHODS

Animal preparation

Seven healthy adult cats were screened for evidence of pathology or infection in the external ears. An injection of pentobarbital sodium was used to induce anesthesia (40 mg/kg weight). A solution of 5% dextrose in lactated Ringer solution with 250 mg of pentobarbital sodium per 1,000 ml was administered continuously by intravenous drip to maintain areflexia and to hydrate the animal. Additional pentobarbital sodium was administered as needed via a three-way valve in the drip line. The cat was placed in a double-walled sound-attenuating chamber (IAC). A tracheotomy was performed to allow unobstructed breathing and reduce respiration noise. The skull was secured to a frame with screws and dental acrylic. The pinnae were resected and earpieces were inserted and acoustically sealed within the transected external auditory canals. A small opening, 1×3 mm, was made in the bone overlying AI.

Stimulus generation and control

For each ear, tympanic sound pressure level (SPL, expressed in dB re 20 Pa) was calibrated from 100 Hz to 30 kHz in 100-Hz steps under computer control using a calibrated probe tube, housed within the earpiece, and a 0.5-in condenser microphone (Brüel and Kjær). Acoustic calibrations for both ears were stored in a computer file for use in controlling attenuators to obtain desired SPLs. Single or paired 50-ms duration tonal stimuli (6-ms rise/fall time) were presented at 1,000–1,500 ms intertrial intervals, depending on the sensitivity of the cell to sequential interactions. This interval between trials is beyond the expected range of sequential interactions. Each stimulus configuration was repeated 30 times. Tone pips were generated digitally by a MALab system (Kaiser Instruments, Irvine, CA) controlled by a Macintosh computer.

Data collection procedure

After making a small hole in the dura, a 5-μm tip parylene-insulated tungsten microelectrode was positioned at the surface of the brain and advanced by a microdrive that was controlled from outside the acoustic chamber. The electrodes were directed orthogonal to the pial surface of AI. Neuronal activity was amplified and sent to a digital oscilloscope and a Macintosh computer for display, waveform discrimination (amplitude $\times$ time) and analysis by the MALab system. The latency of each single-unit discharge was time linked to a protocol of the stimulus configuration (1-μs resolution) and stored in a computer file. Data were usually collected from units in the middle layers (III and IV) of AI, based on electrode depth. All stimuli were pure tones at the characteristic frequency (CF: the tone frequency that evokes a response at the lowest binaural level) of the cells. CF was determined audiovisually. In general, the response of a cell was recorded over a 50-ms window, starting at stimulus onset. In the few cases in which the response lasted >50 ms, the window was extended to capture the entire response.

A stimulus matrix was used to study the binaural and sequential response properties of the cells. The matrix was composed of 5 ILDs ($\pm$20, $\pm$10, 0) by 8 ABLs (0, 10, 20, 30, 40, 50, 60, and 70). The ILD is the contralateral level minus the ipsilateral level; thus positive ILDs favor the contralateral ear and negative ILDs favor the ipsilateral ear. The ABL is the sum of the contra- and the ipsilateral levels divided by two. In the relevant data figures, stimulus points are plotted in terms of SPL at the contralateral and ipsilateral ears. Thus the two formats are equivalent in that the stimulus matrix can be interpreted in terms of either the derived cues (ILD and ABL) or the SPL at the two ears. The stimuli comprising the binaural matrix were used both in isolation (control) and when preceded by another stimulus.

ISI was varied from 10 to 600 ms. The number of ISIs tested depended on the length of time the cell remained stable. To assess stability, responses to the control matrix were obtained several times during the 3–4 h required to collect a useable data set. The criteria of stability were that the total number of spikes evoked by the binaural matrix did not vary by >10–15% and the configuration of the level response areas was nearly identical across repetitions. Only stimulus points that evoked a response in the control condition >10 spikes in 30 trials were included in the analysis.

In the rest of the article, certain terminology will be used to describe stimuli and responses. "Tone 1" refers to the first of a pair of tones; "tone 2" refers to the second of a pair of tones (Fig. 1). The set of stimuli that vary in ILD and ABL will be called the stimulus matrix. A single stimulus point within the matrix will be called a binaural combination. The PBC is the set of binaural combinations that evokes the largest 20% of the control response, i.e., when tone 2 was
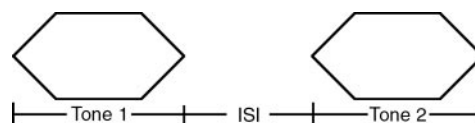

FIG. 1. Schematic of envelop characteristics of 2 sequential tones. ISI, interstimulus interval.

presented alone (Fig. 2, red areas). The level response area (LRA) refers to the profile of the entire set of responses to the stimuli comprising a stimulus matrix.

Recovery functions

A linear fit was made to the recovery of response magnitude evoked by each binaural combination in the matrix as a function of ISI. The linear fits covered the range between 10 and 70% of the control response, thus avoiding spike counts dominated by spontaneous activity and slower or fluctuating convergence to control values that commonly occurred >70% recovery. Responses at 10% of control were invariably above the spontaneous discharge rate. Responses to the majority of binaural combinations in a matrix recovered to 70% of control in a fairly linear manner.

One problem with the linear fits is the sparseness of data points for some recovery functions. The number of data points in each recovery function varied from three to eight. Due to time limitations, it was not possible to acquire data at an equal number of ISIs in each 10–70% recovery range for every binaural combination. However, the majority of functions with more than four points within the 10–70% recovery range were fitted well by a linear regression line. The mean correlation coefficient was 0.88 ± 0.10 (SD).

RESULTS

Data presented in the paper were collected from 24 cells isolated in seven cats. The number of ISIs used for the analysis of each cell varied from three to nine.
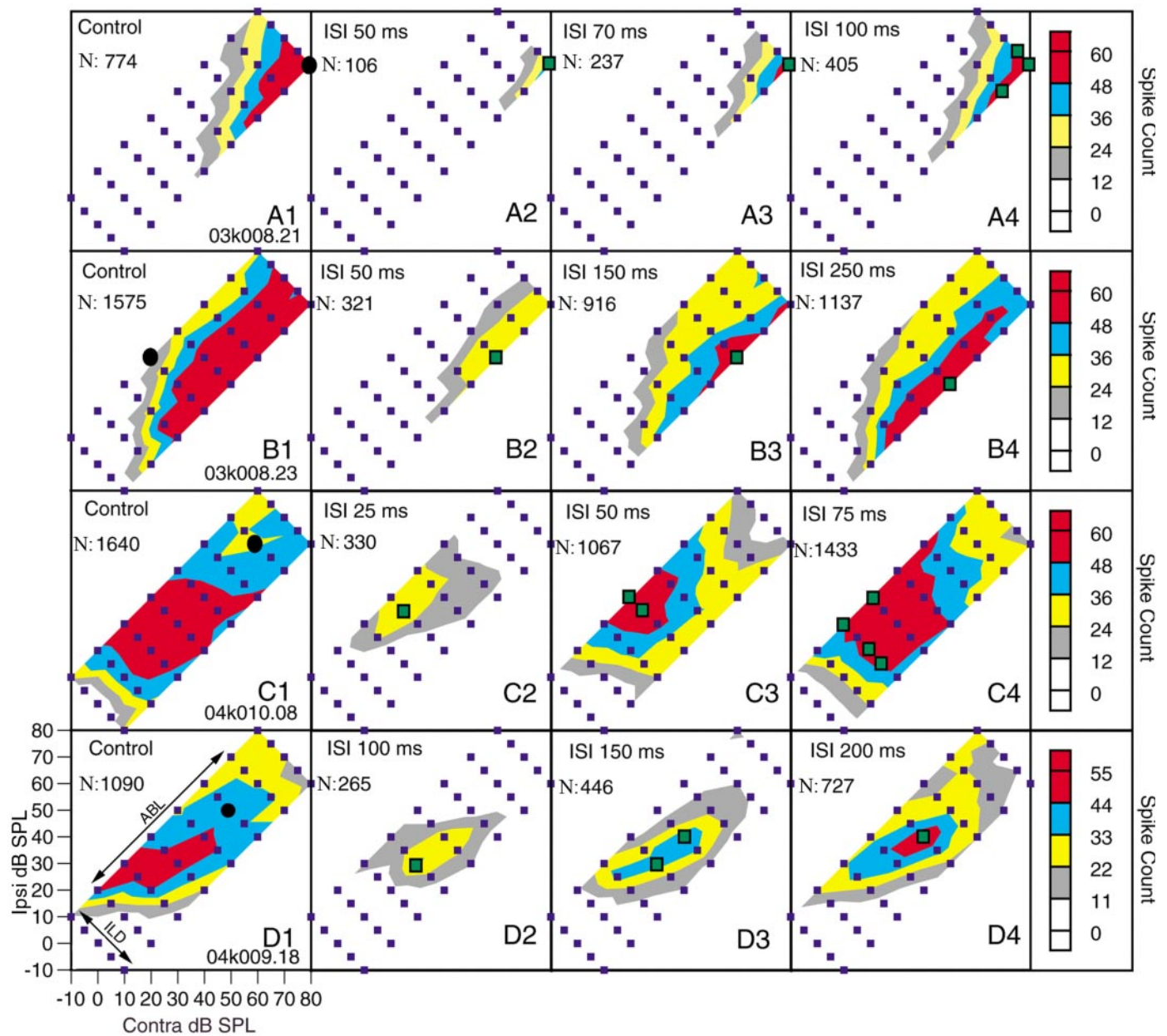

FIG. 2. Spike counts of 4 cells at different ISIs. x and y axes represent contralateral (Contra) and ipsilateral (Ipsi) dB SPL. These axes are the same for all graphs. The z axis, which is the same for each graph in a row, is the spike count, indicated by the legends on the right. Each row of graphs represents data from 1 cell. *A1–D1*: control respone matrix stimuli presented singly. Black squares, matrix stimulus points. Black circles, levels of the preceding tones used in *A2–D4*. ISI is indicated in the top left corner of *A2–D4*: *N*, total number of spikes evoked by all stimuli within the matrix. Green squares: binaural combination that evoked the largest response (top 5%) at the indicated ISI.

Effect of a preceding stimulus on the level response area

Neurons typically responded to a wide range of ILD and ABL combinations when stimuli were presented in isolation (Fig. 2, *A1, B1, C1,* and *D1*). The four units responded to the full range of ILD (±20 dB) and three responded over almost the entire range of tested ABL at one or more ILDs. The variation in shape and response magnitude of these level response areas is typical of our entire database. An effective tone 1 reduced the range of tone 2 ILD and ABL combinations that evoked a response (Fig. 2. *A2–D4*). The effect of sequential inhibition was not solely dependent on the contralateral level of tone 2 in that stimuli with the same contralateral level evoked different responses, e.g., binaural combinations along a vertical line through the matrix had the same contralateral level but often evoked very different responses. The effect of sequential inhibition was also not a simple function of the ABL or ILD of tone 2. For example, in the case of nonmonotonic level response areas (Fig. 2, *C1* and *D1*), tone 1 fully inhibited the response at higher and lower ABLs but not at medium levels where the PBC was located (Fig. 2, *C2–C4* and *D2–D4*). Tone 1 could selectively reduce responses in the ILD dimension, sometimes reducing responses at positive ILDs (Fig. 2*C2*) and sometimes at both positive and negative ILDs (Fig. 2*D2*). Finally, the present data are consistent with our previous findings (Zhang et al. 2005) that presentation of tone 1 does not produce a fractionated level response area; although contracted, the resultant level response area is invariably highly organized, retaining a contiguous core of maximal responses with responses of decreasing magnitudes progressing from this core.

The shape and magnitude of the contracted level response area depended on the ISI. When an effective tone 1 was presented at a short ISI, the level response areas of AI cells were reduced to a fraction of their control size (Fig. 2, *A2–D2*). At the shortest ISIs shown in Fig. 2, ranging from 25 to 100 ms, the average total number of spikes evoked by the stimuli in the binaural matrix was <20% of the control number of evoked spikes. The percentage was smaller at shorter ISIs. For both monotonic and nonmonotonic cells, the persisting portion of the level response area consisted mostly of a subset of the control PBC (top 20% of the control LRA). As ISI increased, the level response area systematically spread from this subset of effective binaural combinations to adjacent binaural combinations. As the level response areas spread to adjacent binaural combinations with increasing ISI, responses that appeared earlier increased in magnitude.

The binaural combinations that evoked the largest 5% of responses across the matrix were relatively stable across ISI (Fig. 2 green squares). For example, the binaural combinations that evoked the strongest responses in the sequential condition for these four cells shifted by no more than one binaural combination across ISI (Fig. 2, *A2–A4, B2–B4, C2–C4,* and *D2–D4*). All of these binaural combinations were within the control PBCs. This behavior was characteristic of the majority (20/24) of cells studied: the area of the strongest response at the ISIs that were tested shifted by no more than one binaural combination in the matrix and those binaural combinations were always within the control PBC. Thus sequential inhibition reduces the size of the level response area; however, the focus

of activity, across increasing ISI, is stable and within the control PBC.

A linear fit of the responses to each binaural combination across ISI was used to estimate the time at which the cells in Fig. 2 recovered 70% of their control responses. Responses of the monotonic cell displayed in Fig. 2*A* recovered fastest to a subset of its PBC and progressively more slowly as the levels of tone 2 shifted away from this area (Fig. 3*A*). At +20 ILD and 70 ABL the rate of recovery was 1.5%/ms and the cell recovered 70% of its response to this stimulus by ~54 ms. As the ABL was lowered or ILD shifted toward the ipsilateral ear, the recovery time systematically increased. Responses of the cells in Fig. 2, *C* and *D,* behaved in a similar manner in that the fastest recovery was to a subset of the PBC, and the recovery was progressively slower as the levels of tone 2 shifted away from this area (Fig. 3, *C* and *D*). The majority of cells (20/24) studied responded in a similar fashion, i.e., recovery was progressively slower as the levels of tone 2 shifted away from a subset of the PBC. Thus for the great majority of cells, recovery from sequential inhibition was fastest, in terms of both the time and rate of the recovery at a subset of the control PBC and systematically declined as the levels of tone 2 shifted away from this subset.

A small group of cells (4/24) did not exhibit monotonic recovery profiles across their level response areas. As an
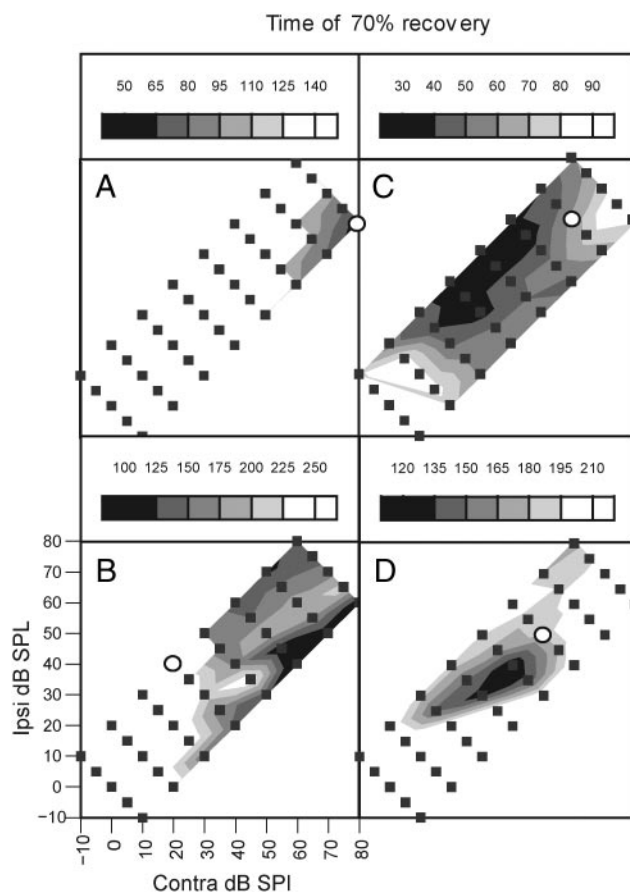

FIG. 3.   The ISI at which the cells in Fig. 2 recovered to 70% of their control responses, estimated by a linear fit. The *x* and the *y* axes are the same as in Fig. 2. The z axis, indicated above each panel, is the estimated ISI at which responses to each binaural combination recovered to 70% of control. Panel letters correspond to the cell designations in Fig. 2. ○, binaural levels of tone 1.

example, the data shown in Fig. 3*B* indicate that responses to a subset of the PBC recovered fastest as is usually found. However, response to several binaural combinations on the ipsilateral side, outside of the PBC, recovered at the same time as responses to other stimuli within the PBC. For this cell, although response magnitude varied monotonically over ILD (Fig. 2*B*), recovery from sequential inhibition varied nonmonotonically over ILD (Fig. 3*B*).

If the inhibition was linear over time, e.g., a constant amount of inhibition across the entire level response area that decreases over time, the response to all binaural combinations within the stimulus matrix would recover at the same time. However, that is not the case. Responses to a subset of the PBC invariably recovered to 70% of their individual control sizes before responses to non-PBC stimuli recovered to 70% of their individual control sizes. The differences among the recovery times, which were sometimes hundreds of milliseconds, demonstrate that recovery across the level response area is nonlinear.

The faster recovery of responses to a subset of the PBC, compared with responses to other binaural combinations, increases the stimulus selectivity of the cell. Figure 4 demonstrates the changing selectivity of a cell during the recovery period. Linear fits of the recovery functions of responses to binaural combinations at three ILDs of the cell shown in Fig. 2*A1* are displayed in the upper row of Fig. 4. The binaural combination at +20 ILD, 70 ABL evoked the response that recovered first. The difference between the recovery function of the response to this stimulus and the recovery functions of responses to other binaural combinations are shown in the *bottom row* of Fig. 4. These difference functions therefore indicate the recovery of responses to the other binaural combinations relative to the response that recovered first, i.e., +20 ILD, 70 ABL. At +20 ILD (Fig. 4*B3*), the difference functions for responses to the 50 ABL (—) and 60 ABL (· · ·) stimuli increased up to the time at which the response to +20 ILD, ABL 70 recovered to 70% of its control value (54 ms) and then decreased. At lower ABLs, the differences were greater and

lasted longer, e.g., at 54 ms the difference for the response to +20 ILD, 50 ABL was 58% and the response recovered at 98 ms; the difference for the response to +20 ILD 40 ABL was 70% at 54 ms and the response recovered at 110 ms. Similarly, at +10 ILD (Fig. 4*B2*) and 0 ILD (*B1*), the difference increased ≤54 ms and decreased afterward. Overall, the difference between the response at 70 ABL, +20 ILD and the response at the other binaural combinations was maximal at an ISI of 54 ms. These data demonstrate that at an ISI of 54 ms, this cell would respond robustly to 70 ABL, +20 ILD and comparatively weakly to any other binaural combination. The largest differences occurring at 54 ms are an artifact of the 70% cutoff of the linear fits of the response functions. At a higher cutoff percentage, the differences would increase to larger values over a longer period. Thus the data shown in Fig. 4 are an underestimate of the actual range of differences in recovery times.

Figure 4 demonstrated that the difference between the shortest recovery time and the recovery time of responses to the remaining binaural combinations creates a window of increased stimulus selectivity. This window can be fruitfully viewed over the level response area as a cumulative plot of the ISI at which the component responses recovered to 70% of their control sizes. The control level response area for the cell shown in Fig. 2*B1* consisted of responses to 29 binaural combinations. A cumulative plot of the recovery of this unit is shown in Fig. 5. The axis on the left is the number of binaural combinations that evoked 70% of their control response; the axis on the right is the percentage of binaural combinations that evoked 70% of their control response. The first response recovered at an ISI of 75 ms, and only 80% of the responses had recovered at a 250 ms ISI. Thus the level response area was far from recovering its control size and magnitude 175 ms after the offset of tone 1. Characteristic of our entire database, the responses that recovered first in the cumulative plot were evoked by a subset of the PBC whereas responses that recov-
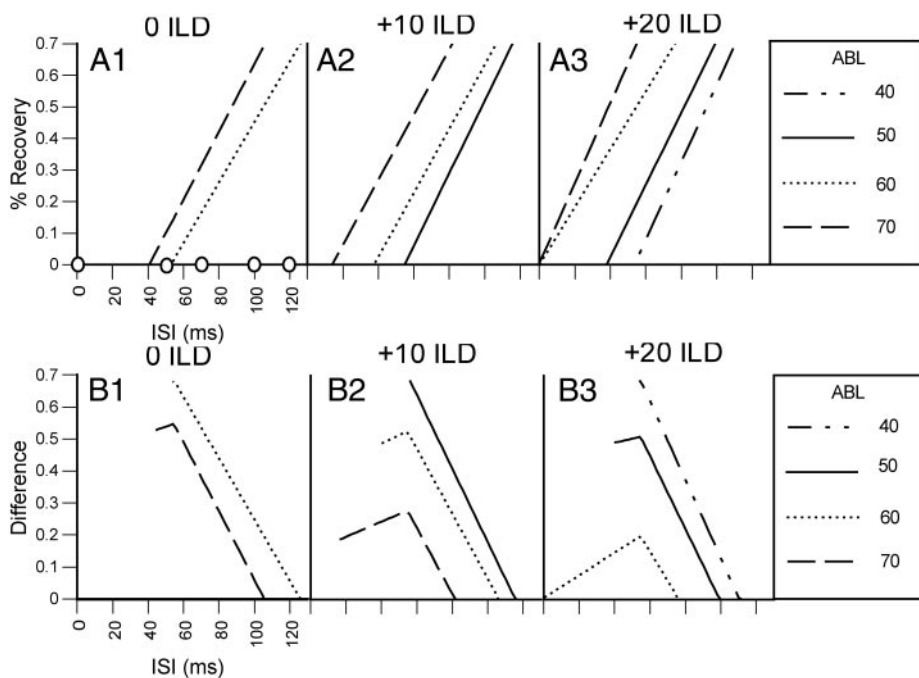

FIG. 4. Linear fits to recovery functions and recovery-difference curves for the cell shown in Fig. 2 *A1, top row*: linear fits of the recovery of the response to each binaural combination. *Bottom row*: difference in the recovery between the 1st combination to recover [+20 inter-aural level (ILD), 70 average binaural level (ABL)] and all other binaural combinations. Each column represents a different ILD, as indicated at the top of each graph. The ABL of each binaural combination is displayed in the legend on the right. ○ on the *x* axis of *A1*, tested ISIs.
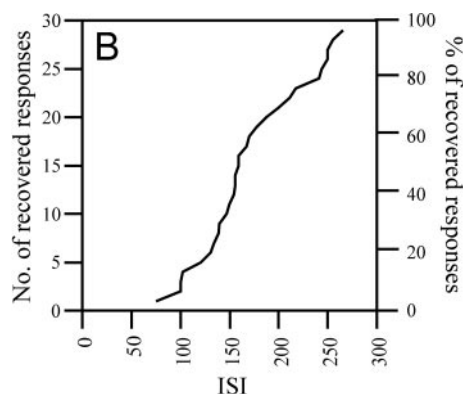
FIG. 5. Cumulative plot of the ISI at which the responses of the unit shown in Fig. 2*B1* recovered to 70% of their control values. The axis on the left shows the number of recovered responses; the axis on the right shows the percent of responses to the 29 effective binaural combinations in the control condition that recovered at the indicated ISIs.

ered later were evoked by binaural combinations that were progressively further away from this subset.

The cumulative recovery plots for the entire data sample are shown in Fig. 6 in terms of percentage of recovered responses, the same as the right axis in Fig. 5. Each line represents the recovery of one level response area for a single tone 1. The shortest ISI at which the response to a binaural combination in the matrix first recovered to 70% of its control response varied from 10 ms (the shortest ISI tested) to 235 ms with a mean of 73.3 ± 53 ms. The ISI at which the latest response to a binaural combination in the matrix recovered to 70% of its control response varied from 81 to 706 ms with a mean of 238.4 ± 132 ms. The difference between the first and last binaural combination to recover varied from 43 to 655 ms with a mean of 187.2 ± 126 ms. The last two statistics involving the last binaural combination to evoke a response that was 70% of its control size are underestimated because five cells never recovered their responses to all of the binaural combinations in their control level response areas at the longest ISI used.

Figure 7 is a cumulative plot of the ISI at which the cells in Fig. 6 recovered 71% of their responses to the binaural combinations, i.e., the point at which the function in Fig. 6 reached 71%. The majority of cells recovered 71% of their responses between 100 and 200 ms after the offset of tone 1. However, some cells did not reach this level of recovery even 400 ms after the offset of tone 1. As only highly effective preceding tones were used in this study, Figs. 6 and 7 and the descriptive statistics presented in the preceding text describe the population response of cells with PBCs near the binaural level of tone 1 and characteristic frequencies at the frequency of the stimuli.

The increased selectivity caused by sequential inhibition is systematic, and not easily attributable to monaural, ABL or ILD parameters. The consequences of increased selectivity on three cells that were studied with the same tone 1 are illustrated in Fig. 8. They had different CFs but we assume that equivalent cells exist that have the same CF. In the control, tone alone condition, the level response areas of these cells were relatively broad (Fig. 8, *A1, B1,* and *C1*). At short ISIs, these cells responded only to a severely restricted portion of their preferred binaural combinations (Fig. 8, *A2, B3,* and *C2*). At longer intervals they responded to a broader range of binaural combinations, generally within their respective PBCs (Fig. 8, *A3, A4, B4, C3,* and *C4*).

The largest 60% (outlines) and 20% (solid polygons) of the level response areas at each ISI are superimposed in Fig. 8, *D1–D4*). Different colors are used to represent each cell; black for *cell A* (Fig. 8, *A1–A4*), blue for *cell B* (Fig. 8, *B1–B4*), and red for *cell C* (Fig. 8, *C1–C4*). Without a tone 1, the level response areas of these cells greatly overlapped each other (Fig. 8*D1*). When tone 1, 50 dB at each ear, occurred before each tone 2, the level response area of each cell contracted to a small fraction of its control size. At a 50-ms ISI, there was no overlap of the response profiles of the three units. At 100- and 150-ms ISIs, there was a minimal overlap of the profiles of *units 04K009.18* and *04K006.11*. At these three ISIs, only *unit 04k009.11* responded to stimuli delivered at the highest ABLs.
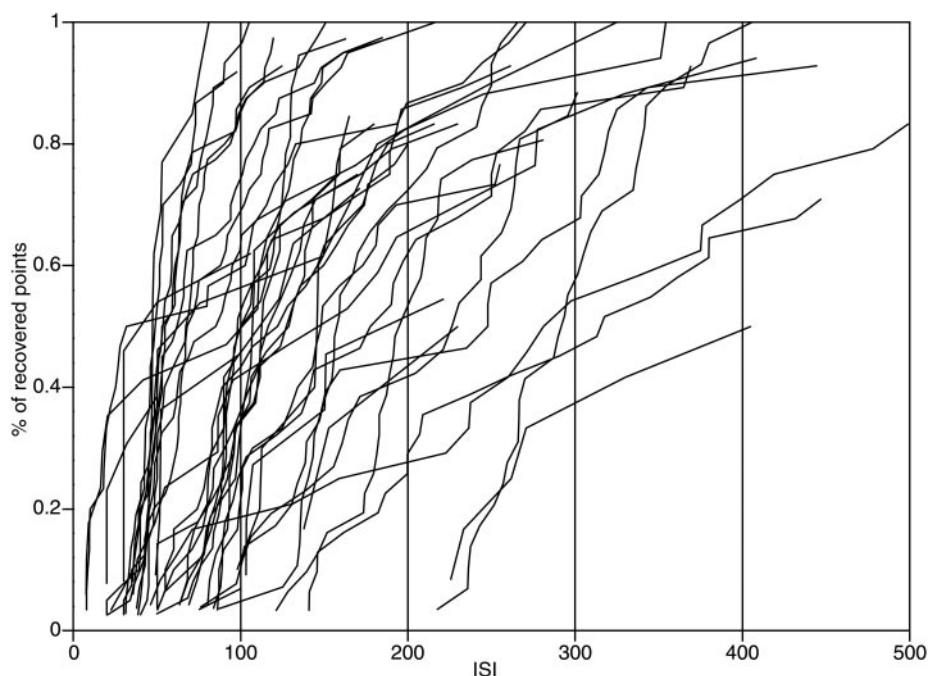

FIG. 6. A cumulative plot of the time course of recovery for the population of cells studied. Each line represents the time course of recovery of the response for a single cell, similar to Fig. 5. The *y* axis is the percentage of binaural combinations evoking responses that had recovered to 70% of their control values, similar to the right axis of Fig. 5. The *x* axis is ISI.
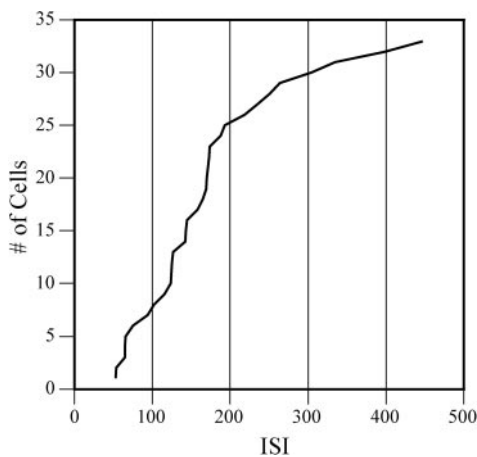
FIG. 7. Cumulative plot, over ISI, of the number of cells in which 71% of the responses to the binaural combinations in their level response areas recovered to 70% of their control values. The *y* axis is incremented at the ISI at which the recovery lines in Fig. 6 reach a value of 71%.

Focusing on the total number of spikes evoked by the stimuli comprising the binaural matrix, two units (*04k009.11* and *04k006.11*) recovered 66% and one unit recovered only 43% of the control number of spikes 150 ms after the offset of tone 1. The behavior of these three units again demonstrate that presentation of tone 2 does not fractionate the level response area and, because of the nonlinearity in recovery across each level response area, the response areas contract and recover around a subset of the PBC.

This format of the data demonstrates most clearly that cells would respond contemporaneously to a wide range of stimuli when those stimuli are presented alone. This means, conversely, that single stimuli should excite a large population of units in AI. The same units would respond only to disparate groups of stimuli when those stimuli are preceded by the same Tone 1 (Fig. 8, *D2–D4*). This means that succeeding stimuli would evoke responses from more restricted sets of AI units. At short ISIs, the only cells that would respond would be those with a PBC that contains the test stimuli. As ISI increases, the population of cells responding systematically increases. Func-
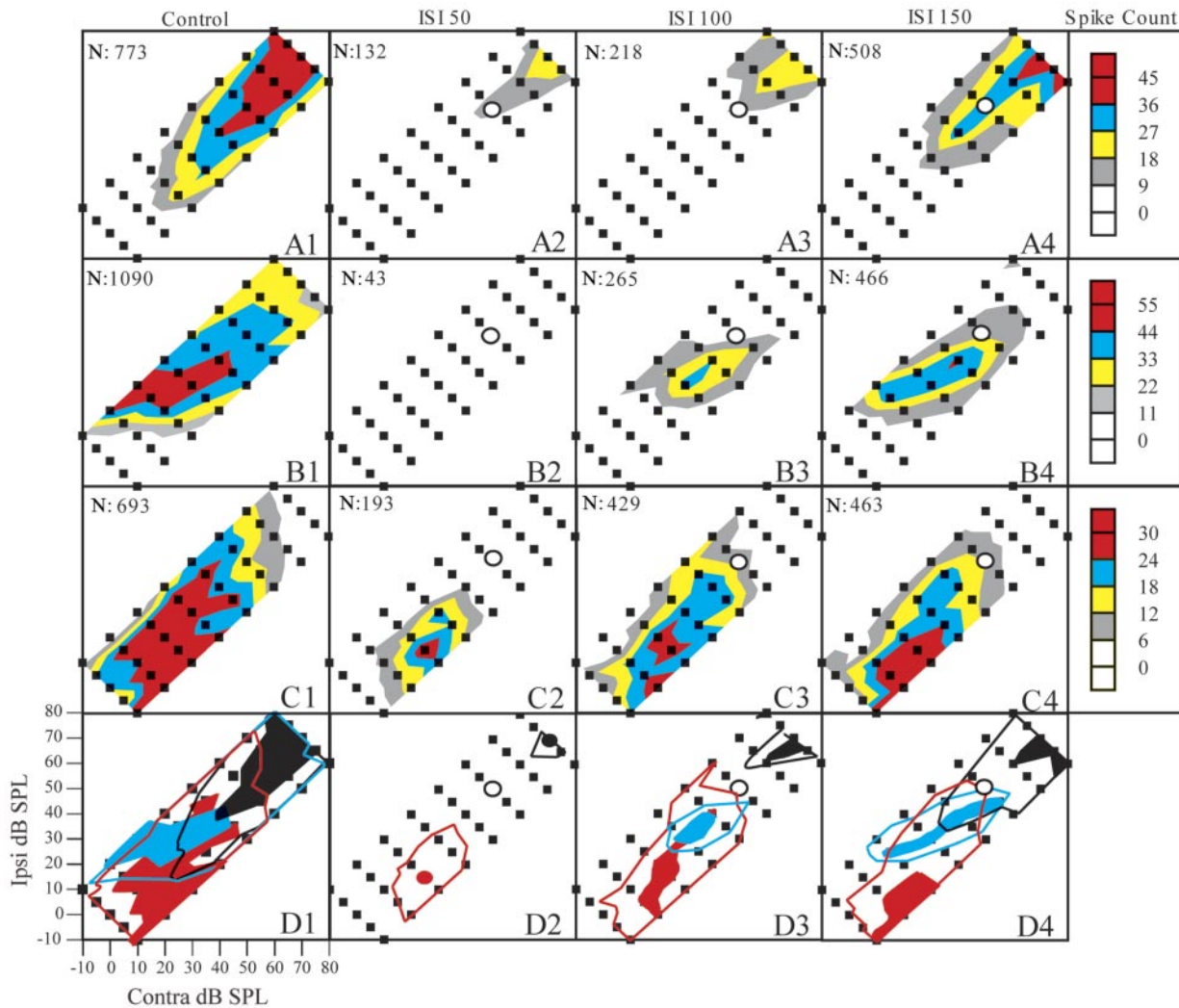
FIG. 8. Responses of 3 cells to the matrix across ISI when preceded by the same tone 1. The layout is the same as Fig. 2, with the exception of the *bottom row*. *Bottom row*: outline plotted of the largest 60% (yellow areas) of the response area of all 3 cells at each ISI. Solid polygons indicate the largest 20% of the response area at each ISI for each cell. The cell in the *top row* is represented by black; the *middle row,* blue; *bottom row,* red. The white circles represent the levels of tone 1.

tionally, this implies that the selectivity of cells is ISI dependent.

DISCUSSION

As we did not explore the effects of stimulus frequency, the following discussion focuses on stimuli delivered at CF. After the offset of an effective preceding stimulus, the shape and magnitude of AI level response areas vary dynamically in time around a subset of the PBC. At short ISIs, an effective tone 1 can completely inhibit the response of a cell. Across the level response area, recovery from sequential inhibition is nonlinear. Responses to a subset of the PBC start to recover earlier and recover faster than responses to other binaural combinations. With increasing ISIs, AI cells respond to a subset of the PBC and then to successive binaural combinations around this subset (Figs. 2 and 3). The average difference between the times when responses to the first and last stimulus in the level response area to recover to 70% of their individual control levels is 187 ms. For the duration of the sequential inhibition, which can last >700 ms, the stimulus selectivity of AI cells is increased for a subset of the stimuli in the level response area. Thus the occurrence of a preceding stimulus with certain binaural levels can determine over an appreciable time period whether and how strongly a unit in AI will respond to all the stimuli in its level response area.

Zhang et al. (2005) demonstrated that a preceding stimulus evokes a nonlinear suppression of responses across the level response area. Responses to binaural combinations in the PBC were reduced significantly less than responses to binaural combinations outside of the PBC. The results of the present study demonstrate that the configuration of the contracted level response areas is caused by differences in the recovery over time between responses to PBC and non-PBC stimuli.

The impact of sequential interactions on responses of AI units can be appreciated by considering the effects of diverse preceding stimuli on the response to particular subsequent stimuli in the level response area. A response in the periphery of a level response area can be eliminated from it by almost any preceding stimulus in the level response area. Once eliminated, recovery of that response will not start for tens to hundreds of milliseconds and will not be completed for additional tens to hundreds of milliseconds. A response to a PBC stimulus, by contrast, can be eliminated from a level response area only by other PBC stimuli and occasionally by some stimuli very near the PBC. Eliminated responses to PBC stimuli start to recover first and recover most rapidly. Overall, eliminated responses recover in a nonlinear manner across the level response area. Thus rather than being static, the temporal dynamics of sequential interactions vary with the proximity of both the preceding and subsequent stimuli in the level response area to the PBC of the unit.

This discussion raises the interesting question, which we are presently examining, whether stimuli that are excluded from the level response area have any effect on the cortical unit. At CF, the inhibitory level response area is essentially the inverse of the excitatory response area (Zhang et al. 2005). The question therefore is whether a stimulus remains in the inhibitory level response area after it has been excluded by a preceding stimulus from the excitatory level response area. If it does, then the consequence of its occurrence would be to maintain the level response area in a contracted condition and prolong its recovery period. Such dynamics of these temporal-binaural level interactions indicate some of the factors in the stimulus history that could determine the probability and magnitude of a response by an AI unit to a stimulus in its receptive field.

Stimulus selectivity

The selectivity of cells in AI for their preferred binaural combinations is increased by the nonlinear recovery of responses to stimuli in the level response area. Responses to a subset of the PBC recover first to their respective control values. Therefore during hundreds of milliseconds after the occurrence of an effective tone 1, the magnitude of responses to a subset of the PBC will be similar to control, whereas responses to all other stimuli in the level response area will be smaller than their control. The cumulative plots shown in Figs. 5–7 demonstrate the duration of the increased stimulus selectivity. Thus considering a population of cells responding in this manner, the occurrence of an effective tone 1 creates a temporal window of one to a few hundreds of ms during which the selectivity for binaural level of a portion of AI is increased.

The present data suggest that in a complex acoustic environment, the shape and magnitude of the level response areas of AI cells are continuously modulating around a subset of the PBC as a function of the ISI and stimulus parameters of the preceding sound. The increased stimulus selectivity caused by differences in recovery time of responses to PBC and non-PBC stimuli has two effects. First, for short intervals (tens of milliseconds) after the offset of a preceding stimulus, the population of cells with PBCs near the binaural levels of the preceding stimulus will respond primarily to subsequent PBC stimuli and weakly, if at all, to stimuli with binaural levels outside of their PBCs. For repeated presentations of a tone, or a train of stimuli with small level differences, a large population of AI cells will respond to the initial stimulus. At short ISIs (estimated at ≤75 ms) small changes in binaural level could be encoded by a population of AI cells with contracted level response areas. As the ISI increases, a progressively larger population would respond; however, the degree of overlap in level response of these cells would increase, reducing the specificity of their responses. Second, AI cells with PBCs substantially different from the preceding stimulus would be unaffected, allowing them to respond vigorously to all succeeding stimuli within their level response areas. Thus after the occurrence of a stimulus, a large distinct population would respond to a succeeding tone that differed greatly from the preceding stimulus, whereas a specific subset of the initially responding population would respond to a succeeding tone that differed little from the preceding signal.

Topography of AI and sequential interactions

The populations discussed in the preceding text might be topographically organized in AI. The topographical organization of several level-related parameters has been described in AI (for review, see Schreiner et al. 2000). Previously we described the topographical organization of binaural responses in an isofrequency contour of AI (Nakamoto et al. 2004). High-density recording of single units revealed closely juxta-

posed or interdigitating patches of similarly responding units. The patches or modules were ~1.0 mm in extent. Patches categorized by average ILD and average ABL within the PBC are particularly relevant. Within a 1.5–2.0 mm extent of tissue, patches of each type covered most of the relevant range of each dimension. However, the categories of units were large, e.g., greater or less than 45 ABL and –20 < ±10 > 20 dB ILD.

Focusing on the ILD dimension, it seems reasonable to expect that a stimulus with equal levels at the two ears would cause the greatest contraction of the level response areas of units in the patches of cells the PBCs of which are within ±10 dB ILD. The level response areas of units in neighboring patches the PBCs of which are outside this ILD range would be either minimally or not affected by the stimulus. For tens to hundreds of milliseconds after the occurrence of the equal-level stimulus, the level response areas of cells in the ±10 dB ILD patches throughout the isofrequency contour would be contracted. Those of cells in the other ILD patches throughout the isofrequency contour would remain near or at their control dimensions and magnitudes. Thus for a period of time ranging up to hundreds of milliseconds after the stimulus, the isofrequency contour would consist to a large extent of patches of cells with unmodified level response areas and patches of cells with contracted level response areas. The selectivity of cells in the latter patches for stimuli with binaural levels similar to those of the initial stimulus would be increased in an ISI-dependent manner. As discussed in Zhang et al. (2005), patches of units with large, unmodified level response areas might be suitable for detecting stimuli within their ILD ranges, whereas patches of units with contracted level response areas might be suitable for discriminating among stimuli with similar binaural levels. The functional implication of this speculation is that the topographical organization of responses along an isofrequency contour in a complex sound environment could consist of spatially segregated subpopulations of units with receptive fields modulating in shape and magnitude around their PBCs in a time dependent manner.

Recovery times

Recovery times in AI, IC, and lower auditory nuclei are substantially different (Fitzpatrick et al. 1999). The auditory nerve, cochlear nucleus, and the superior olivary complex recover to 50% of control within a 10-ms ISI (Fitzpatrick et al. 1999; Parham et al. 1996; Parham et al. 1998; Wickesberg 1996; Wickesberg and Stevens 1998). In the IC, half-maximal recovery ISI is 35 ± 29 ms for clicks (20- to 500-μs duration) presented in free field and 38 ± 36 ms when the clicks are presented dichotically (Litovsky and Yin 1998). Half-maximal recovery ISI for noise (1- to 40-ms duration) is generally 5 ms longer (Litovsky and Yin 1998). Twenty percent of the population studied had half-maximal ISIs of 10 ms. The ISIs of this population falls into the 10-ms range that encompasses the precedence effect. Whether or not AI plays a role in the precedence effect remains questionable. The average 50% recovery ISI of AI cells varies broadly from 20 to 150 ms, which is clearly beyond the temporal domain of the precedence effect (Brosch and Schreiner 1997; Calford and Semple 1995; Fitzpatrick et al. 1999; Reale and Brugge 2000; Zhang et al. 2005). The increase in recovery times along the auditory pathway raises fundamental questions about sequential inter-

actions in the auditory system. Is the temporal accuracy lost along the auditory pathway or is it encoded differently at different auditory nuclei? Are the temporally shorter psycho-physical phenomena the result of processing in lower auditory areas, whereas higher auditory areas underlie temporally longer psychophysical phenomena? Clearly, more research is required to answer these important questions.

Neural mechanism of sequential inhibition

Throughout this paper, we have used the word "inhibition" as a descriptor of the reduction in response magnitude with no implications regarding the underlying mechanism. GABA-mediated inhibition appears to be an unlikely candidate mechanism. In ketamine-anesthetized rats, inhibitory conductances evoked in auditory cortex cells are too short-lived to account for the suppression of responses to the second of a pair of stimuli (Wehr and Zador 2005). Systemic administration of sodium pentobarbital in ketamine-anesthetized rats increased the duration of the inhibitory conductances. Suppression of responses to the second stimulus was increased at an ISI of 128 ms but did not differ from the means observed under ketamine anesthesia at 64- and 256-ms ISIs. Responses in auditory cortex to the second of two consecutive stimuli of unanesthetized marmosets are often reduced over much longer time periods (Bartlett and Wang 2005). When the first stimulus was ≥500 ms in duration, suppression of the response to the second stimulus often lasted from 500 ms to >1 s. These authors argued that such prolonged suppression is inconsistent with the much shorter duration of GABA-mediated inhibition. The depression of excitatory synapses has been proposed as an attractive alternative to GABA mediated inhibition (Wehr and Zador 2005). It is presently unknown, however, whether the duration and the rate of recovery from depression is consistent with the behavior of AI cells over the ISIs used in this and other studies.

Stable organization of the level response area; comparisons with monaural functions

In the present and our previous study (Zhang et al. 2005), the level response areas of AI cells obtained in the control condition were invariably highly organized. They always exhibited a centralized core of contiguous, most effective stimuli, and diminishing response magnitude for stimuli progressively removed from that core. The only exceptions to this general appearance were the few units the level response areas of which consisted of asymptotic responses evoked by a large proportion of the stimuli in the stimulus matrix (e.g., Fig. 6 in Zhang et al. 2005). Level response areas that were contracted due to preceding stimuli are equally well organized. The present data sample and the data sample from our previous study contain no instance of a level response area fractionating into discontinuous response profiles because of preceding stimuli. Moreover, we have observed no instance of an increased response to test stimuli at any ISI that we tested, as has been previously described in anesthetized cat and macaque and in unanesthetized marmoset (Bartlett and Wang 2005; Brosch and Schreiner 1997, 1999). Preceding stimuli invariably caused a contraction of level response areas and a reduction of responses to the component binaural stimuli.

From auditory nerve to auditory cortex, presentation of a preceding stimulus shifts *monaural* rate-level function to higher SPLs (Bauer 1978; Harris and Dallos 1979; Kaltenbach et al. 1993; Phillips et al. 1985; Smith 1977, 1979). The more intense the preceding stimulus, the greater the shift. Intense stimuli can shift the monaural rate level function by 30 dB. After a 800-ms noise burst, the thresholds of monaural rate-level functions of AI cells to tonal stimuli shift upward by 20 dB (Phillips et al. 1985). Unfortunately, the rate-level functions were normalized to 100%, so we know only the form of the functions and not the actual response magnitudes. Responses are evoked at 0- and 20-ms ISIs. The effect of the preceding signal on the rate level function is almost entirely dissipated at an ISI of 100 ms, i.e., the monaural rate-level function obtained at a 100-ms ISI is not significantly shifted in SPL from the control response function. Such monaural effects could lead to the expectation that the binaural level response areas would shift to higher ABLs during recovery from the effects of preceding stimuli and that AI units would be able to respond immediately (ISI = 0 ms) to subsequent stimuli.

However, such monaural behavior is very different from the effect of preceding stimuli on binaural responses. There was no systematic shift in the location of level response areas to higher ABLs at any ISI, including the very shortest ISI. The ability of a preceding stimulus to contract a level response area depends on its proximity to the PBC rather than on its absolute binaural levels (Zhang et al. 2005). The circuitry that configures the binaural level response area appears to be inoperative for a period of time after the offsets of the most effective preceding stimuli. Rather than being able to respond immediately to a succeeding stimulus, the period during which the unit does not respond to any stimulus in the binaural matrix is typically <100 ms but may extend to >200 ms (mean = 73.3 ms; Fig. 6). Recovery of the binaural circuitry is first demonstrated by the response to a stimulus within the control PBC (Fig. 2), whether the PBC is located at high, medium, or low ABLs. Recovery then proceeds to surrounding stimuli in an orderly progression until responses to the stimuli comprising the original level response area have recovered. Full recovery (to 70% of control) of the entire level response area requires an additional 43–655 ms (mean = 187.2 ms). Moreover, the recovery of the determining mechanisms is nonlinear in that responses to PBC stimuli recover to 70% of their control sizes faster than do responses to non-PBC stimuli. This mode of recovery is independent of the absolute binaural levels of the preceding stimuli (present data; Zhang et al. 2005).

These differences between monaural and binaural consequences of a preceding stimulus suggest that the neural mechanisms that configure level response areas provide a certain stability to binaural responses that apparently is not operative monaurally. The stability is in the form of the stationarity of the level response area in the binaural level domain, i.e., the level response area is not displaced to higher ABLs. In contrast to monaural responses, the penalty attached to this stationarity is the inability of units in AI to respond to binaural stimuli within their level response areas for tens to hundreds of milliseconds after a preceding stimulus the binaural configuration of which is within or near its PBC. We do not know yet if the binaural stationarity is inherited from thalamic and brain stem physiology or an emergent property of cortical processes.

An interesting corollary of this binaural level stationarity involves the concept of response threshold. Response threshold, as commonly used, applies to stimulus level. For example, a manipulation that causes a unit to respond only to stronger stimuli than it normally did prior to the manipulation is said to have increased the unit's response threshold. The shift of monaural rate-level functions to higher SPLs caused by a preceding stimulus exemplifies this change in response threshold. Empirically, this means that the levels of the stimuli capable of evoking a monaural response are shifted by a preceding stimulus to higher SPLs. Such adjustments of required stimulus levels apparently do not occur binaurally. After an effective preceding stimulus, binaural level response areas are not displaced to higher ABLs. The first stimulus able to evoke a response is within the control PBC as is the stimulus that evokes the largest response at any ISI. Thus the stimulus levels required to evoke a binaural response remains stationary. In contrast to the changes in monaural response thresholds, the parameter governing the changes in binaural response thresholds appears to be the dissipation over tens to hundreds of milliseconds of the underlying sequential inhibition.

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