Neural Representations of Temporally Asymmetric Stimuli in the Auditory Cortex of Awake Primates

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Lu, Thomas, Li Liang, and Xiaoqin Wang. Neural representations of temporally asymmetric stimuli in the auditory cortex of awake primates. *J Neurophysiol* 85: 2364–2380, 2001. The representation of rapid acoustic transients by the auditory cortex is a fundamental issue that is still unresolved. Auditory cortical neurons have been shown to be limited in their stimulus-synchronized responses, yet the perceptual performances of humans and animals in discriminating temporal variations in complex sounds are better than what existing neurophysiological data would predict. This study investigated the neural representation of temporally asymmetric stimuli in the primary auditory cortex of awake marmoset monkeys. The stimuli, ramped and damped sinusoids, were systematically manipulated (by means of half-life of the exponential envelope) within a cortical neuron's presumed temporal integration window. The main findings of this study are as follows: *1)* temporal asymmetry in ramped and damped sinusoids with a short period (25 ms) was clearly reflected by average discharge rate but not necessarily by temporal discharge patterns of auditory cortical neurons. There was considerable response specificity to these stimuli such that some neurons were strongly responsive to a ramped sinusoid but almost completely unresponsive to its damped counterpart or vice versa. Of 181 neurons studied, 140 (77%) showed significant response asymmetry in at least one of the tested half-life values of the exponential envelope. Forty-six neurons showed significant response asymmetry over all half-lives tested. Sustained firing, commonly observed under awake conditions, contributed to greater response asymmetry than that of onset responses in many neurons. *2)* A greater proportion of the neurons (32/46) that exhibited significant overall response asymmetry showed stronger responses to the *ramped* sinusoids than to the damped sinusoids, possibly contributing to the difference in the perceived loudness between these two classes of sounds. *3)* The asymmetry preference of a neuron to ramped or damped sinusoids did not appear to be correlated with its characteristic frequency or minimum response latency, suggesting that this is a general phenomenon that exists across populations of cortical neurons. Moreover, the intensity of the stimuli did not have significant effects on the measure of the asymmetry preference based on discharge rate. *4)* A population measure of response preference, based on discharge rate, of cortical neurons to the temporally asymmetric stimuli was qualitatively similar to the performance of human listeners in discriminating ramped versus damped sinusoids at different half-life values. These findings suggest that rapid acoustic transients embedded in complex sounds can be represented by discharge rates of cortical neurons instead of or in the absence of stimulus-synchronized discharges.

INTRODUCTION

It is well known from psychophysical studies that humans are able to perceive and discriminate between rapid temporal variations in sounds. These rapidly modulated components are important for speech perception. Variations in temporal features can determine the identity of a phoneme that is perceived, such as the duration of voice-onset time between /ba/ and /pa/ (Liberman 1996). Animal communication sounds such as species-specific vocalizations of primates are also rich in rapid temporal variations (Wang 2000).

Neurophysiological investigations into the auditory cortical representation of time-varying signals have largely concentrated on stimulus-synchronized responses (Bieser and Muller-Preuss 1996; de Ribaupierre et al. 1972; Eggermont 1991, 1994; Phillips et al. 1989; Schreiner and Urbas 1986, 1988). Little attention has been given to responses that are not synchronized to the stimulus waveform. It has long been known that more centrally located auditory nuclei show greater limitations in their stimulus-synchronizing capacity as compared with auditory-nerve fibers (for review, see Langner 1992). Whereas peripheral neurons have cutoff frequencies of their modulation transfer functions near 1 kHz (Joris and Yin 1992; Palmer 1982), stimulus-synchronized firings of cortical neurons in anesthetized animals are limited to much lower modulation frequencies (<100 Hz) and are generally dominated by onset responses (Eggermont 1991; Lu and Wang 2000; Phillips et al. 1989; Schreiner and Urbas 1988), preventing them from representing rapid temporal variations explicitly by their temporal discharge patterns. Although there is evidence that the stimulus-synchronizing ability of neurons was less limited in unanesthetized cortex (Bieser and Muller-Preuss 1996; Creutzfeldt et al. 1980; de Ribaupierre et al. 1972; Goldstein et al. 1959; Liang et al. 1999; Lu et al. 1999; Steinschneider et al. 1998), it appears that perceptual abilities of both humans and animals are still not fully accounted for by stimulus-synchronized responses of cortical neurons.

How does the cortex encode acoustic transients that occur beyond the limit of representation by temporal discharge patterns? There are indications that a discharge rate-based representation may be present in some cortical neurons at high modulation frequencies (Lu and Wang 2000). Our recent study suggested that cortical neurons integrate rapidly successive

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acoustic events within a "temporal integration" window (Wang et al. 2000). In the auditory cortex of awake marmosets, the length of this window appears to be on the order of 20–30 ms (Lu et al. 1999). The present study explored the extent to which cortical neurons can represent temporal features that occur within this integration period by means of average discharge rates or temporal discharge patterns.

Manipulations of sounds to alter temporal characteristics often introduce spectral changes that can be used as additional cues. A common method to reduce spectral cues is to use the time-reversed version of a signal. The advantage of time-reversed sounds is that the time-reversed signals have identical long-term frequency profiles as their forward versions, an important property for studying single neurons. The technique of time-reversing stimuli has been used in both psychophysical experiments to investigate issues in temporal processing (Akeroyd and Patterson 1995; Fay et al. 1996; Patterson 1994a,b) and in neurophysiological experiments to study neural selectivity to species-specific communications sounds (Esser et al. 1997; Margoliash 1983; McCasland and Konishi 1981; Wang et al. 1995). Cortical neurons have been observed to be highly selective to the forward version of a vocalization as opposed to the time-reversed version (Margoliash 1983; McCasland and Konishi 1981; Wang et al. 1995). However, the degree of complexity in these natural sounds makes it difficult to establish whether the selectivity is a highly specialized feature of a neuron or if it is partially a consequence of a more general temporal processing mechanism such as the sensitivity to temporal asymmetry.

Psychophysical experiments have shown that human listeners are able to discriminate between pairs of temporally asymmetric sounds, ramped and damped sinusoids, which are time-reversed versions of each other (Patterson 1994a,b). According to Patterson (1994a), ramped sinusoids (slow onset/fast offset amplitudes) have a stronger tonal percept while damped sinusoids (fast onset/slow offset amplitudes) have a more percussive percept. It was also demonstrated that sounds with rising amplitudes produce a louder perception (Neuhoff 1998; Stecker and Hafter 2000). These works showed the extent to which human listeners can use temporal cues to discriminate between time-reversed but spectrally identical stimuli. Animal perceptual performance in discriminating temporally asymmetric sounds has similarities to humans. Behavioral studies of goldfish showed qualitatively similar results to human in discriminating ramped and damped sinusoids (Fay et al. 1996), suggesting that these stimuli are perceived similarly across a wide range of species. Furthermore, because psychophysical evidence suggests that the perception of time-varying signals (Moody 1994) and temporal integration (Brown and Maloney 1986) for primates are similar to humans, it is likely that primates also discriminate the ramped and damped sinusoids similarly to humans. Behavioral studies of temporal asymmetry, however, have yet to be conducted in primates, including marmosets.

Neurophysiological studies of subcortical auditory structures using the ramped and damped sinusoids have demonstrated some degree of disparity between responses to the two types of stimuli (Fay et al. 1996; Pressnitzer et al. 2000; Winter and Patterson 1998). Fay et al. (1996) showed that responses of the goldfish auditory-nerve to ramped sinusoids were temporally different from the responses to damped tones. However,

modeling studies by Patterson and Irino (1998) suggest that the perception of temporal asymmetry is not fully accounted for by cochlear mechanics and transduction. Response asymmetries observed in the ventral cochlear nucleus (VCN) of the guinea pig (Pressnitzer et al. 2000) appeared to be more pronounced than those observed in the auditory nerve (Fay et al. 1996) with different VCN neuron types showing different degrees of response asymmetry. Neurons at the level of the inferior colliculus (IC) also exhibited response asymmetry (Winter and Patterson 1998). These studies suggest that neural processing of temporal asymmetry begins subcortically, but it is unknown to what extent further enhancement of the response asymmetry occurs more centrally beyond the IC. The present study investigated the cortical representations of temporally asymmetric ramped and damped sinusoids of short periods (25 ms) and explored the implications for the perception of these sounds from their cortical representations. The experiments were conducted in the auditory cortex of awake marmoset monkeys to avoid the side effects of anesthesia. The present study is part of our effort to understand cortical processing of communication sounds in this vocal species (Wang 2000).

METHODS

Animal preparation and recording procedures

Marmoset monkeys (*Callithrix jacchus jacchus*) were adapted to sit quietly in a semi-restraint device through an acclimation period of several weeks. Two head posts were attached to the skull of an animal by dental cement during an implant surgery, which was performed under sterile conditions with the animal deeply anesthetized by isoflurane (1.0–2.0%, mixed with 50% oxygen and 50% nitrous oxide). These posts were used to immobilize the animal's head during later recording sessions. During the implant surgery, the skull covering the auditory cortex was exposed and covered by a thin layer of dental cement (<1.0 mm in thickness) and surrounded by a wall built with dental cement. Subsequently, small holes, <1.0 mm in diameter and separated by ~0.5 mm, were made to allow the access to the underlying brain tissue by a single microelectrode. This was done by drilling through the thin layer of dental cement and ~80–90% of the thickness of the bone (before reaching the dura) in a target site using a custom-made micro-drill with a fine drill bit mounted on a micromanipulator (SM-11, Narishige) either while the animal was briefly anesthetized by ketamine or while it stayed awake. The remaining bone covering the dura surface was carefully removed using handheld fine instruments under an operating microscope (Carl Zeiss) at ×25–40 magnification to ensure accuracy. Because a marmoset's skull is thin (~1.0 mm in thickness), it was relatively easy to make an opening quickly with little or no disturbance to the animal. A second experimenter was also present to monitor the condition and reaction of the animal during the procedure. At the end of each recording session, the recording hole was thoroughly rinsed with sterile saline and filled with an antibiotic ointment. The area containing the hole was then filled with a polyvinylsiloxane dental impression material (Kerr) that provided a tight seal and could be removed easily at the next recording session. Each hole was permanently sealed by dental cement after several days of recordings. Typically 5–10 electrode penetrations were made within each recording hole. Necessary steps were taken to ensure the sterility during all procedures. There was usually only one opened hole at any given time during the period of recording sessions lasting up to several months. The advantage of this procedure was that it only left a very small portion of the cortex exposed, which greatly increased the recording stability, avoided excess tissue growth, and reduced the chance of infections through the opening.

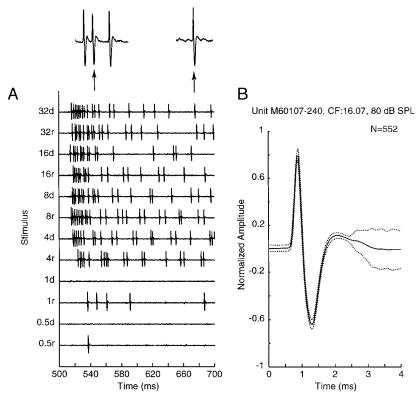All recording sessions were conducted within a double-walled,

FIG. 1. Examples of digitized traces of extracellular recordings from the auditory cortex of an awake marmoset in response to a set of ramped and damped sinusoids. *A*: the traces are ordered according to the stimulus type (stimulus half-lives are indicated on the left, see Fig. 2). One repetition for each stimulus condition is shown. Signal-to-noise was typically >10:1 in our recordings. *Insets*: enlarged views of individual action potentials. *B*: average waveform of all action potentials recorded during the presentation of an entire set of ramped and damped sinusoids. —, the mean value; · · ·, 1 standard deviation. Sampling rate was 30 kHz.

soundproof chamber (Industrial Acoustics). The interior of the chamber was covered by 3-in acoustic absorption foam (Sonex, Illbruck). Daily recording sessions, each lasting 3–5 h, were carried out for several months in each animal. Single-unit activities were recorded using a tungsten microelectrode of impedance typically ranging from 2 to 5 MΩ (A-M Systems). For each cortical site, the electrode was inserted nearly perpendicularly to the cortical surface by a micromanipulator (Narishige) and advanced by a hydraulic microdrive (David Kopf Instruments). Action potentials were detected by a template-based spike sorter (MSD, Alpha Omega Engineering) and continuously monitored by the experimenter while data recordings progressed. We typically sorted one single unit, and less often two single units, from signals recorded with an electrode. On average, one to three well-isolated single neurons were studied in each session. Examples of typical recording traces in these experiments are shown in Fig. 1. The signal-to-noise ratio in our recordings was generally >10:1 (Fig. 1*A*). For each neuron encountered, the shapes of the action potentials were highly consistent throughout the duration of presentation of all studied stimulus protocols (Fig. 1*B*). The template matching method prevented any unwanted noises (e.g., due to the animal's movement) from triggering false spikes. Single neurons were encountered at all cortical layers, but the majority of the recorded data were from layers 2 and 3 (~150–900 μm), and to a lesser extent from layer 4 (~900–1,150 μm), judging by the depths and characteristics of the recordings. The location of the primary auditory cortex was determined by its tonotopic organization, its relationship to the lateral belt area (which was more responsive to noises than tones), and by its response properties (highly responsive to tones with short latencies).

Acoustic stimuli

Acoustic signals were generated digitally and delivered in free-field through a speaker located ~1 m in front of the animal. The characteristic frequencies (CF) and thresholds were initially estimated using a manually controlled oscillator (4200B, Krohn-Hite) and attenuator (PA4, Tucker-Davis Technologies) and then precisely determined by a computer-controlled stimulus protocol. Once a neuron was isolated

and its basic response properties (e.g., CF, latency and rate-level characteristics) determined, other stimulus protocols were executed in randomized blocks.

Experimental stimuli were ramped and damped sinusoids (Patterson 1994a) as shown in Fig. 2. These were generated by modulating a sinusoidal carrier at a neuron's CF with an exponential function. The half-life of the exponential function determined the time course of the amplitude modulation of the stimulus, and a range of them was tested (0.5–32 ms). The values chosen matched those used in previous psychophysical studies (Patterson 1994a). The length of a stimulus was 12.5, 25, 50, or 100 ms. The majority of the data was collected using a stimulus length of 25 ms such as those in Fig. 2*A*. Each stimulus was repeated, with a period equal to its length to a total duration of 500 ms. The sinusoidal carrier, set at a neuron's CF, was continuous in phase throughout the entire stimulus duration. For each pair of ramped and damped sinusoids at a particular half-life, the long-term frequency spectra (i.e., the analysis window was longer than the stimulus length) were identical (Fig. 2*B*). Only the phase characteristics were different. As the half-life increases, the width of the spectral peak of a ramped or damped sinusoid decreases. Sound intensity was typically set at the peak in the neuron's rate-level function if it was nonmonotonic or 10–30 dB above threshold if it was monotonic.

Data analysis

Data were analyzed using custom software under the MATLAB (Mathworks) environment. Discharge rates were calculated over the entire stimulus duration plus an additional 100 ms to include responses that lasted beyond the stimulus offset. Spontaneous discharge rates were estimated from recordings prior to stimulus presentation and subtracted from the discharge rates. To quantify the asymmetry preference of a cortical neuron to ramped or damped sinusoids, we defined an *asymmetry index* (I) at each half-life value of the stimulus as follows: $I = (R_r - R_d)/(R_r + R_d)$ where R_r and R_d were the discharge rates to the ramped and damped sinusoids, respectively. The discharge rate was set to 0 spikes/s for the asymmetry calculation if a neuron's firing was suppressed below its spontaneous level during
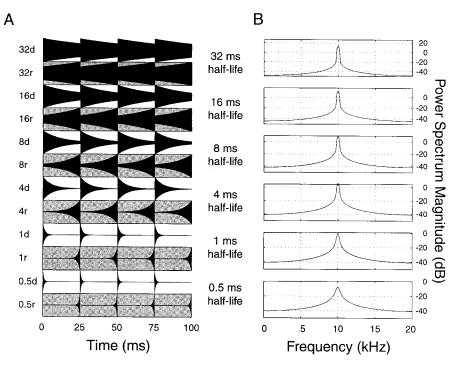
FIG. 2. Ramped and damped sinusoidal stimuli. *Middle*: the half-life of each pair. The examples shown have 25 ms periods and 10 kHz carrier frequencies. *A*: time-amplitude waveforms. Only the first 100 ms of the stimuli is shown. Ramped sinusoids are shown in the shaded blocks. *B*: power spectra of the corresponding sinusoids shown in *A*. The power spectrum is identical for each pair of ramped and damped sinusoids at a particular half-life. The width of the spectral peak increases as the half-life value decreases.

stimulus presentation (i.e., when the calculated discharge rate was <0 spikes/s). A positive asymmetry index indicated that a neuron responded more strongly to the ramped stimuli, while a negative asymmetry index indicated that a neuron responded more strongly to damped stimuli. An asymmetry index of 0 indicated that the discharge rates were equal in response to ramped and damped sinusoids. Statistical significance of the asymmetry index was assessed using a *Wilcoxon rank-sum test* (Rice 1988). At each half-life, the firing rates to the ramped sinusoids, on a trial-by-trial basis, were tested against those to the damped sinusoids. If the asymmetry index was not significant at the $P < 0.05$ level, it was set to zero. This ensured that nonsignificant asymmetry values (due to factors such as low spike rates) did not detrimentally affect further analyses based on these values. An *overall asymmetry index* was calculated to indicate the general preference of a neuron to the ramped or damped sinusoid. This was done by calculating an asymmetry index using the average discharge rate over all half-lives tested rather than at each single half-life value. The statistical significance ($P < 0.05$) of this measure was determined with a *Wilcoxon signed-rank test* (Rice 1988) using paired discharge rates from corresponding ramped and damped sinusoids at each half-life value. Consistent asymmetry preferences across the different half-lives tend to result in significant overall asymmetry index measures. For the population of neurons showing significant overall asymmetry, two pools of discharge rates corresponding to the ramped and damped sinusoids (including all half-life conditions) were compared ($P < 0.05$, Wilcoxon rank-sum) to provide a statistical indication of the difference in neuronal activity resulting from the temporally asymmetric stimuli.

We also calculated asymmetry and overall asymmetry index measures using the discharge rates of the onset responses. The lengths of the onset responses, if any, were determined manually based on the poststimulus histograms. Differences between the onset response and the total (onset + sustained) response in response asymmetry were assessed using the overall asymmetry index measure.

To study the role of temporal discharge patterns, we evaluated asymmetry preference using measures of stimulus synchronized discharges. Stimulus-synchronized temporal patterns were quantified by means of synchrony rate (R_s) and vector strength (VS) (Goldberg and Brown 1969). The statistical significance ($P < 0.001$) of the synchronized response was assessed with a *Rayleigh test* (Goldberg and

Brown 1969; Lu and Wang 2000; Mardia and Jupp 2000). Onset responses were excluded from the calculation of the vector strength and insignificant values of the vector strength were set to zero. An asymmetry index based on the vector strength at each half-life was defined as $I_{VS} = (VS_{ramped} - VS_{damped})$, where VS_{ramped} and VS_{damped} were the vector strengths calculated for the responses to the ramped and damped sinusoids, respectively. The statistical significance of I_{VS} was determined in a similar manner to the discharge rate-based asymmetry index. At each half-life, the trial-by-trial vector strengths were compared between the responses to the ramped and damped sinusoids with the Wilcoxon rank-sum test. Insignificant I_{VS} values ($P > 0.05$) were set to zero. A value of I_{VS} equal to 1 indicated that the responses were perfectly synchronized to the ramped sinusoids with no significant synchronization to the damped sinusoids, while a value of -1 would mean the opposite. An I_{VS} value of zero indicated no difference in synchronized responses or no significant stimulus-synchronized discharges for both responses.

Minimum response latencies were calculated from responses to tones presented at a neuron's CF with the sound level set at the peak of a neuron's rate-level function if it was nonmonotonic or 30 dB above threshold if it was monotonic. If tone data were not available (4/44), the minimum response latencies were calculated from the responses to the ramped and damped stimuli.

RESULTS

The results reported here are based on 181 single neurons recorded from three marmoset monkeys. The units were sampled from the left primary auditory cortex, and the CFs ranged from ~1 to 22 kHz. Response asymmetry was primarily judged by mean firing rate while stimulus-synchronized discharges were also analyzed. For the majority of units, the discharge rates in response to ramped and damped sinusoids were different with 140 (77%) neurons showing significant asymmetry in their response in at least one value of the half-life of the ramped and damped stimuli tested. Forty-six neurons showed significant overall asymmetry in their responses. Changing the sound level or stimulus period did not significantly alter a neuron's overall asymmetry preference.

Sensitivity to temporal asymmetry of ramped and damped sinusoids

PREFERENCE TO RAMPED SINUSOIDS. Over half of the units studied responded more strongly to the ramped sinusoids, measured by average discharge rate, for at least one half-life. Figure 3 shows examples of units with asymmetry preferences to ramped stimuli. For the neuron shown in Fig. 3A, when a ramped sinusoid with a half-life of 0.5 ms was presented, this
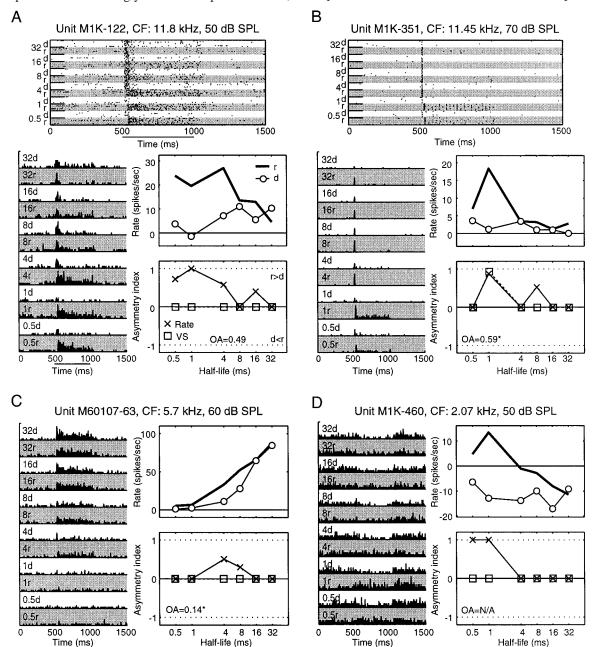

FIG. 3. Examples of neurons that showed preference to ramped sinusoids. Responses are plotted in the same order as the stimuli shown in Fig. 2 with alternating ramped and damped sinusoids and increasing half-lives, which are indicated on the ordinate. Dot-raster plots are shown in A and B. Each point represents a single action potential. Poststimulus time histograms (PSTH) are shown in A–D. Bin size is 1.0 ms, and heights are normalized to the maximum bin count over all stimulus conditions. Stimuli onsets were at 500 ms, and the durations were 500 ms. Driven discharge rates are plotted as a function of half-life for ramped (thick line) and damped (thin line with open circles) sinusoids, respectively. Asymmetry index values marked with a cross are based on discharge rate. Nonzero values based on discharge rate are statistically significant ($P < 0.05$, Wilcoxon rank-sum). Response asymmetries based on vector strength (see METHODS) are marked by boxes with all nonzero values being statistically significant ($P < 0.05$, Wilcoxon rank-sum). The overall asymmetry index (OA), based on discharge rate, is indicated for each unit, and statistically significant ($P < 0.05$, Wilcoxon signed-rank) values are indicated with an asterisk. A: significant asymmetry preference based on discharge rate to ramped sinusoids was present over most half-lives tested in this example unit. No statistically significant stimulus-synchronized activity was present. B: statistically significant asymmetry based on both discharge rate and synchrony was found at 1 ms half-life. C: additional example of a neuron that showed statistically significant asymmetry preference based on discharge rate. In contrast to B, this neuron responded more strongly at larger half-life values. No statistically significant stimulus-synchronized activity was present. D: example of a neuron that showed inhibition during the presentation of damped sinusoids.

neuron discharged at ~25 spikes/s over the duration of the stimulus. However, with a damped sinusoid of the same half-life (0.5 ms), the neuron was nonresponsive after a weak onset burst. No sustained activity with discharge rates greater than spontaneous level was observed for the duration of the damped sinusoid. For the half-lives tested between 0.5 and 4 ms, the driven rate to the ramped sinusoid was still higher than that to the damped sinusoids, which remained consistently low over most half-lives. Figure 3A, bottom right, shows the asymmetry index, based on discharge rate, calculated at each half-life. Values >0 indicate that the response was significantly stronger to the ramped sinusoids, clearly seen in both the dot-raster plot and the discharge rate curves. All nonzero asymmetry index values shown in this and the following figures were statistically significant ($P < 0.05$, Wilcoxon rank-sum). No statistically significant asymmetry index measures based on vector strength (see METHODS) were found at the tested half-lives for this neuron.

Stimulus-synchronized discharges were observed in discharges of some neurons as illustrated by the example in Fig. 3B, usually found in response to both ramped and damped sinusoids. Although further analysis of the stimulus-synchronized discharges revealed that there was a significant difference between the vector strengths at 1 ms half-life (Fig. 3B, bottom right), the difference was due mainly to the absence of discharges in response to the damped sinusoids. There was a broad range of discharge rates evoked by the ramped and damped sinusoids among the units studied, and the examples in Fig. 3 show the variety of this property. In general, the responsiveness of the neurons appeared to depend on the stimulus half-life as illustrated by the examples in Fig. 3, B and C. For example, the neuron in Fig. 3C had discharges that almost reached 100 spikes/s and showed asymmetry only for half-lives of 4 and 8 ms. For most units that showed sensitivity to ramped and damped sinusoids, the asymmetry preference for stimulus type was generally maintained across the stimulus half-lives. Collectively, the preferences for ramped sinusoids were observed at all half-life values across our samples.

Discharges of cortical neurons could also be inhibited by ramped or damped sinusoids as shown in Fig. 3D. At half-lives of 0.5 and 1 ms, the driven discharge rates were between 5 and 12 spikes/s for the ramped sinusoids and less than the spontaneous discharge rate for damped sinusoids. As the half-life was further increased, the responses to both ramped and damped sinusoids dropped below spontaneous rates.

PREFERENCE TO DAMPED SINUSOIDS. Figure 4 shows representative examples of a class of neurons that responded more strongly to damped sinusoids. For the neuron shown in Fig. 4A, onset responses were seen at all half-lives tested. At half-lives of 0.5 and 1.0 ms, sustained responses were present, but discharge rates to ramped and damped sinusoids were approximately the same. For half-lives of 4 and 8 ms, however, sustained responses occurred exclusively during the presentation of the damped sinusoids but not during the ramped sinusoids, and significant asymmetry was observed at these half-life values (Fig. 4A, bottom right). At half-lives >8 ms, little sustained responses were observed. Stimulus-synchronized responses were clearly visible in this unit. At 4-and 8-ms half-lives, the asymmetry in vector strength was significant. As with

the unit in Fig. 3B, this difference was correlated with the rate-based response asymmetry.

No stimulus-synchronized responses were observed for the unit shown in Fig. 4B, and no statistically significant differences in the vector strength asymmetry were found. Discharge rates were nearly 0 spikes/s at 0.5-ms half-life. Increasing the half-life to 1.0 ms produced strongly driven discharges to both ramped and damped sinusoids. However, the discharge rates were almost the same, and no significant asymmetry was present at this value. At half-life values of 4 and 8 ms, the driven rate to the damped stimuli remained consistently high near 15 spikes/s, while the responses to the ramped stimuli dropped close to 0 spikes/s by 8 ms. The asymmetry indices were significant at these two half-lives. At longer half-lives of 16 and 32 ms, the neuron barely responded to the damped sinusoids and did not respond to the ramped sinusoids at all. The neuron in Fig. 4C showed sustained driven responses over all half-life values tested. Only at half-lives of 16 and 32 ms were there significant asymmetries in the responses. While there appeared to be some onset responses to the ramped sinusoids at 16 and 32 ms half-life values, the sustained parts of the driven responses were not present. In contrast, the responses to the damped sinusoid at these half-lives were as strong as those at the shorter (<16 ms) half-lives.

We also observed preferences to damped sinusoids that appeared to result from inhibition (Fig. 4D). For the example shown in Fig. 4D, when half-lives were <8 ms, there were strong discharges at ~40 spikes/s to the damped stimuli. The corresponding responses to the ramped sinusoids did not show any increases in discharge rate above the spontaneous level. At 4 and 8 ms half-life values, the driven rate to the damped sinusoid began to decrease. There were very few discharges in response to the ramped sinusoid at 4 ms and only a few spikes at 8 ms half-life for the duration of the stimuli. By the time the half-life reached 16 and 32 ms, responses to both the ramped and damped sinusoids were completely inhibited. Strong offset responses were observed for half-life values >4 ms.

OTHER TYPES OF RESPONSES. A small percentage of cortical neurons did not show consistent asymmetry preferences to either ramped or damped sinusoids over the half-life values tested. They showed either no asymmetry preference in their responses or their asymmetry preferences changed directions depending on the stimulus half-life. Examples of such neurons are shown in Fig. 5. The neuron shown in Fig. 5A was driven by stimuli with half-lives >0.5 ms, and the driven rate increased with the stimulus half-life to almost 30 spikes/s at 32-ms half-life. Discharge rates between the responses to the ramped and damped sinusoids were nearly the same for most half-life values. There were no statistically significant differences found between the driven rates to ramped and damped sinusoids over all half-lives tested. Another example (Fig. 5B) showed similar responses. The driven rate increased from ~0 to 20 spikes/s with increasing stimulus half-life (>1 ms) while the asymmetry index remained at 0 (no stimulus preference) for all half-lives even where the driven rate was sufficiently high.

Some units exhibited inconsistent asymmetry preference that appeared to be dependent on the stimulus half-life (Fig. 5, C and D). The driven rate to ramped stimuli for the neuron in Fig. 5C dropped from 100 to 20 spikes/s as the half-life was increased. The driven rate to the damped stimuli also showed
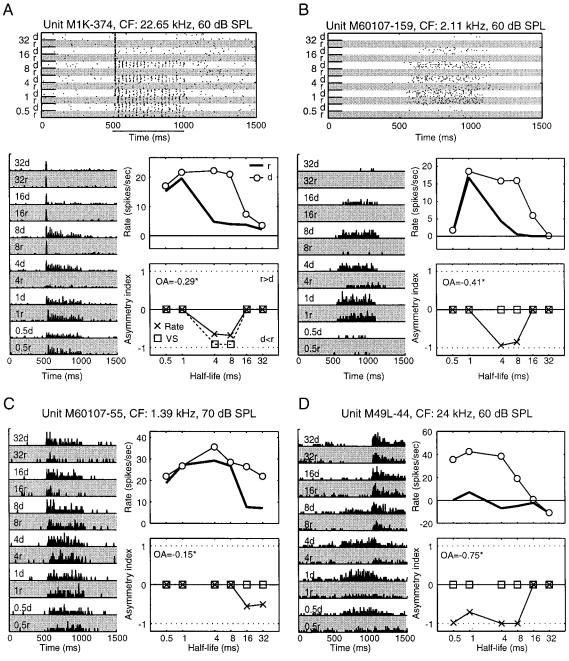
FIG. 4. Examples of neurons that showed preference to damped sinusoids. The format is the same as in Fig. 3. *A*: statistically significant asymmetry preference to damped sinusoids based on discharge rate and synchrony were clearly observed at 4 and 8 ms half-life values. *B*: statistically significant asymmetry preference was visible only for the discharge rate-based measure. No stimulus-synchronized responses were observed. *C*: additional example of asymmetry preference to damped sinusoids. No stimulus-synchronized responses were present. *D*: responses to ramped stimuli were apparently inhibited at half-lives >1 ms.

a decrease, with smaller changes, from 60 to 40 spikes/s. While the response to the ramped stimuli was stronger at 0.5 ms half-life, it was weaker at 32 ms half-life. The asymmetry index showed the corresponding change from ~0.25 (preference for ramped) to −0.25 (preference for damped). Stimulus-synchronized responses were apparent (Fig. 5*C*, *left*). Only a very a small, though statistically significant, difference in the vector strength asymmetry was detected at the half-life of 0.5 ms. Another example of inconsistent asymmetry preference is shown in Fig. 5*D*. The asymmetry index of this neuron also changed from preferring ramped

sinusoids to preferring damped sinusoids as the half-life was increased.

OVERALL ASYMMETRY INDEX. Of 181 units studied, 46 had significant overall asymmetry index values ($P < 0.05$, Wilcoxon signed-rank). The distribution of the index values is shown in Fig. 6. The overall asymmetry index provides a measure of a neuron's preference to the ramped or damped stimuli over the entire range of half-lives tested. Neurons with asymmetry indices close to 0 were generally not significantly different in their responses to ramped versus damped sinusoids
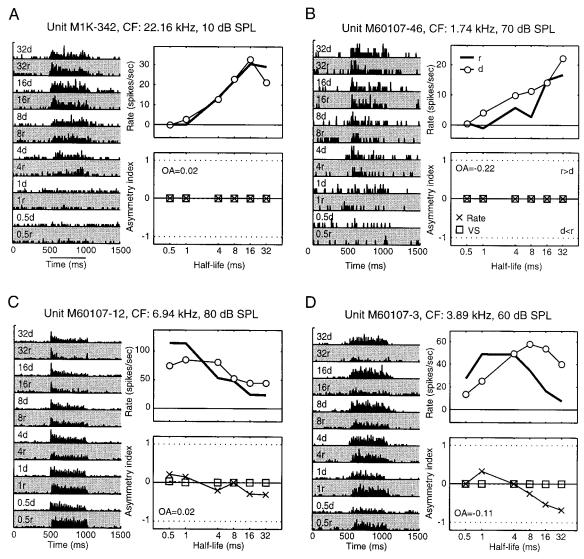
FIG. 5. Other types of neural responses to ramped and damped sinusoids. The format is the same as in Fig. 3. These neurons showed no consistent statistically significant overall preference to either ramped or damped stimulus but were sensitive to stimulus half-life. *A*: discharge rates were nearly identical for all stimulus half-lives tested. No stimulus-synchronized responses were observed. *B*: no statistically significant asymmetry preference was found. *C*: statistically significant asymmetry preference based on discharge rate switched from ramped at short half-lives to damped at longer half-lives. Stimulus-synchronized responses were present, but the asymmetry based on synchrony was significant only at 0.5 ms half-life. *D*: another example of inconsistent asymmetry preference.

and thus were not included in the histogram. Of the 46 neurons that had significant overall asymmetry index values, 32 (70%) neurons had index values greater than zero (preferring ramped sinusoids), and 14 (30%) had index values less than zero (preferring damped sinusoids). Most of the asymmetry indices (30/46) fell between −0.5 and 0.5. Six neurons showed overall asymmetry values that were close to 1, indicating that the responses at nearly all half-lives were driven by the ramped sinusoids. Only one neuron had an overall asymmetry index near −1, indicating a nearly exclusive preference for the damped sinusoids. For this population of neurons showing significant overall asymmetry, the discharge rate to ramped sinusoids, including all half-life conditions, had a median value of 6.7 spikes/s [(25%, 75%) = (2.6, 20.2) spikes/s]. Discharge rates to damped sinusoids had a median value of 6.0 spikes/s [(25%, 75%) = (0.9, 17.2) spikes/s]. This difference was statistically significant ($P < 0.05$, Wilcoxon rank-sum).

Temporal discharge patterns produced by ramped and damped sinusoids

TEMPORAL DISCHARGE PATTERNS WITHIN A STIMULUS PERIOD. We also investigated the possibility that stimulus asymmetry may be represented by temporal discharge patterns on a fine time scale. Figure 7 shows period histograms of four representative units that are also illustrated in Figs. 3–5. Examining the period, however, histograms show that no substantial and consistent differences exist in the temporally patterned responses to ramped and damped sinusoids with 25-ms stimulus periods. The neuron in Fig. 7*A* (also shown in Fig. 3*C*) responded more strongly to the ramped sinusoid at 4- and 8-ms half-lives as measured by discharge rate. At half-lives >8 ms, no clear temporal patterns were observed despite strong sustained firings throughout the stimulus period. At half-lives of 16 and 32 ms, the responses to ramped and damped sinusoids were in-
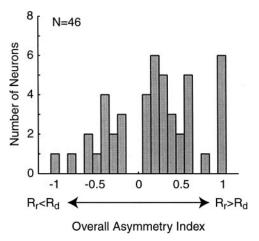
FIG. 6. Histogram of statistically significant ($P < 0.05$, Wilcoxon signed-rank) overall asymmetry indices (see METHODS) from 46 neurons. Neurons with positive overall asymmetry index preferred ramped sinusoids, whereas neurons with negative overall asymmetry index preferred damped sinusoids. In this population, the difference between the median discharge rates in response to ramped and damped sinusoids over all half-lives (6 conditions for each of the 46 neurons) was statistically significant ($P < 0.05$, Wilcoxon rank-sum). Discharge rate to ramped sinusoids: median 6.7 spikes/s, (25%, 75%) = (2.6, 20.2) spikes/s. Discharge rate to damped sinusoids: median 6.0 spikes/s, (25%, 75%) = (0.9, 17.2) spikes/s.

distinguishable by discharge rates (Fig. 3C) and by temporal discharge patterns within a period of the stimuli. The neuron in Fig. 7B (also shown in Fig. 4A) displayed prominent stimulus-synchronized activity and a stronger response to damped sinusoids at 4 and 8 ms half-lives. While the neuron clearly

responded to both the ramped and damped stimuli equally strongly in discharge rates at half-lives of 0.5 and 1 ms, the temporal patterns of responses to the two stimuli were not clearly distinguishable beyond noisy variations except for the difference in the latencies of spike bursts. Another example of this kind is shown in Fig. 7C. This neuron (also shown in Fig. 10C) showed large differences in the discharge rate between the ramped and the damped sinusoids at 0.5- and 1-ms half-life values but only small differences at half-lives of 4–32 ms. While the neuron responded strongly at half-lives of 4–32 ms, the period histogram did not show clear differences between the responses to the ramped and damped sinusoids in the period histogram. For neurons like the one in Fig. 7D (also shown in Fig. 5A) that showed no differences in their discharge rates to ramped and damped sinusoids at all half-lives tested, there were no differentiable temporal patterns in the period histograms between ramped and damped stimuli.

STIMULUS-SYNCHRONIZED DISCHARGE PATTERNS. The response patterns of neurons were analyzed for stimulus-synchronized discharges. As shown in Fig. 7, differences in the temporal response to the two types of stimuli were usually not readily apparent within one period of a stimulus. The possibility exists that temporal discharge patterns on a larger time scale could be used to distinguish ramped and damped sinusoids. Stimulus-synchronized responses were already seen in Figs. 3B, 4A, and 5C, but in these examples, significant asymmetries in vector strength were always accompanied by significant asymmetries in discharge rate. In Fig. 8A synchronized discharge rates (see METHODS) are plotted against the average discharge rate for all
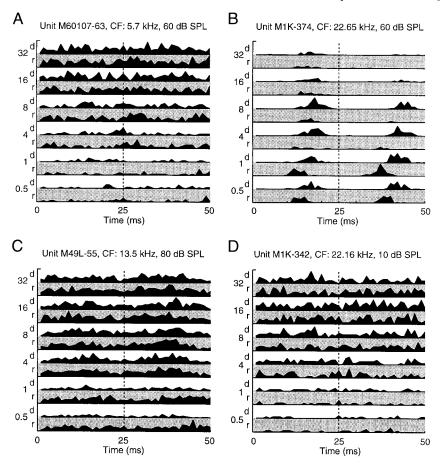

FIG. 7. Temporal discharge patterns within a short stimulus period. The period histograms are ordered similarly to the poststimulus histograms in Fig. 3. Two stimulus periods are shown, and bin size is 1 ms. A: this neuron (also in Fig. 3C) showed asymmetry preference in discharge rate to ramped sinusoids at 4- and 8-ms half-life values. No temporal patterns were observed within a stimulus period (25 ms). B: an example of a stimulus-synchronized neuron (also in Fig. 4A) with preference in discharge rate to damped sinusoids. The period histogram showed clustered responses. Except for latency, no clear and consistent differences in the temporal discharge patterns separate the responses to ramped and damped sinusoids. C: additional example of the temporal response of a neuron (also in Fig. 10C) with preference to ramped sinusoids. D: an example of a neuron with no significant asymmetry preference by discharge rate (also in Fig. 5A). Temporal discharge patterns did not provide additional information to separate ramped sinusoids from damped ones.
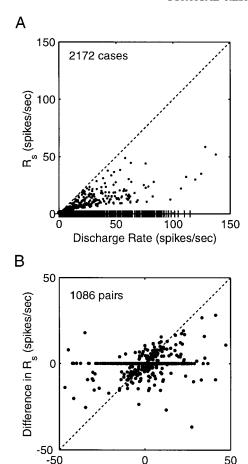
FIG. 8. Analysis of stimulus-synchronized discharges patterns. *A*: synchrony rate (R_s) is plotted against average discharge rate. Each point represents a single stimulus condition (12 stimulus conditions for each of 181 neurons). The vast majority of cases (1,889/2,172, 87%) did not have statistically significant ($P <$ 0.001, Rayleigh test) stimulus-synchronized responses (points on the *x* axis). *B*: differences in the synchrony rate, R_s(ramped)–R_s(damped), are compared with differences in average discharge rate for each of the stimulus half-life conditions (6 half-lives for each of 181 neuron). The vast majority of cases (878/1,086, 81%) did not have significant differences in their synchrony rate (points on the *x* axis).
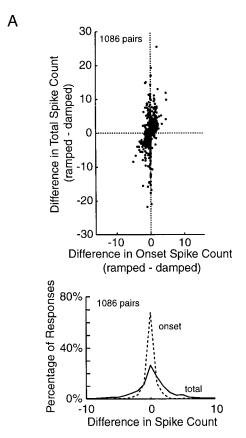
12 stimulus conditions (ramped and damped at 6 half-lives) and 181 neurons. Statistically insignificant stimulus-synchronized responses were set to zero. The vast majority of instances (1,889/ 2,172 cases, 87%) did not show significant stimulus-synchronized activity. Figure 8*B* compares the differences in the synchrony rate of the responses to the ramped and damped sinusoids to those in the average discharge rate. Overall the range of synchrony rate differences for the majority of the data points is less than the range of differences in the average spike rate. In many cases, the difference in the synchrony rate is near zero, but the difference in the average discharge rate is large. The suggestion of these data is that although synchronized responses are present in some of the neural responses, the differences in the synchronized responses at a given stimulus half-life are usually less pronounced than those measured by the average discharge rate.

Onset versus sustained responses

An important response characteristic of the awake auditory cortex is prominent sustained discharges that are generally

absent under anesthetized conditions. Onset responses are generally observed under both experimental conditions. In Fig. 9, we compared response asymmetry measured by onset or total (onset plus sustained) responses. When total spike counts were considered, the difference between responses to the ramped and damped sinusoids was in general much larger than that measured by onset spike count (Fig. 9*A*). There were many points that had negligible differences in the onset response but
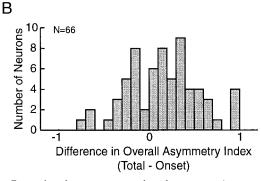

FIG. 9. Comparison between onset and total responses. *A, top*: each point represents the difference in spike count per repetition between the ramped and damped sinusoids at a given half-life based on the onset response (*x* axis) or the total response (*y* axis). Six conditions corresponding to the stimulus half-lives are plotted for each of 181 units. *Bottom*: histogram of the difference in spike counts for onset (- - -) and total responses (—). Spike count differences between the ramped and damped sinusoids based on onset responses were generally smaller than those based on the total response. *B*: histogram of the difference between the overall asymmetry index calculated with the onset response and the total response. Values >0 indicate that the overall asymmetry index calculated from the total response is greater than that calculated from the onset response. Sixty-seven percent (44/66) of neurons showed greater overall asymmetry with the total response.

large differences in the total spike count. Most data points fell into the upper right or lower left quadrant, indicating that the directions of asymmetry preference were the same between the two measures. This was reflected in the vertically elongated distribution of the data points (Fig. 9A, *top*) and in the greater spread of total firing rates compared with the onset firing rates (Fig. 9A, *bottom*). This indicated that sustained firings contributed toward greater response asymmetry. Furthermore a large number of data points along the y axis in Fig. 9A (*top*) show that response asymmetry is only present in sustained firings in those cases. In Fig. 9B, a comparison of the overall asymmetry calculated with the total response versus one using only onset activity showed that overall asymmetry generated by the total response was greater than those produced by the onset response in 44 of 66 (67%) neurons with significant values of overall asymmetry index from either of the two calculations (onset and total).

Stimulus selectivity remained unchanged across sound levels

Since the calculation of the asymmetry is based on discharge rate, it is important to know whether the asymmetry preference of a neuron is influenced by sound level. If the response of a neuron was mainly due to the temporal context of the stimuli, the sound intensity should not significantly affect a neuron's asymmetry preference. Figure 10 shows examples of responses over a range of sound levels from two neurons. For both of the neurons shown in Fig. 10, the asymmetry preference did not change direction (e.g., from ramped sinusoid to damped sinusoid) over the sound levels tested.

For the first example shown here, at 40 dB SPL (Fig. 10A), the asymmetry indices at half-life values of 0.5 and 1 ms were near 0.5, with the responses to the ramped sinusoids ~25 spikes/s greater than the responses to the damped sinusoids. At 60 dB (Fig. 10B), the asymmetry indices remained consistent for half-lives of 0.5 and 1 ms. After increasing the sound level to 80 dB (Fig. 10C), the discharge rate also increased, but the asymmetry indices at 0.5 and 1 ms remained close to the values found in the lower sound levels. Despite the large changes in sound level, the direction of the response asymmetry remained the same over the different sound levels tested. The neuron in Fig. 10, E–G, also showed an increase in the firing rate with increasing sound level, and its stimulus preference for ramped sinusoids remained unchanged.

We summarize the effect of sound level on asymmetry preference in Fig. 11. Figure 11A shows the mean, minimum, and maximum overall asymmetry index for neurons that were tested at multiple sound levels. The range of sound levels tested for each neuron is shown in Fig. 11B. Most of these neurons had overall asymmetry indices that were either all positive or all negative, meaning that their selectivity was unchanged at all sound levels tested. For most units, the minimum and maximum overall asymmetry index values generally had the same direction (same sign) of preference and were within 0.5 of each other in terms of the asymmetry index. Except for a small number of neurons, the direction of preference did not change with sound level. The four units that had a preference change generally had small values of mean overall asymmetry index. Since most neurons did not change preference with sound level, the proportion of neurons preferring the ramped or damped stimuli remained largely consistent over the

range of sound levels tested. Thus the representation of temporal asymmetry in the auditory cortex could remain tolerant of changes in sound level.

Response asymmetry is independent of stimulus period

The time course of AM in ramped and damped sinusoids depends on both the half-life and the stimulus period. For longer half-life values that grow or decay slowly, a longer time is necessary to produce an equivalent amount of change in the AM within a period of a stimulus. One question is whether the asymmetry preference we observed was dependent on the stimulus period. Figure 12, A and B, shows examples of responses over different stimulus periods ranging from 12.5 to 100 ms. In both of these cases, changing the stimulus period did not affect the general pattern of the asymmetry preference. In Fig. 12A, the asymmetry preference was for ramped sinusoids since there was little response to the damped sinusoids for half-life values <4 ms at all periods tested. In Fig. 12B, responses to the ramped sinusoids were weaker than those to the damped sinusoids at nearly all half-lives and for all stimulus periods tested. The response asymmetry was consistent over the different periods for each of the two neurons shown. At periods of 50 and 100 ms, the discharges were visibly stimulus-synchronized to the individual segments of the ramped and damped stimuli.

Figure 12C shows the mean, minimum, and maximum overall asymmetry index for neurons tested with multiple stimulus periods. For most neurons, the difference between the maximum and minimum was typically <0.4 (vs. 0.5 in Fig. 11). The variation in the overall asymmetry index in the neurons tested appeared to be less than that seen by changing the sound level (Fig. 11). Most neurons were found to prefer a particular temporal direction (ramped or damped) despite changes in stimulus period. The results of this analysis suggest that the shape of the envelope (e.g., ramped vs. damped) has a greater effect on the neuron's responsiveness than does the time course of the modulation (e.g., period).

Effect of stimulus half-life

Discrimination and perception of these temporally asymmetric stimuli by a human or marmoset may rely on the relative numbers of neurons sensitive to the ramped and damped stimuli. The number of neurons showing significant asymmetry index values (based on discharge rate) at each half-life value is shown in Fig. 13. For units that preferred the ramped stimuli, the number of neurons appeared to be greater at half-lives of 1–8 ms than at other values, while the number of neurons preferring the damped sinusoids is greater at half-lives of 4–8 ms than at other half-lives. At half-lives <16 ms, the number of neurons preferring the ramped sinusoids was greater than the number of neurons preferring the damped stimuli. For either of the two neuronal populations, the curves generally increase starting at 0.5-ms half-life, reaching a peak between 1 and 8 ms before decreasing. At half-lives >8 ms, the proportion of units was roughly equal among those preferring ramped or damped sinusoids.

Correlation with CF and latency

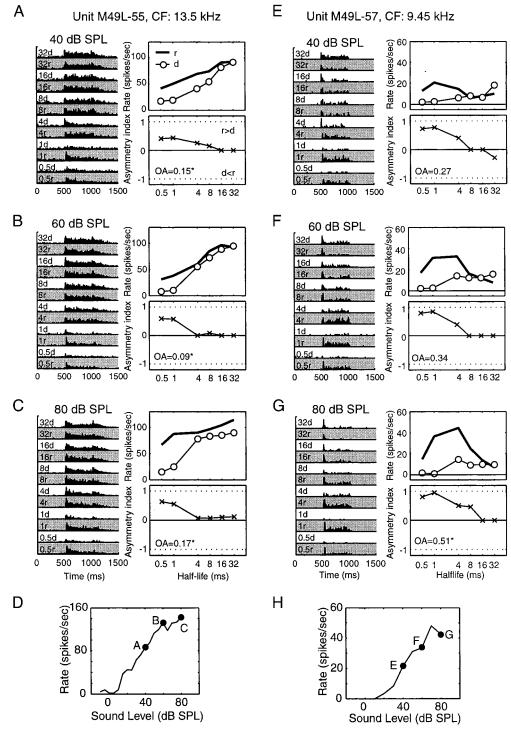Figure 14A shows the relationship between a neuron's CF and its overall asymmetry index. The overall asymmetry index

FIG. 10. Effect of sound pressure level on asymmetry preference. The format is the same as in Fig. 3. *A–C*: example of a neuron's responses to ramped and damped sinusoids at 40, 60, and 80 dB SPL, respectively. The direction of overall asymmetry preference of the neuron was unchanged over the range of sound levels tested. *D*: the rate-level function for the neuron shown in *A–C*. The sound levels used in *A–C* are indicated. *E–G*: another example of responses to ramped and damped sinusoids at 40, 60, and 80 dB SPL. The direction of overall asymmetry preference was unchanged. *H*: the rate-level function for the neuron shown in *E–G*. The sound levels used in *E–G* are indicated.

was not correlated with CF. Neurons at all CFs showed preferences to either the ramped or damped sinusoids. Because the latency of the response is related to the number of synapses traversed (i.e., more synapses in the pathway result in a longer latency), a plot of the asymmetry index against the response latency for these neurons may provide some insight into the

generation of stimulus preference. Latencies of neurons that showed significant overall asymmetry ranged from 14 to 85 ms with the majority having latencies <40 ms. There was no clear correlation between the first-spike latency and the overall asymmetry index (Fig. 14*B*). Asymmetry indices were proportionally distributed, consistently with the histogram in Fig. 6,
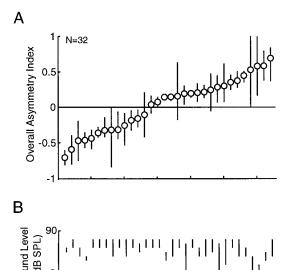
A

B

FIG. 11.   Summary of population properties to changes in sound level. *A*: ○, the mean overall asymmetry index for each neuron over the sound levels tested. The units shown have ≥1 significant overall asymmetry index over the range of sound levels tested and are ordered by their mean asymmetry index values (from negative to positive). |, the range of minimum and maximum asymmetry index values calculated for each neuron over all sound levels tested. The direction of overall asymmetry in most neurons was unchanged over the range of sound levels tested. *B*: the corresponding ranges of sound levels tested for each neuron shown in *A*.

between positive and negative values for the entire range of latencies. In addition, there was no observable trend within the two subpopulations of the neurons that preferred ramped or damped sinusoids. The direction and strength of a neuron's preference to ramped and damped stimuli did not appear to be at all correlated to its response latency. Together, the data in Fig. 14 suggest that the sensitivity of cortical neurons to ramped or damped stimuli exists across populations of neurons in the primary auditory cortex.

DISCUSSION

Comparison with previous neurophysiological studies

Neural responses to ramped and damped sinusoids have been studied in some subcortical structures (Fay et al. 1996; Pressnitzer et al. 2000; Winter and Patterson 1998). Recordings of auditory nerve (AN) in goldfish showed that both ramped and damped sinusoids resulted in strong responses and the firing patterns to the ramped sinusoid were temporally different from those to the damped sinusoids (Fay et al. 1996). It has been shown that a class of sounds (single-formant stimuli), similar to the damped sinusoids used in the present study, produced strong discharges in all types of AN fibers in cats (Wang and Sachs 1993). The temporal discharge patterns of AN fibers resemble the waveforms of the single-formant stimuli, a property not observed in the cortical responses to the damped sinusoids for the short stimulus period tested (25 ms). Pressnitzer et al. (2000) reported that onset and chopper neurons showed more pronounced response asymmetry to ramped and damped sinusoids than did the primary-like neurons, and response asymmetry appeared to be greater in some VCN neurons than in AN. Preliminary observations in IC also

showed various degrees of response asymmetry (Winter and Patterson 1998). Asymmetry in these VCN and IC studies were determined using a "peak-to-total" measure of the period histograms. Since this particular measure was based on temporal discharge patterns of responses rather than on mean firing rate, it was not appropriate for our cortical responses to the stimuli tested, as they did not generally display regular temporal patterns within the time window of 25 ms (Fig. 7). A more comparable measure used in these subcortical studies was total spike count. In AN, VCN, and IC, the total spike count elicited by ramped sinusoids were reported to be generally greater than those by damped sinusoids (Fay et al. 1996; Pressnitzer et al. 2000; Winter and Patterson 1998). It appeared, however, that cortical neurons exhibited much greater asymmetry preference than subcortical neurons. It was quite common for a cortical neuron to respond nearly exclusively to either ramped or damped sinusoids. Additionally, the responses of subcortical neurons exhibited prominently stimulus-synchronized discharge patterns. In contrast, cortical neurons showed response asymmetry with or without exhibiting stimulus-synchronized activity (Figs. 3 and 4).

It has long been documented that responses recorded in the auditory cortex of anesthetized animals are largely phasic (e.g., Eggermont 1991, 1994; Phillips et al. 1989). In general, onset discharges to stimuli dominate the majority of responses in anesthetized cortex, and little sustained activity was observed. This is, however, not the case in unanesthetized cortex where, as we demonstrated in this study, sustained discharges are commonly observed. Although the direction of the response asymmetry in the onset discharges was usually correlated with those based on sustained responses, our analysis showed that the response asymmetry can be more pronounced in the sustained portion of the response than during the onset (Fig. 9). An issue we attempted to address in the present study is whether A1 represents temporal asymmetry by mean discharge rate or temporal discharge patterns.

The stimuli used in this study contain features that are often found in natural stimuli such as human speech (Olive et al. 1993) and marmoset vocalizations (Wang et al. 1995). For example, the envelopes of the damped sinusoids resemble the envelopes of steady-state vowels as well as marmoset twitter calls, whereas the envelopes of the ramped sinusoids resemble the envelopes of the time-reversed versions of these sounds. The advantage of using these simpler stimuli is that the amplitude fluctuations are systematically generated, and their spectral and temporal characteristics are well controlled. In comparison, natural stimuli such as animal vocalizations can be full of spectral and temporal complexities that would make interpretation of their cortical responses difficult. The neural mechanisms involved in producing the response asymmetry are likely to contribute to neural selectivity of complex vocalizations that have been reported (Esser et al. 1997; Margoliash 1983; McCasland and Konishi 1981; Wang et al. 1995).

There are several possible mechanisms that could account for a neuron's responsiveness to a ramped or damped sinusoid but not to the time-reversed version. One is that the neuron does not receive excitatory inputs from subcortical pathways during the presence of a damped or ramped sinusoid. Another is that the neuron receives excitatory subcortical inputs that are actively suppressed by cortical inhibition. The presence of inhibition under a particular stimulus condition was clearly
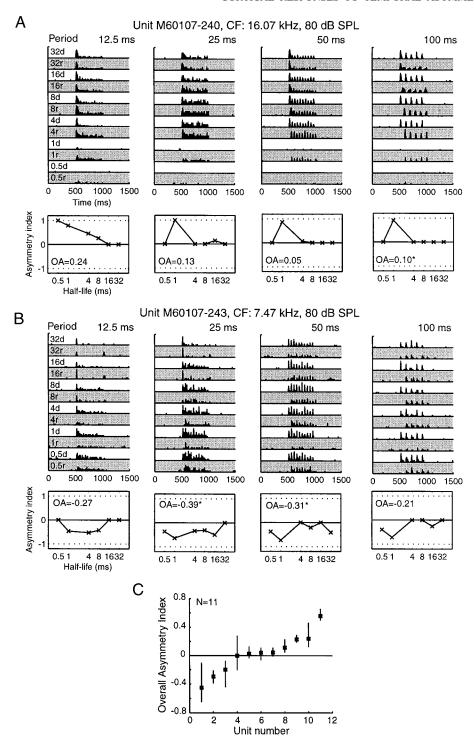
FIG. 12. Effect of stimulus period on overall response asymmetry. Stimulus periods tested were 12.5, 25, 50, and 100 ms. *A*: example of a neuron which responded more strongly to ramped sinusoids at short half-lives for all stimulus periods tested. *B*: example of a neuron that responded more strongly to damped sinusoids for all stimulus periods tested. *C*: summary of variations in the overall asymmetry index values with different stimulus periods tested in a subpopulation of neurons. The format of the plot is the same as Fig. 11. Units shown have ≥1 significant asymmetry value over the range of periods tested and are ordered by their mean overall asymmetry value (■). |, the range of minimum and maximum asymmetry index values. The direction of overall asymmetry was unchanged in the majority of neurons for which different periods were tested.

observed in some units with high spontaneous rates (Figs. 3*D* and 4*D*); this suggests that at least part of the response asymmetry observed were cortical in origin. The studies by Heil (1997a,b) on cortical onset responses to acoustic transients may to some extent explain some of the observations reported here, although they do not account for sustained and nonsynchronized discharges.

Correlation with psychophysics

The form of the ramped and damped sinusoids used in our experiments has been directly tested in human psychophysical studies (Akeroyd and Patterson 1995; Patterson 1994a,b). In these studies, human subjects were randomly presented ramped or damped sinusoids and asked which stimuli had a more sinusoidal characteristic. The results showed that the difference in the perception was strongest between 2 and 16 ms half-life (Patterson 1994a). At longer half-lives, the performance of the subjects decreased because the difference in AM between a ramped and damped sinusoid was small. Thus the subject had fewer temporal cues to work with. At shorter half-lives, the envelopes of ramped and damped sinusoids became more similar in their shapes and more like narrowband clicks. At
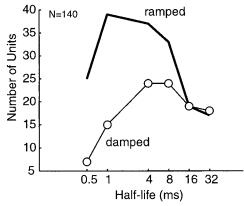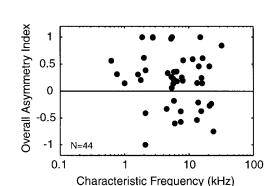
FIG. 13. Effect of stimulus half-life on asymmetry preference. The thick line indicates the number of neurons preferring ramped stimuli as a function of half-life. The thin line with open circles indicates the number of neurons preferring damped sinusoids as a function of half-life.

these two extremes, discrimination between these two stimuli would be expected to be more difficult.

Although ramped and damped sinusoidal stimuli have not been studied by imaging techniques, existing studies suggest that cortex is involved in processing temporal features (Griffiths et al. 1997, 1998; Zatorre 1988). The results of this study point to a correlation with human psychophysical performance. When the percentage of units with significant asymmetry index ($P < 0.05$, Wilcoxon rank-sum) for either ramped or damped sinusoids is plotted as a function of stimulus half-life (Fig. 15), the shape of the curve is qualitatively similar to data available
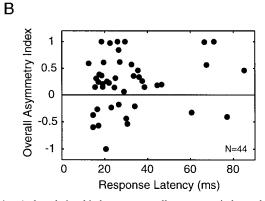

FIG. 14. A: the relationship between overall asymmetry index and neuron's characteristic frequency (CF). No significant correlation was observed. B: the overall asymmetry index vs. minimum response latency. There was no visible correlation between the two.
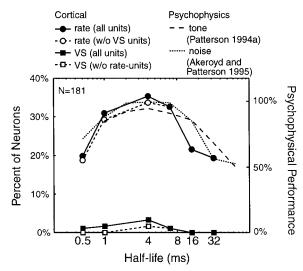

FIG. 15. Comparison between asymmetry preference of cortical neurons and human psychophysical performance in discriminating the ramped and damped sinusoids. The percentages of units (left ordinate) having significant asymmetry indices based on discharge rate are shown with a solid line and filled circles. - ○ -, the percentages of neurons showing significant discharge rate-based asymmetry preference, excluding those units that also showed asymmetry preference based on vector strength (VS). – ■ –, the percentages of neurons with significant asymmetry indices in VS. - □ -, the percentages of neurons that showed significant VS-based asymmetry preference but not rate-based asymmetry preference. There was a small percentage of neurons that showed significant VS-based asymmetry preference without also showing significant discharge rate-based asymmetry preference (- □ -). Human psychophysical performance curve (right ordinate) using ramped and damped sinusoids (tones) was based on data in Patterson (1994a), averaged over the different carrier frequencies used. Psychophysical performance on ramped and damped wideband noise stimuli was based on data reported in Akeroyd and Patterson (1995).

from human psychophysics (Akeroyd and Patterson 1995; Patterson 1994a). Psychophysical data from ramped and damped stimuli with both sinusoidal carriers (Patterson 1994a) and wideband noise carriers (Akeroyd and Patterson 1995) are overlaid on the plot in Fig. 15. The percentage of units showing strong asymmetry preference was much greater at half-lives of 1–8 ms than at 0.5 and 16–32 ms. Human psychophysical performance was better at half-lives of 1–16 ms than at 0.5 and 32 ms. The psychophysical performances at each half-life appear to be related to the active number of neurons that show significant response asymmetry.

The amplitudes of the ramped and damped stimuli in Patterson (1994a) were adjusted to maintain equal loudness perception across half-lives. Our stimuli maintained consistent amplitude, and only one parameter, the half-life, was changed. The asymmetry index was calculated at each half-life, and each pair of the ramped and damped sinusoid had the same energy. Because our analysis showed that response asymmetry was tolerant of changes in sound level (Figs. 10 and 11), the comparison between our cortical data and psychophysical data is justified. Our neurophysiological data were collected from neurons with a broad range of CFs (1–22 kHz). Since the psychophysical data from the two studies cited in the preceding text are similar to each other, and our results qualitatively match well with both of them, the similarity suggests that the cortical responses are strongly dependent on the temporal features of the envelope and less so on the specific spectral content of the carrier.

The results of our neurophysiological study also have relevance to other psychophysical studies that investigate temporal asymmetry. Neuhoff (1998) noted that subjects judged complex harmonic sounds with rising amplitudes as having a larger intensity change than those with falling amplitudes even though the two have equal but opposite changes in sound level. Stecker and Hafter (2000) tested human subjects' perception loudness of temporally asymmetric stimuli. While their stimuli had a different form than the ramped and damped sinusoids used in our study (a single segment hundreds of milliseconds long with different onset/offset shapes), the result of their study showed that stimuli with slow onsets followed by a fast offset were consistently judged as louder than ones with a fast onset and slow offset. The data from those studies might be explained by the proportion of neurons that responded more strongly to the ramped stimuli. We observed in our study a greater proportion of neurons that preferred ramped sinusoids (Figs. 6 and 14). Furthermore for the 46 neurons that showed significant overall asymmetry, the median discharge rate to the ramped sinusoids was significantly higher than the median discharge rate to the damped sinusoids (Fig. 6). Our hypothesis is that these two factors (larger number and higher discharge rates) contribute to the asymmetry in the perception of loudness.

Rate versus synchrony representation

Our analysis of the temporal response properties of auditory cortical neurons with respect to their stimulus-synchronized discharge patterns showed that the response measures based on discharge synchrony were strongly dependent on the average discharge rate (Fig. 8A). The significance of response asymmetry measured by vector strength was generally dependent on the overall responsiveness of the neuron as illustrated by the examples in Figs. 3B and 4A. Although stimulus-synchronized responses were present in these cases, there were no statistically significant differences between the vector strengths of pairs of ramped and damped sinusoids unless those differences in discharge rates were also significant. The majority of responses observed in the present study in the unanesthetized auditory cortex included sustained and nonsynchronized discharges.

Overall, the percentage of neurons showing significant asymmetry in vector strength was small compared with that of the rate-based measure. They constituted <5% of the neurons studied at each stimulus half-life value as shown in Fig. 15. When these neurons were excluded from the curve of units with significant rate-based asymmetry, the shape of the curve was only slightly lowered. The difference between the two curves demonstrates that there were only small percentages of neurons that had significant VS-based asymmetry preference while also having significant discharge rate-based asymmetry index. It is suggested that a rate-based representation for determining temporal asymmetry appeared to be the more prominent scheme that correlated well with psychophysical results. The method of calculating the significance of response asymmetry in the vector strength or in the average discharge rate is based on a trial-by-trial analysis of responses (see METHODS). The data in Fig. 15 show that rate-based measures can provide reliable information to the discrimination of ramped versed damped sinusoids on a trial-by-trial basis. They also indicate that stimulus-synchronized discharges are less likely to play a major role in coding stimulus asymmetry within a short time window. These observations, however, do not necessarily exclude contributions of temporal response properties in encoding other stimulus features by cortical neurons. The key point is the time scale. At the level of the cortex, the responses to rapid acoustic transients on the order of 25 ms appear to be transformed largely into a rate representation. At longer time scales, however, temporal response properties may be significant in cortical coding. In fact, data in Fig. 12 showed that as the stimulus period was increased to 100 ms, ramped and damped sinusoids produced different temporal discharge patterns within the stimulus period that reflect the temporal asymmetry in the stimulus waveform.

Implications for temporal integration

Although cortical neurons exhibit limited stimulus-following ability to sequences of acoustic events, the information is not lost but rather transformed into a rate-based representation (Lu and Wang 2000; Lu et al. 1999). As the findings in this study demonstrate, the modulation of the discharge rates by the fine temporal structure of sounds can be considerable such that a neuron can be turned on or off depending on the nature of stimulus envelope, despite similarities in the long-term frequency content. This suggests that the auditory cortex is capable of integrating temporal information occurring on short time scales (<25 ms).

Neural mechanisms that generate the response asymmetry reported here may underlie some of the specificity of cortical neurons to the temporal acoustic structure of complex vocalizations (Margoliash 1983; McCasland and Konishi 1981; Wang et al. 1995). More specifically, the results suggest that the rapid acoustic transients that are often found in complex communication sounds can be represented by the discharge rate of cortical neurons despite the fact that stimulus-synchronized discharge activities of auditory cortical neurons may not be sufficient to track acoustic transients temporally. The sensitivity to temporal asymmetry may give rise to the selectivity of cortical neurons for certain temporal aspects of complex sounds such as animal vocalizations. Although the selectiveness of an individual neuron for a particular call is probably not sufficient to adequately analyze an entire call, it might be possible with a population of such neurons showing varying degrees of selectivity.

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