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Responses of single auditory cortical neurons to tone sequences

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The responses of single neurons in the primary and secondary auditory cortex of cat were recorded during the presentation of sequences consisting of five tones of different frequencies. Discharges to tones within these sequences usually (84%) exhibited a dependence on the 'direction' of the sequence (ascending, descending, or mixed frequencies). For sequences consisting of 5 tones of identical frequency (monotone) the response often depended on serial position, including cases in which the neuron only responded to later tones in the sequence. Comparison of responses to heterogeneous and monotone sequences showed that response dependence on serial position was a factor in response dependence on sequence direction. Auditory cortical neurons can exhibit stronger responses to a tone presented in a sequence than to the same tone presented alone. Hence, the responses to tones within sequences may not be highly predictable from the responses to isolated tones.

INTRODUCTION

There is a period of decreased responsiveness (time constant = 30–300 ms) following discharges of single VIIIth fibers to an effective tone. Such short-term adaptation[43] or forward masking[19] has been observed also for more complex stimuli (phonemes) presented sequentially[8]. The duration of influence of evoked responses on later responsivity appears to lengthen at higher levels[13]. At the auditory cortex, the suppressive effects of identical tones presented sequentially last as long as 900–1600 ms[20]. In part motivated by the need to avoid these refractory-like effects, investigators routinely employ single tones separated by one or more seconds. Since acoustic signals used in communication have a temporal structure with different components occurring at rates substantially higher than this (roughly 100 ms per phoneme in speech, or tones in music[24,46]), it is germane to investigate the interaction of responses to stimuli presented in sequence, at higher rates.

Evidence of cortical involvement in tone sequences comes from various sources. Some neurons in bird forebrain respond to the second but not the first of two sequentially presented identical tones[26]. Also, ablation of auditory cortex in cats impairs tone pattern discrimination[10,33,37]. Moreover, damage of auditory cortex in humans is associated with impairment of discrimination of both tone sequences[35] and the order of tonal stimuli[7,11,45].

Tone sequences may be considered intermediate in complexity between single-frequency tone bursts and species-specific vocalizations; the sequential structure of the latter is critical in the response of primate auditory cortical neurons[16]. In the present study, we compared the responses of single neurons in auditory cortex to isolated tones and to sequences of 5 tones. A preliminary report of some of these findings has been presented in abstract form[29].

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MATERIALS AND METHODS

Subjects, surgery and preparation for recording

The subjects were 12 healthy adult male cats, maintained in a modern animal facility, under strict supervision of the University veterinarian. Animals were housed individually in approved stainless steel cages with water and Purina cat chow available on an ad libitum basis. They became accustomed to handling and were groomed by the experimenters. Details of surgery and the preparation have been reported previously[28]. Briefly, animals were anesthetized (pentobarbital sodium 40 mg/kg, i.p.), a pedestal of dental acrylic was affixed to the skull, within which two threaded metal spacers were embedded to provide for comfortable fixation of the head during recording sessions. A smooth ridge of dental acrylic was built surrounding bone overlying auditory cortex and the skin was sutured so that the calvarium was exposed. Small burr holes were placed over AI and AII and sealed with sterile bone wax. Following recovery in an incubator, and antibiotic prophylactic therapy (Combi-pen, i.m., Panalog and Neosul locally applied) the animals were allowed at least one week before recording began.

On the day of recording, Flaxedil (gallamine triethiodide) was administered (10 mg/kg, i.p.), the local anesthetic Cetacaine (benzocaine) was applied by spray to the oral cavity and a standard pediatric endotracheal catheter coated with xylocaine jelly was inserted immediately into the trachea under laryngoscopic control. Animals were artificially ventilated, and expired carbon dioxide levels were maintained within normal limits, continuously monitored with a Beckman gas analyzer. Neuromuscular blockade, to insure stimulus constancy at the periphery[4,6,15,22,23,39,48], was maintained with Flaxedil (15 mg/h, i.v.)[1]. [Responses to sequences could not be studied in a preliminary experiment (two animals, 11 neurons) using general barbiturate anesthesia; following response to the first tone, responses to subsequent tones were either greatly depressed or partially 'masked' by after discharges.] The corneas were coated with ophthalmic ointment to preclude possible discomfort from drying, the subject was positioned on cushions and the pedestal was bolted to a rigid attachment to the stereotaxic frame. A selected burr hole was cleared of bone wax with the aid of a surgical microscope.

Throughout the recording session, pupils were constricted but small dilations could be elicited easily by incidental noise. Tonic dilation, a highly sensitive indicator of discomfort[25], was never observed. The EEG was generally spindling or slow wave, indicative of quiet waking, drowsiness or sleep; the relaxing effects of gallamine on the cat appear due to the withdrawal of proprioceptive input[21]. Human subjects report relaxation and no discomfort during neuromuscular blockade produced by gallamine[44]. At the end of a session, neuromuscular blockade was reversed by Tensilon (edrophonium chloride, 10 mg, i.m.). Following grooming by the experimenters, and verification that full muscle control was restored, the animal was returned to its home cage and allowed 1–2 weeks between further (2–3) recording sessions.

Recording, experimental protocol and data analysis

Acoustic stimulation was delivered to the ear contralateral to the recording electrode by a Beyer earphone coupled to a calibrated earpiece via a short length of polyethylene tubing. The earpiece was seated peripherally in the ear canal and the concha was filled with cotton gauze soaked in local anesthetic jelly (Xylocaine). Cross-head transmission was 60–70 dB below levels at the stimulated ear. The acoustic delivery system was calibrated with a probe tube using a Hewlett-Packard wave analyzer and provided for presentation of designated frequencies and intensities via a computer-controlled oscillator and attenuator. Tone pulses were shaped with a rise/fall gate set at 5 ms to preclude switching transients. Although exact intensities at the tympanic membrane could not be determined in the unanesthetized preparation[14], the findings do not depend upon such measurements because intensity was kept constant for each neuron; only tone-order was permuted. Similar stimulus delivery and measurement methods are routinely used by other laboratories for unanesthetized cats[39].

Single-unit discharges were recorded with tungsten microelectrodes (1 μm diameter tips) insulated with glass and epoxylite (2–4 MΩ impedance at 1 kHz). The electrode entry angle was set to be within 10° of perpendicular to the surface. Discharges were recorded via a Dagan 2400 amplifier (bandpass 0.3–3.0 kHz), displayed on a storage oscilloscope,

recorded on a Hewlett-Packard 4-channel instrumentation recorder, and led to a PDP 11/03 computer. Following isolation of a single stable waveform, a standard protocol was employed to determine the frequency response of the cell to tonal stimulation (e.g. 200 ms, 60 dB, 0.5–32.0 kHz). Stimulus sequences were selected to include frequencies eliciting the best responses.

A stimulus sequence consisted of a 100 or 300 ms prestimulus period, followed by a series of 5 iso-intensity tones (40–80 dB, 300 ms) each separated by 300–900 ms of silence. Sequences were repeated 25 times with an intersequence interval of 600–900 ms. Within sequences, tones were presented as *ascending*, *descending* or *mixed* order of frequencies (e.g. Fig. 1). Sequences consisting of tones of identical frequency ('monotone') or *isolated* tones (3200 ms intertone intervals) were also employed.

Evoked responses were analyzed independent of spontaneous activity by subtracting discharges in the prestimulus period from those elicited by acoustic stimuli. Temporal windows were chosen for analysis based on inspection of the response histograms, and the mean rates and variances for these windows were computed for each tone in a sequence. Tests of statistical significance (t-test), were used to compare mean rates for identical windows and tones between different sequences.

Following the final session, the brains were perfused with normal saline and 10% formalin while the animal was under deep barbiturate anesthesia. The calvarium was removed, and the sites of penetration noted with respect to sulcul landmarks. Although primary and secondary auditory cortex cannot be unequivocally located on the basis of the anterior and posterior ectosylvian sulci and the suprasylvian sulcus, they are nonetheless reported to be included within the zone so delimited. Physiological criteria indicative of primary and secondary auditory cortex were also met: for primary auditory cortex best frequencies could be identified, discharges to pure tones generally included short latency (<20 ms) onset responses, and best frequencies increased along the posterior to anterior axis[3,17,18,32,36,38]; for secondary auditory cortex the criteria were broad frequency tuning, ventral location, and heterogeneity of best frequencies[40].

RESULTS

Effects of direction of frequency change

The data reported here were obtained from 70 neurons; 47 from primary auditory cortex (AI), and 23 from secondary auditory cortex (AII). Of these, 65 (93%) exhibited responses that were dependent on the structure of the tonal sequences (AI = 42/47, AII = 23/23). There were no statistically significant differences in the probability of obtaining effects between AI and AII (χ^2, all $P > 0.05$).

The most common finding (51/61, 84%; AI = 37/44, AII = 14/17) was that the responses to one or more tones differed significantly when the same tones were presented in sequences which had different *directions* (i.e. ascending, descending, or mixed). An example of this effect is given in Fig. 1, which shows data obtained during presentation of 10–14 kHz tones; for statistical comparisons see Table I. The magnitude of responses at tone onset were significantly different for ascending vs descending sequences (10.0, 11.0, and 13.0 kHz; Fig. 1A,C), ascending vs mixed sequences (11.0 and 13.0 kHz; Fig. 1A,D), and mixed vs descending sequences (10.0, and 11.0 kHz; Fig. 1C,D). The effect of direction on the response to 10 kHz is particularly striking: the response was very small in the ascending and mixed sequences but quite prominent in the descending direction of frequency change.

The responses to tone sequences were very consistent across the 25 repetitions of the sequence as seen in the raster displays above the histograms (Fig. 1). Habituation or 'build-up' of responses was rarely observed within the neurons sampled. The response patterns were also stable across repetitions of the identical set of tone sequences, e.g. for 'Ascending-1' vs 'Ascending-2' tone sequences (Fig. 1A,B and Table I). To assess the stability of response patterns for identical tone sequence sets, we analyzed 15 cells which exhibited frequency direction effects for the 'on' response to at least one tone and which also had replications of at least one of the relevant tone sequences. Pearson correlation coefficients were computed for the 5 'on' responses for pairs either of identical or different tone sequences for each of these neurons. For example, for the neuron in Fig. 1, the correlation coefficient for the 'on' responses to Ascending-1 and Ascending-2 tone sequences was

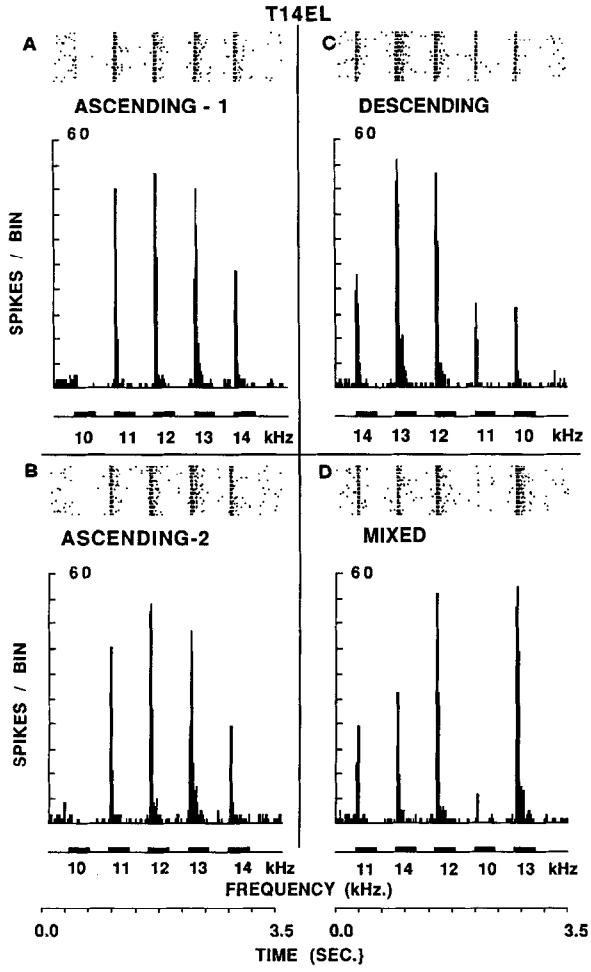

Fig. 1. Data from neuron T14EL, recorded at a depth of 1153 μ in AI. Histograms and rasters for discharge response to 5 tone sequences, repeated 25 times. The histograms show responses to A: Ascending-1; B: Ascending-2; C: Descending, and D: Mixed sequences. The Ascending-2 set was delivered 45 min following Ascending-1, after all other sequences. The 300 ms tones were delivered at 60 dB (binwidth = 10 ms).

0.995, while the correlation for Ascending-1 and Descending-1 was 0.684 (significantly different, $P < 0.05$). For 14/15 neurons, the correlation of responses was greater for identical tone sequences than for different tone sequences. The distributions of the correlations for identical and different tone sequences (Table II) are significantly different (Wilcoxon signed-rank test, $P < 0.05$).

TABLE II

*Distribution of Pearson correlation coefficients for 'on' response of 15 neurons tested with both different and same stimulus sets**

	Range of correlation coefficient				
	0–0.2	*0.2–0.4*	*0.4–0.6*	*0.6–0.8*	*0.8–1.0*
Different sets	3	5	1	3	3
Same sets	0	2	1	1	11

*$r = \dfrac{n\Sigma xy - \Sigma x\Sigma y}{n^2\sigma_x\sigma_y}$ where:

r = Pearson correlation coefficient; n = number of paired observations; x,y = values of each observation in a pair; σ_x,σ_y = standard deviation of observations.

The dependence on sequence direction of 'on' responses could be extremely selective, i.e. limited to responses to only one tone for a single direction. Fig. 2 shows data from a neuron which responded only to 4.0 kHz tones when presented within an ascending sequence (2A), but not when the same tone was presented in descending (2B) or mixed (2C) sequences (see also comparison of peak rates Fig. 2F,G). This response selectivity was stable as evidenced by the 'on' response at 4.0 kHz to the second presentation of the ascending sequence 40 min following the first presentation (Fig. 2A,D,H).

As previously reported[17], neurons could exhibit responses to the offset of tone, as well as to the onset of tones. The effects of sequence direction could be quite specific for the 'on' and 'off' responses within the same neuron. A total of 29 cells which exhibited both 'on' and 'off' responses were tested for dependence on direction of frequency change. Of these, 24

TABLE I

Neuron T14EL: statistical summary

Freq. (kHz)	*Ascending 1*	*Ascending 2*	*Descending*	*Mixed*	*P values*			
					A1:A2	*A1:D*	*A1:M*	*M:D*
10.0	8.0 (3.6)	3.2 (2.5)	46.1 (3.0)	4.8 (2.4)	n.s.	0.002	n.s.	0.002
11.0	129.1 (66.8)	118.4 (4.7)	57.5 (3.8)	66.7 (4.6)	n.s.	0.002	0.002	0.01
12.0	159.4 (6.3)	157.0 (5.1)	161.2 (4.6)	157.0 (5.4)	n.s.	n.s.	n.s.	n.s.
13.0	133.0 (5.4)	137.7 (6.1)	181.2 (5.0)	178.8 (5.9)	n.s.	0.002	0.002	n.s.
14.0	75.8 (3.7)	65.3 (3.1)	75.6 (5.7)	81.9 (5.6)	n.s.	n.s.	n.s.	n.s.

(83%) showed significant dependence on direction; 14 of these neurons (58%) showing this effect only for 'on' responses (AI = 8, AII = 6), 7 (29%) showed it for both 'on' and 'off' responses (AI = 4, AII = 3), and 3 (13%) showed it only for 'off' responses (AI = 2, AII = 1).

Fig. 3 illustrates the responses of a neuron which exhibited dependence on sequence direction for 'on' but not for 'off' responses to tones varying from 1.0 to 3.0 kHz. The 'on' responses were greater for 1.0, 1.5 and 2.0 kHz, and the 'off' responses were greater for 2.0, 2.5, and 3.0 kHz tones (Fig. 3A–C). The 'on' response to 1.0 and/or 1.5 kHz tones was significantly different in the ascending vs descending (Fig. 3D), ascending vs mixed (Fig. 3E), and descending vs mixed (Fig. 3F) sequences. In contrast, the 'off' responses were not significantly altered by direction of frequency change (Fig. 3G–I).

The 'off' response could also exhibit a high degree of selectivity for sequence direction. Fig. 4 provides data for a neuron which exhibited an 'off' response only to 5.2 kHz presented in the mixed sequence.

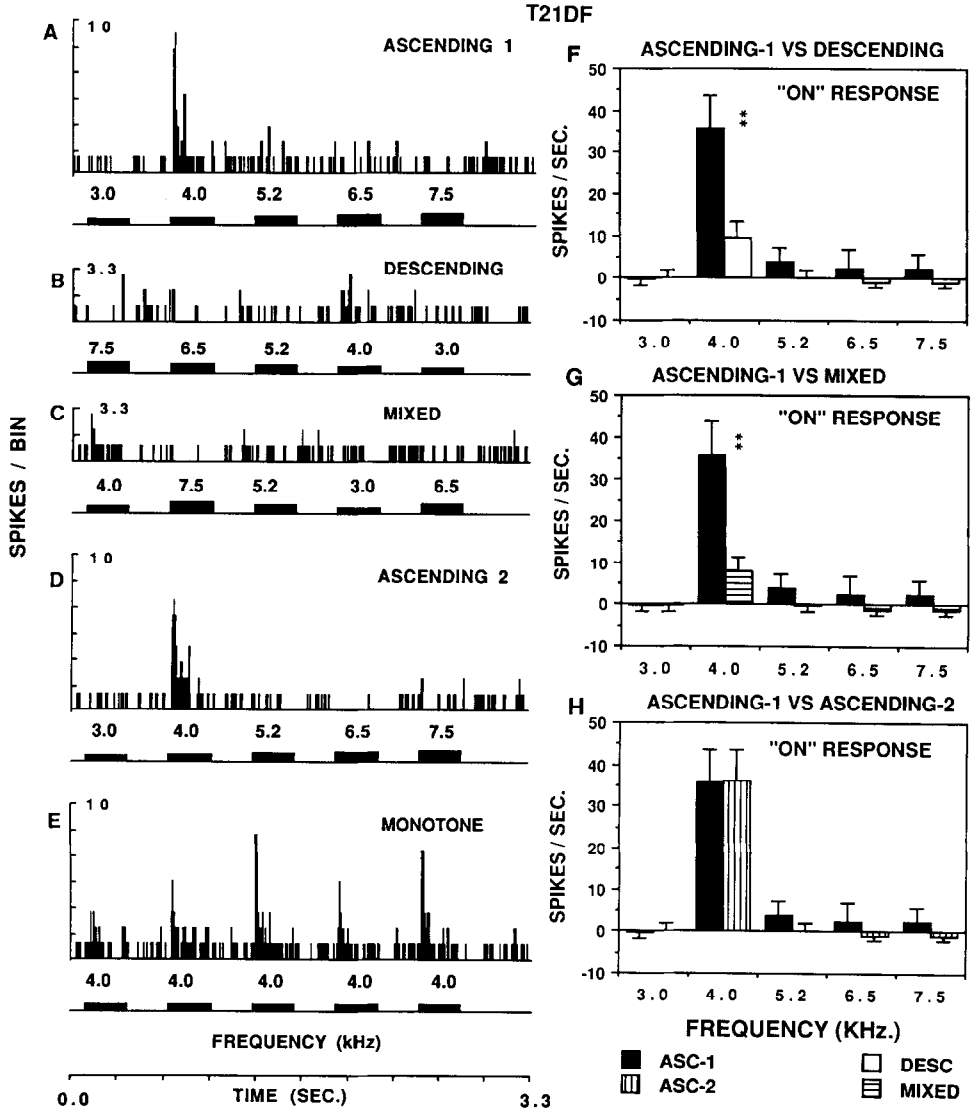

Fig. 2. Neuron T21DF (1656 μ, AI cortex). Histograms for A and D: ascending; B: descending; C: mixed; and E: monotone sequences delivered at 70 dB. The bar plots show comparisons of mean rate for F: Ascending-1 vs Descending; G: Ascending-1 vs mixed; and H: Ascending-1 vs Ascending-2. The period of activity selected for analysis was the 'on' response (latency 20 ms, duration 30 ms, 10 ms binwidth).

Such specificity for the 'off' response did not preclude specificity for the 'on' response for the same cell which responded better to 6.5 kHz in the ascending vs mixed sequences. Of particular interest, these effects were observed with long intertone intervals of 900 ms.

Effects of serial position of tones

Among the factors that might determine the effects of direction dependence are the serial position of the tone in the sequence, because (except for tone 3) a change in direction also involves a change in serial position. Although we could not examine all possible combinations of tone order for the 5 tones, the data obtained do provide some support for the effect of serial position. The test for a position effect was to present sequences consisting of one frequency ('monotone' sequences). The frequencies tested were the same as those found effective in the ascending, descending, or mixed sequences. The criterion for a position effect was that the responses to tones were significantly different ($P < 0.05$, t-test) for different serial positions within the monotone sequence.

Fig. 5 depicts the responses of two neurons to monotone sequences. These data are from the same two neurons which were shown in Figs. 1 and 3 to exhibit response dependence on direction. Fig. 5A (same neuron as Fig. 1) shows a clear example of response dependence on serial position: the neuron responds to 10.0 kHz tones in positions 2 through 5, but *not* in the first position. Thus, the failure of this neuron to respond well to 10.0 kHz in the ascending direction is likely due to the fact that this frequency was in position one (Fig. 1A,B).

This position effect is not due to the duty cycle of the repeating tone sequence, since omitting the 3rd tone (presenting two consecutive tone pairs) shows

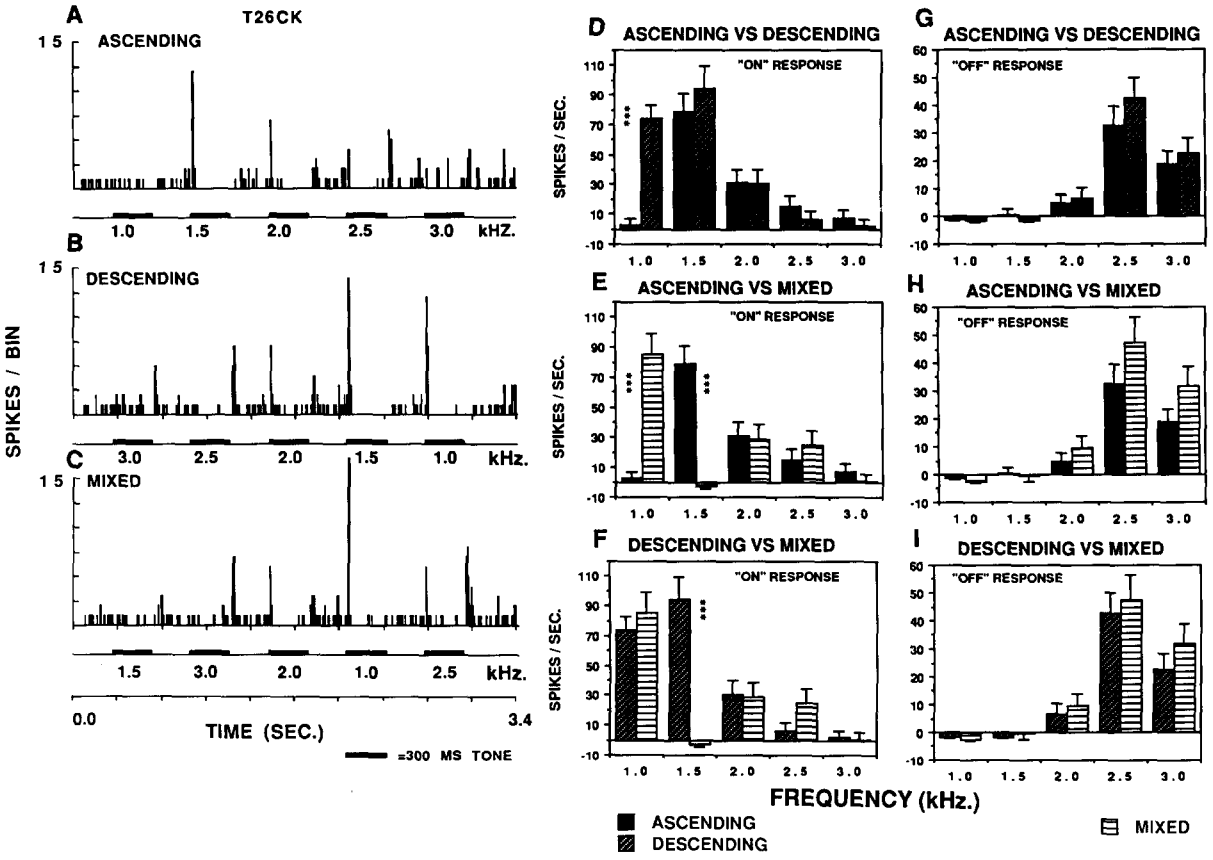

Fig. 3. Neuron T26CK (1823 μ, AII cortex). Histograms for the responses to: A: ascending; B: descending; and C: mixed sequences of tones presented at 70 dB. The bar plot comparisons of mean rate are shown for both the 'on' response in D–F (latency from tone onset = 10 ms, duration 10 ms, 10 ms binwidth) and 'off' response in G–I (latency from tone offset = 20 ms, duration 20 ms).

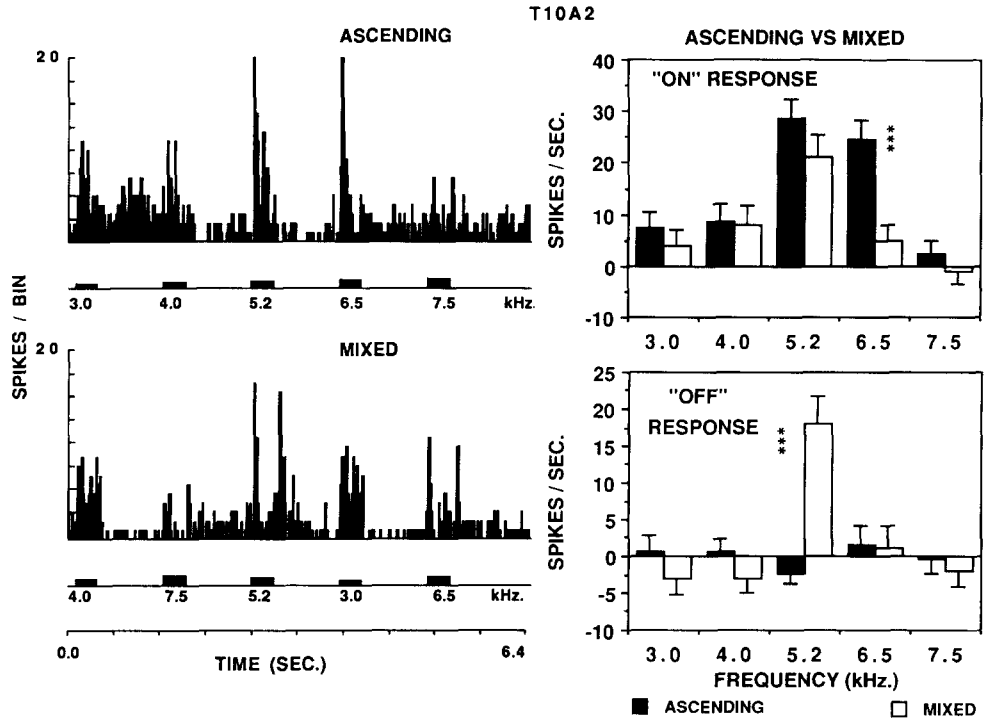

Fig. 4. Neuron T10A2 (912 μ, AI). Histograms and bar plots for 25 repetitions of ascending and mixed sequences delivered at 80 dB. Tone duration was 300 ms, intertone interval 900 ms. The bar plots show the mean rates during 'on' (latency 30 ms, duration 40 ms, 10 ms binwidth), and 'off' (latency 70 ms from tone offset, duration 40 ms) response peaks.

that the neuron responds only to the second of each tone pair. The data also constrain the temporal domain of the position dependence: with a 300 ms intertone interval, the first tone is capable of facilitating the response to the second tone, but when a 900 ms intertone interval is produced by the tone omission,

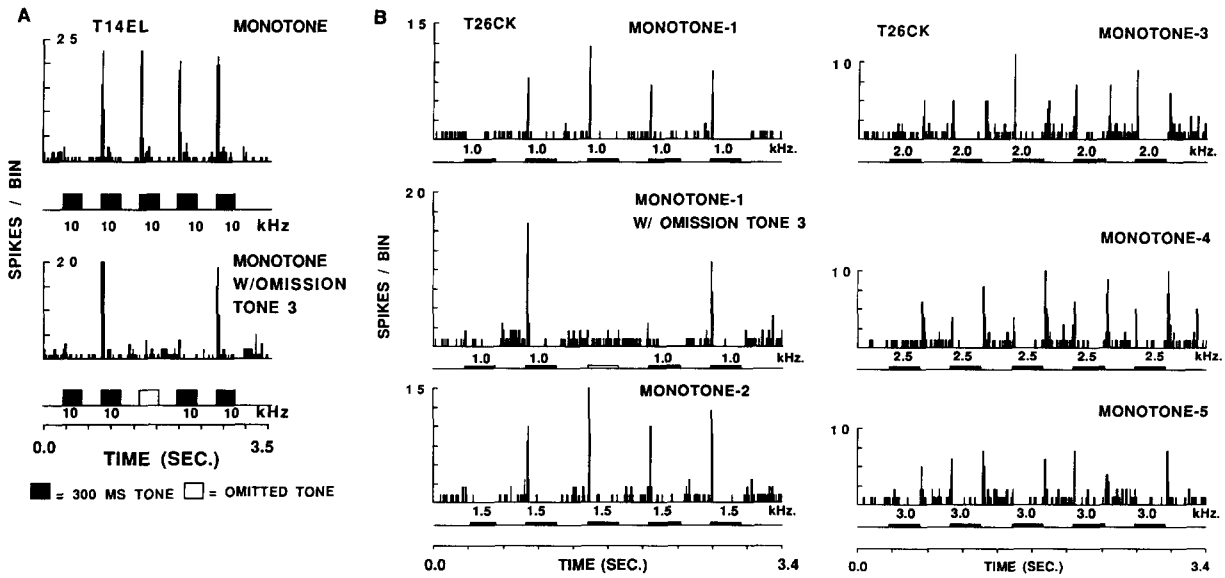

Fig. 5. Neuron T14EL (A), and T26CK (B). Sequences consisting of 5 tones with identical frequency ('monotone') are presented for 25 repetitions. A: the neuron responds to 10.0 kHz tones in positions 2 through 5, but not position 1. When the 3rd tone is omitted, the cell responds to the second of each tone pair. Identical results are seen in B, for 1.0 kHz tones.

the succeeding tone is not effective in eliciting a response. A similar result for another cell is shown in Fig. 5B: a position effect with no response at position one is seen for 1.0 kHz tones, and omission of the 3rd tone produces a response at every second tone, all observed over the same time domain. We designate this kind of serial position effect 'posttone facilitation'.

While this position dependence can explain some aspects of direction dependence, e.g. in Fig. 1 (notably the absence of a response to 10.0 kHz tones in the ascending sequence), one or more additional unknown factors are necessary to explain the response to 10 kHz tones in the descending sequence (5th tone position), but lack of response to 10 kHz tones in the mixed sequence (4th tone position). One such factor may be facilitation by nearby frequencies immediately preceding 10.0 kHz tones. Thus, the 11.0 kHz tones in the descending sequence are closer in frequency than the 12.0 kHz tones in the mixed sequence. While the data are consistent with this possibility, they are not conclusive in the absence of data for a greater range of frequencies preceding a 10.0 kHz tone.

A position dependence for 'on' responses is also evident in the responses to monotone sequences shown in Fig. 5B (same cell as Fig. 3). There are no 'on' responses in the first position for any of these monotone sequences, although 'off' responses are evident for 2.0, 2.5, and 3.0 kHz in the first position. The position dependence of unit discharges can explain aspects of the sequence direction dependence shown in Fig. 3. For example the absence of 'on' responses in position one for 1.0 kHz tones in the ascending, 1.5 kHz in the mixed and 3.0 kHz in the descending sequences can be explained by the absence of responses in position one in the monotone sequences.

A response dependence on tone position also seems to be a factor in the sequence selective response seen in Fig. 2 (Cell T21DF). The monotone sequence shown in Fig. 2E for 4.0 kHz tones reveals a weak response in the first tone position and this could explain why the cell did not respond to 4.0 kHz in the mixed sequence when this stimulus was presented in the first position. However, as with many other neurons, position dependence cannot be the only factor, because the responses to 4.0 kHz tones in the 2nd and 4th positions do not differ in the monotone sequence, yet these are the positions of the 4.0 kHz tones in the ascending (strong response) and descending (weak response) sequences, respectively.

Position dependence was observed in 16/28 neurons tested with monotone sequences (57%), (AI = 10/17, AII = 16/28). A total of 26 cells were tested for both direction dependence and position dependence. Of these, 11 exhibited both effects (AI = 8/17, AII = 3/9). Of these 11 cells, 8 showed direction dependence for at least one tone frequency that might be accounted for by the position (AI = 5, AII = 3). That is, a difference in response magnitude was seen at a particular frequency for sequences differing in direction, but in one of these sequences this frequency occurred at a position where relatively weak responses were seen in the monotone sequences (e.g. the cell described in the preceding paragraph).

Comparison of responses to sequences and isolated tones

If monotone sequences for some frequencies reveal no response in the first tone position, then one would predict that the neuron would not respond to isolated tones at those identical frequencies. This is shown in Fig. 6 (same cell as Figs. 3 and 5B). Isolated tones at 1.0, 1.5 and 2.5 kHz elicit virtually no 'on' responses (Fig. 6A–C) which matches the weak or absent response in position one in the monotone sequences for these frequencies (Fig. 5B). The lack of response to isolated tones at these frequencies contrasts sharply with the robust responses observed at later positions in tone sequences (Fig. 3, Fig. 5B). Fig. 6 shows that responses of this neuron to tones in the ascending (Fig. 6F), descending (Fig. 6G) and mixed (Fig. 6H) sequences (intertone interval 300 ms) could be significantly greater than the responses to the same frequencies presented as isolated tones (intertone interval 3300 ms). For example, in the descending sequence (Fig. 3B), the responses to 1.0, 1.5, and 2.0 kHz (which occur late in the sequence) are significantly greater than the responses to these tone frequencies delivered as isolated tones (Fig. 6A–C,G).

A total of 11 cells was examined with both isolated tones and tone sequences; 6 of these neurons had significantly stronger responses to tones in the sequences than to isolated tones (AI = 2, AII = 4).

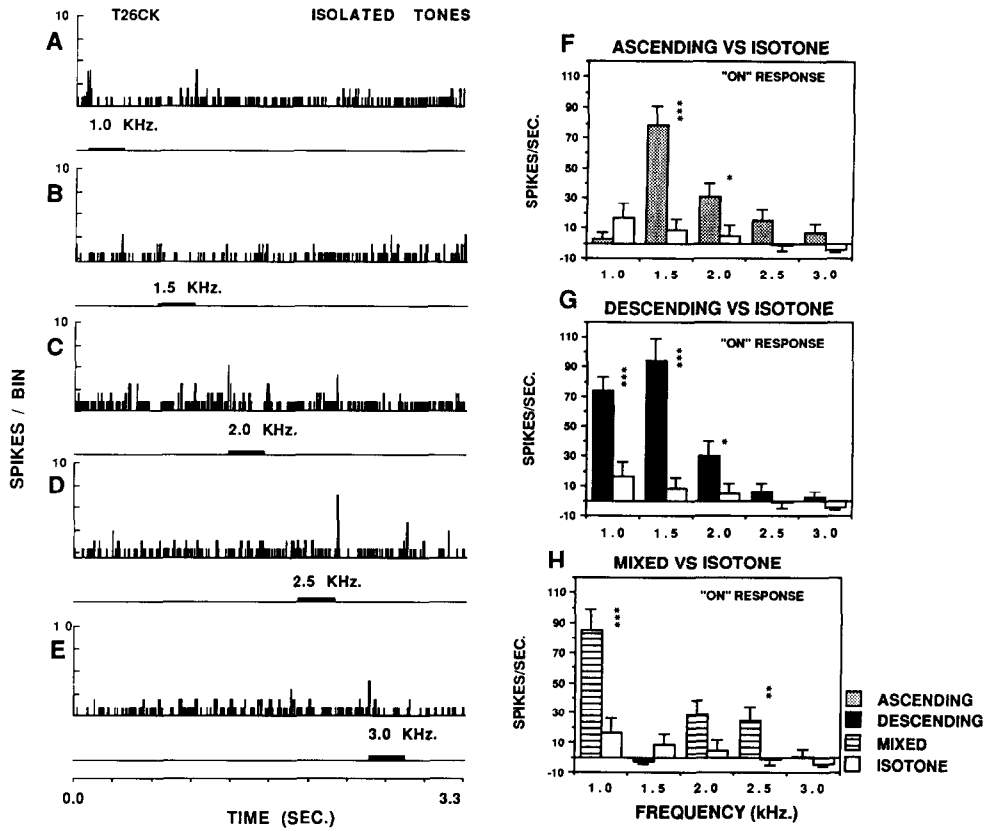

Fig. 6. Neuron T26CK. The response histograms for isolated tones (intertone interval = 3300 ms) is shown in panels A–E. The bar plots on the right compare the 'on' responses to isolated tones with the responses to these frequencies within F (ascending), G (descending) and H (mixed tone sequences) (histograms in Fig. 2, analysis period same as Fig. 2).

Four of these cells showed stronger responses to the isolated tones than to the same frequencies in sequences (AI = 1, AII = 3); the latter is the result that would be expected by short-term adaptation.

DISCUSSION

Since it has been reported that responsiveness of auditory cortical neurons can vary over time[5], it is important to review our controls for random change: (1) within a stimulus set the rasters did not show trends over the 25 tone sequence presentations, (2) spontaneous activity was subtracted from discharges during tones, eliminating its effects on measures of evoked discharges, (3) when responses differed between two sequences, there was almost always one or more tones to which the responses did not differ, providing an internal control for changes in general excitability, and (4) responses were replicable as indicated by higher correlations between responses to the same sequences vs different sequences.

A major effect was dependence of response on the direction of frequency change. Previously, such dependence has been demonstrated for direction of FM sweeps[31,47]. In this study some other aspects of frequency change were observed. For example, 'mixed sequences' elicited responses that differed from those evoked by either monotonic increasing or decreasing frequency change; the latter two are more closely related to FM stimuli. Further, the effects of direction of frequency change transcended periods of silence (300–900 ms). Additionally, we observed response dependence on the serial position of a tone within a sequence consisting of five identical tones. For some neurons, this position dependence may be due to the fact that they respond to a frequency only when it is preceded by identical or nearby frequencies.

The loci and mechanisms involved in the effects reported here are not known and future studies should

be directed to the subcortical auditory system and also to other regions that project to AI and AII. However, a prior physiological investigation suggests involvement at the level of auditory cortex. Espinosa and Gerstein[12] found that the cross-correlation between pairs of neurons in auditory cortex depends on the order of frequencies within sequences of three tones. This effect appears due to alterations in local functional connectivity. Interestingly, the mathematical model of sensory cortex developed by Shaw and colleagues[41,42] predicts the types of findings reported here and elsewhere[12,34] for permutations of stimuli within sequences[27].

Also related to locus of effect is our finding that cortical neurons can exhibit stronger responses to tones within sequences than to isolated tones, both for sequences of identical tones or different tones. This 'posttone facilitation' differs from what would be predicted from the poststimulus depression at the 8th nerve[19,43]. This short-term adaptation or forward masking has a time constant of 40 to 310 ms[43]. Since we did not routinely examine intertone intervals less than 300 ms, we may have underestimated the incidence of short-term adaptation at the level of the auditory cortex. However, with the stimulus parameters used in this study, a *facilitation* of tone response following a preceding identical tone was seen as often as a decrease in response for the monotone sequences. The posttone facilitation was observed with 300 ms intertone intervals, but was absent when the interval was extended to 900 ms (e.g. Fig. 5A, monotone sequence with omission of tone 3).

Absence of posttone facilitation in auditory cortex has been reported but the present findings appear not to be in actual conflict with prior studies. For example, in cats under nitrous oxide anesthesia, increasing the intertone interval of monotone sequences from 550 to 900 ms, or from 900 to 1600 ms, produced a 24% decrease in firing rate[20]. These intertone intervals may have been too long to detect a facilitation. Also, anesthesia may depress such facilitation[30]. Abeles and Goldstein[2] found suppression of response to the second of two tones over intervals of 20 to 200 ms after the offset of the first tone. However, the tones overlapped in contrast to a separation of 300 to 900 ms used here. The overlap may have precluded facilitation.

The current findings may be relevant to human pattern perception[9]. For example, people can discriminate between sound sequences differing in the *overall order* of their elements even when they cannot distinguish between the order of individual elements or the elements themselves[46]. This 'wholistic pattern recognition' may be related to the present results because neurons in AI and AII can encode permutations of tone sequences as discharge patterns which are not simply a concatenation of the responses to the individual tones.

Posttone facilitation was evident at some frequencies but not others. By analogy with two tone suppression, there may exist regions within the response area of auditory cortical neurons at which tone responses may be facilitated by a preceding tone delivered at the appropriate intertone interval. The present findings appear to warrant more extensive parametric studies of tone sequences, including determination of the temporal domain of neuronal sensitivity to the structure of sequences. A satisfactory model of the responses of neurons to such temporally-extended acoustic stimuli is likely to depend upon greatly expanded inquiry.

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