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Long-Term Frequency Tuning of Local Field Potentials in the Auditory Cortex of the Waking Guinea Pig

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ABSTRACT

The goal of our study was to determine the extent of changes in frequency tuning in the auditory cortex over weeks. The subjects were awake adult male guinea pigs ($n = 8$) bearing electrodes chronically implanted in layers IV–VI of primary auditory cortex. Tuning was determined by presenting sequences of pure tone bursts (~0.97–41.97 kHz, −20 to 80 dB, 100-ms tone duration, 5-ms rise–fall, 800-ms intertone intervals, 1.5-s intersequence interval) either in 0.5-octave steps ($n = 5$, 14 probes) or 0.25-octave steps ($n = 3$, 9 probes) delivered to the ear contralateral to recording sites. Tuning curves were determined for local field potentials (LFPs), which were tuned to frequency (negative potential, latency to peak 15–20 ms), repeatedly for up to 27 days (0.5 octave) or 12 days (0.25 octave). Characteristic frequency (CF), best frequency at 10 and 30 dB above absolute threshold (BF10, BF30), threshold (TH), and bandwidth (10 dB above threshold; BW) were measured. Absolute amplitude often decreased across weeks, necessitating normalization of amplitude. However, there were no significant trends in tuning over days for CF, BF10, or BF30 for either the half- or the quarter-octave group. Both groups exhibited random daily variations in frequency tuning, the quarter-octave group revealing larger variations averaging 0.228, 0.211, and 0.250 octave for CF, BF10, and BF30, respectively. Therefore, frequency tuning in waking animals does not exhibit directional drift over very long periods of time. However, daily tuning variations on the order of 0.20–0.25 octave indicate that the peaks of tuning curves (CF, BF) represent a preferred frequency range rather than a fixed frequency.

Keywords: receptive fields, frequency selectivity, evoked potentials, chronic animals, plasticity

INTRODUCTION

Sensory processes constitute an extensive and fundamental aspect of brain/behavioral function. Neurophysiological investigations have delineated neural response properties to various sensory stimuli within all sensory systems at all levels, sensory receptors to cortical fields. The field of sensory neurophysiology has provided critical insights into the organization and function of sensory systems, particularly by delineation and analysis of the receptive fields of neurons (Hartline 1940).

Parallel investigations of learning and memory within the field of the neurobiology also focused on sensory systems. Early studies of classical conditioning in the auditory cortex revealed that click-evoked potentials were significantly increased when the click served as a signal for impending footshock (Galambos et al. 1955). Despite the growth of a large and replicable body of findings of learning-induced plasticity within sensory cortical fields, there was little if any impact among sensory neurophysiologists, perhaps because such findings were difficult to relate to receptive field properties. Receptive fields show how a cell responds to many stimuli across a sensory dimension, such as tonal frequency, thus revealing its frequency tuning. In contrast, studies of learning typically

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assessed changes in response to a single stimulus (e.g., a conditioned stimulus; CS) or at most two stimuli (e.g., a reinforced CS+ vs. an unreinforced CS−).

A link was forged between the two fields of neurophysiology and neurobiology when the effects of learning on neuronal receptive fields were first investigated (Diamond and Weinberger 1986). Subsequent experiments have revealed that learning shifts the tuning of neurons toward or to the frequency of the CS and that receptive field plasticity has all of the characteristics of memory—specificity to the CS, associative origin, rapid development within a few trials, consolidation over hours and days, and retention over weeks and months (reviewed in Weinberger 1998, 2001a, b). It is now recognized that the responses to sensory stimuli are governed by two factors: the physical parameters of stimuli and their acquired behavioral relevance (Weinberger 1995; Scheich et al. 1997; Edeline 1999; Rauschecker 1999).

Both sensory neurophysiology and neurobiology of learning and memory share a fundamental assumption, one that is so implicit that it is almost never mentioned. This is the belief that sensory systems, particularly sensory cortex, are generally stable in the absence of sensory system insult (both peripheral and central) or learning. This issue has been raised directly by Kisley and Gerstein (1999), who repeatedly obtained receptive fields over several days and reported spontaneous drifting of frequency tuning in the auditory cortex of the rat. The present report concerns the degree of drift and daily variations of frequency tuning of local field potentials (LFPs; Eggermont and Smith 1995) evoked by pure tone stimuli in the primary auditory cortex of waking guinea pigs. LFPs in the auditory cortex are known to be tuned to acoustic frequency and exhibit tonotopic organization in auditory cortex (e.g., Woolsey and Walzl 1942; Tunturi 1944; Galli et al. 1971; Walloch 1975; Eggermont 1996; Ohl et al. 2000). LFPs are generally agreed to represent extracellularly recorded synchronous excitatory postsynaptic potentials (Creutzfeldt et al. 1966; Humphrey 1968; Mitzdorf 1985), therefore presenting an opportunity to study the long-term frequency tuning of synaptic potentials. In this article, we report on the relative stability of several receptive field parameters over periods of 12–16 days. Some of these data have been reported in abstract (Galván et al. 1999).

METHODS

Subjects and surgical preparation

The subjects were eight male adult Hartley guinea pigs (Hilltop Farms, Scottsdale, PA), weighing 300–520 g at the time of surgery. They were housed in groups of 2 or 3 in standard guinea pig cages with *ad libitum* food and water, on a 12-h light/dark cycle (lights on at 7 a.m.). On the day of surgery, they were premedicated with atropine sulfate (0.22 mg/kg i.p.) and diazepam (9.0 mg/kg i.p.), followed by sodium pentobarbital (25 mg/kg i.p.) 15 minutes later. Supplements of sodium pentobarbital (8.3 mg/kg i.p.) were administered as needed to maintain a state of areflexia. Body temperature was maintained at 37°C with the use of a homeothermic heating pad (Harvard Apparatus, Cambridge, MA), and ophthalmic ointment was applied to keep the eyes moist. Subjects were mounted in a stereotaxic instrument (Kopf, Tujunga, CA), the scalp was resected after subcutaneous administration of lidocaine, and the calvaria was cleared. Stainless-steel screws were threaded into several small burr holes, a silver ball electrode was placed in a burr hole near bregma to serve as the reference electrode, and a craniotomy was performed over the left auditory cortex. A pedestal of dental acrylic was constructed into which threaded spacers were embedded, these were bolted to a rigid support, allowing removal of ear bars.

The auditory cortex was identified physiologically by recording local field potentials elicited by clicks using a roving microelectrode. A general frequency map was then obtained using tones of various frequencies. The guinea pig's tonotopic auditory cortex consists of two major mirror-image areas, an anterior field with low-to-high-frequency organization along the anterior–posterior axis and a posterior field with the reverse organization (Redies et al. 1989; Robertson and Irvine 1989). The dura was removed and an electrode array was lowered slowly into the cortex using a Narishige stepping microdrive (Model SM21, Narishige, Tokyo, Japan) and fixed after the surface positive LFP reversed (~900–1100 μm depth). As this reversal takes place in the region of the border between Layers III and IV, consistent with a current sink in Layer IV, the recording sites were in Layer IV or below (Borbély 1970; Mitzdorf 1985; Barth and Di 1990). The electrode array consisted of a linear arrangement of four ($n = 1$), seven ($n = 3$), or eight ($n = 4$) teflon-coated tungsten wire electrodes (0.004 in.; California Fine Wire Co., Carlsborg, WA) in a Wire-Pro Inc. (Salem, NJ) connector strip. Thus, a total of 57 probes were implanted. The distance between adjacent electrodes was ~0.55 mm and impedance at 1.0 kHz was ~0.5 MΩ. The brain was covered with a layer of Gelfoam (Upjohn/Pharmacia, Kalamazoo, MI), and the electrode array was affixed to the pedestal with dental acrylic. An antibiotic ointment (Panalog, Solvay Inc., Mendota Heights, MN) was applied before suturing the scalp. Subjects were given a subcutaneous injection (2–5 mL) of physiological saline at body temperature, an additional injection of atropine sulfate

(0.22 mg/kg i.p.), and allowed to recover in an incubator before being returned to the vivarium. All procedures were performed in accordance with the of the University of California Irvine Animal Research Committee and the NIH Animal Welfare guidelines.

Acoustic stimulation and recording of LFPs

Pure-tone stimuli were generated by a Wavetek digital synthesizer and a digital attenuator bank (model 5100, WWG, San Diego, CA), controlled by a minicomputer (Digital 11/73, Digital Equipment Corp., Cambridge, MA), and delivered to a calibrated 1.5 in. speaker. Rise and fall times of tone bursts were 5 ms (type S84-04 acoustic gate, Coulbourne Instruments, Lehigh Valley, PA). The speaker housing was placed at the entrance to the ear canal contralateral to the recording sites and calibrated at this position (model 4134 condenser microphone, B & K, Copenhagen, Denmark; re: 0.0002 dyn/cm^2) because calibration at the tympanic membrane requires invasive procedures that are stressful to waking animals (Suga and Manabe 1982). Tone-evoked LFPs were recorded by a multiple-channel amplifier (Dagan, Minneapolis, MN, Model No. EX-1000, gain = 1000, 1–300 Hz) and digitized on a personal computer using commercial software (Datawave Technologies, Longmont, CO).

Determination of frequency tuning

Tuning was determined using either 0.5-octave frequency steps or 0.25-octave steps. For all subjects, receptive fields (RFs) were determined at 11 stimulus intensities (−20 to 80 dB) by presenting 20 repetitions of an ascending frequency sequence of tones (100 ms tone duration, 800 ms intertone intervals, 1.5 s intersequence interval) across a broad frequency range. For the half-octave group (n = 5), 11 tones were used to cover the frequency range of 0.97–30.0 kHz. Frequency steps of 0.5 octave are large but were initially used so that tuning variability could be determined from low to high frequencies for the multiple electrodes within an animal in a recording session that generally lasted no more than an hour.

After obtaining data from the half-octave group, we then repeated the study using 0.25-octave frequency steps to determine if tuning variability over days was greater with a finer-grain stimulus set. For quarter-octave subjects (n = 3), RFs were obtained using 16 tones within the frequency range of 1.56–41.97 kHz.

After recovery from surgery, the half-octave subjects were placed in an acoustic room in a hammock with the head fixed via the electrode pedestal (IAC, Inc., Bronx, NY). The first day of restraint was also the first day of recording that yielded data for this report. Tuning functions for the half-octave group were determined approximately every 1–3 days for up to 27 days (mean = 8.43 sessions over 14.43 days). In contrast, the first day of restraint and recording for the quarter-octave group did not yield data used in this report. That is because it was necessary to use 0.5-octave steps on their first day to determine the responsive frequency range within each subject so that a 0.25-octave set of frequencies could be chosen. The next day was the first day of 0.25-octave stimulation ("Day 1" for data analysis purposes), and the data from this and all subsequent days are reported here. This group was run on the same days; tuning was determined thereafter on Days 3, 6, 8, 10, and 12.

Analysis of frequency response parameters

Tone-evoked LFPs typically consisted of a very small, inconsistent positivity (P1, ~8–12 ms), followed by a large and consistent negativity (N1, ~15–20 ms) and a smaller, longer-latency positivity of variable amplitude (P2, ~30–40 ms) (Borbély 1970; reviewed in Shaw 1988). Offline analysis was accomplished using the Experimenter's Workbench software package (Datawave, Inc., Longmont, CO). The average baseline (5 ms during rise of tone presentation, preceding shortest-latency-evoked responses) to peak or valley values was calculated for the P1, N1, and P2 components over the 20 tone repetitions of every combination of frequency and intensity for all days of recording. The P1 components were too small and inconsistent to analyze. The P2 data were analyzed and found to not exhibit systematic tuning and are not reported here. The N1 component yielded both consistent LFPs and systematic tuning and constitute the subject of this report.

The following receptive field parameters were measured: (a) characteristic frequency (CF), the frequency evoking a response at threshold; (b) best frequency (the frequency evoking the largest response) 10 dB above threshold (BF10) and (c) 30 dB above threshold (BF30); (d) absolute threshold (TH), the minimum intensity for response evocation; and (e) bandwidth (BW), the octave distance between the positive and negative slopes of the tuning curve at half the amplitude of BF10.

Tuning variability was assessed by calculating the mean value of the CF, BF10, BF30, and BW for each probe across all of its recording sessions and then subtracting the mean from the daily value, yielding the deviation from the parameter mean. Thus, if CFs on a day were lower than the mean CF, the value for that day would be below the parameter mean. Average daily values of deviations from the parameter mean were then calculated across all probes within the half- and the quarter-octave groups. Deviations of threshold

from the parameter mean were calculated in the same manner. However, thresholds are considered measures of sensitivity rather than specificity of frequency tuning.

A major issue was the extent to which tuning exhibits directional drift over days following the beginning of recording. Therefore, we used several statistical analyses to compare parameter values on later days with the values on Day 1 of tuning determination. The distribution of deviations from the parameter mean were not normally distributed, calling for nonparametric statistics. Moreover, the half-octave group was not run in a block design with exactly equal daily intervals between successive recordings and the same number of probe recordings on each day. Therefore, while nonparametric statistics were appropriate, a nonparametric analysis of variance (e.g., the Friedman analysis of variance by ranks) could not be used (Siegel and Castellan 1988); the Wilcoxin signed ranks test was used to compare each day with Day 1. The repeated use of the same test can yield false positives, but that was not a problem in this study because the directional drift findings did not turn out to be positive. The quarter-octave group did have the same number of recordings on each day and so the Friedman test could be used.

Histology

After completion of the protocol, subjects were euthanized with an overdose of sodium pentobarbital. The brains were perfused with saline and formalin and removed for examination. Frozen sections (40 μm) were obtained and stained with cresyl violet. Electrode tracks could be detected in many cases, and the depths were consistent with recording sites in Layers IV or below. However, the inversion of the LFP with depth was used as the defining criterion of recording below Layer III (Borbély 1970).

RESULTS

Descriptions of the data set

As noted in the Methods section, a total of 57 electrodes were implanted in eight subjects. Data from 23 probes are reported here. Thirty-four electrodes were excluded prior to quantitative analysis of the recordings for the following reasons: average LFPs with very small amplitude (e.g., <30 μV) or unstable waveforms, $n = 10$; no auditory responses, $n = 6$; thresholds >40 dB, $n = 6$; fragmentary tuning functions, either at the lower or higher limit of the range of frequencies presented to a subject, $n = 6$; tuning identical to an adjacent electrode that had larger LFPs, $n = 6$. In the latter case, it was assumed that the electrode tips were too close together within the cortex and that the data from the rejected electrode would be redundant.

The five subjects from the half-octave group yielded data from 14 probes (mean = 2.88 probes per subject; range = 1–4 probes) over a period of 8–27 days (mean = 14.43 days). The three subjects from the quarter-octave group yielded data from 9 probes (mean = 3.0 probes per subject; range = 2–4 probes) over a period of 12 days. All probes yielded good recordings throughout the duration of the experiment. Responses were typically evoked from 0 to 80 dB. A total of 2480 tuning functions across stimulus levels were obtained from these 23 electrodes.

The location of some recording sites could be approximated physiologically to be in the anterior or the posterior mirror-image field because implantation of the electrode array was guided by a prior general mapping of the two fields. Thus, if the most anterior electrode exhibited low-frequency tuning, it may be considered to be in the anterior field because of the low-to-high-frequency, anterior–posterior organization. Complementary logic holds for the most posterior electrodes being tuned to low frequencies, indicative of posterior field placement. This approach was reinforced in those subjects having more than one acceptable tuned recording site. For example, a subject whose most anterior electrode exhibited an average BF of 3.03 kHz and whose next electrode had a BF of 6.48 kHz was considered to have both recording sites in the anterior field. However, because the high-frequency regions of the two fields are adjacent to each other, one cannot draw any conclusion about the field location of electrodes exhibiting high frequency (e.g., >20.0 kHz) tuning because there is no way to know when the border had been crossed in this experiment. For both half-octave and quarter-octave groups, presumptive fields were assigned either as anterior, posterior, or high-frequency indeterminate. The majority (16/23) of recording sites appeared to be in the anterior field, while four were indeterminate and three were in the posterior field. However, in the absence of detailed tuning information, we do not consider field locations to be sufficiently precise to warrant definite conclusions. Therefore, while the recordings were obtained from tonotopically organized (primary) cortical fields, we do not further consider the presumptive locations of any recording sites within this combined area.

General tuning and amplitude characteristics

The LFPs recorded from infragranular layers ($\sim$1.1 mm depth) have a typical form consisting of a promi-

nent negative component with a latency to peak of ~15–20 ms, followed by a more variable positive peak at ~30–40 ms. Figure 1A presents an example of an average LFP. The negative wave ("N1") exhibits systematic frequency tuning. Figure 1B shows an example of LFPs across frequency (0.97–30.0 kHz) and stimulus level (−10 to 80 dB). Note the tuning, with CF, BF10, and BF30 at 7.78 kHz, and increasing bandwidth as stimulus level increases.

The absolute LFP amplitude generally decreased over days (see Figs. 2 and 3). For example, average CF amplitudes decreased from 126 to 97 μV and BF 30 decreased from 228 to 185 μV over 12 days for the quarter-octave group. Significant decreasing trends were obtained for CF, BF10, and BF30 for this group and for BF30 in the half-octave group (Page test, $p < 0.05$) (Siegel and Castellan 1988).

Half-octave group

Evaluation of tuning trends. LFP tuning can be highly similar at suprathreshold levels across days. Figure 2 presents examples of LFPs at 20 dB, 10 dB above threshold, from 5 of 11 recording sessions for one subject across 16 days. Note that the response range is similar (3.9–15.6 kHz) and BF10 (maximum response) is the same (7.80 kHz) across more than two weeks. Tuning can also be very similar at threshold. Figure 3 presents LFPs at threshold intensities (0–20 dB) across 9 days for another subject. Note that the characteristic frequency (CF = 15.6 kHz) is the same across 9 days although the threshold intensity varied between 10 and 20 dB. However, it must be noted that the CF and BF values are only within ±0.5 octave and would not necessarily be the same with a smaller-frequency step size.

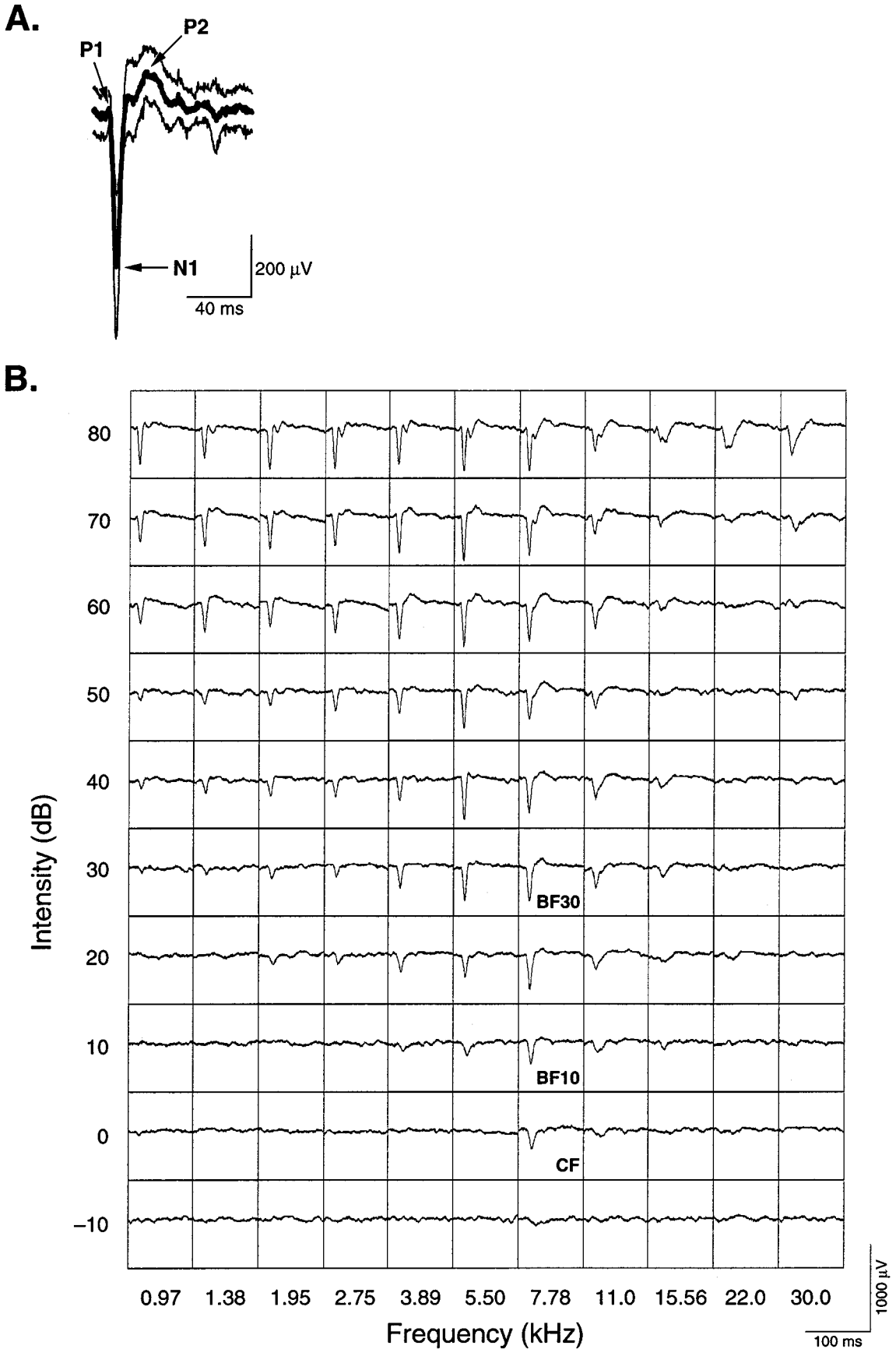
Examination of tuning data at multiple intensities revealed that tuning may be quite stable at threshold and suprathreshold stimulus levels across days. Figure 4 presents normalized tuning functions for a single subject over stimulus levels (threshold to 70 dB above threshold) for 10 days of recording over a period of 11 days. Note that the CF (Fig. 4A) and the BFs (Figures 4B–H) are the same. Again, the accuracy of this estimation is ±0.5 octave for this group. As expected, bandwidth increases with increasing stimulus level. Tuning variability at non-BF frequencies is greatest at highest intensities, often associated with response saturation. A summary of tuning function parameter values for this recording site is presented in Figure 5. Note the higher threshold on Days 1 and 2. This proved to be characteristic of the half-octave group.

Recordings were obtained from one subject for 18 days and for another subject for 27 days. Their tuning exhibited little variation over these long time periods. For example, subject GFP 19 yielded tuning functions on 8 sessions over 18 days and all but one (Day 9) had a CF = 15.56 kHz. GFP 17 provided tuning data from 12 sessions over 27 days and every CF had the same value. Thus, tuning over several weeks can be at least within ±0.5 octave. However, group data sufficient for statistical analyses were available over a period of only 16 days. Thus, recordings beyond this period were not included in further analyses.

Half-octave group data are presented in Figure 6. For deviations of CF, the values for Day 2 (vs. Day 1) approached statistical significance (Wilcoxin test, $z = 1.89$, $p = 0.059$) and no other days differed significantly from Day 1. There were no significant differences for BF10 or BF30. Thresholds were significantly lower on Days 4, 5, 8, and 11. These significant differences were not surprising given that Day 1 was about 6.5 dB higher than the mean. Bandwidth, indicative of tuning selectivity, was significantly broader on Day 8 than Day 1.

Individual tuning functions over days also were examined. The Runs test (Siegel and Castellan 1988), which calculates measure-by-measure variation around the mean of a series of values, has been applied to seek deviation from stationarity (departure from stochastic order) for spike rate counts over time (e.g., Ohl and Scheich 1996). This test is sensitive to trends but can also yield false-positive outcomes. For example, if the value for the first day differs from succeeding days, all of whose values are identical, then the Runs test is likely to be significant despite the absence of an actual trend. Also, it will be significant if all days have the same value. Therefore, it should be interpreted with caution. The Runs test requires a minimum of nine data points (i.e., days of recording). Ten of 15 probes had 10–12 days of data and so were analyzed. The Runs test yielded 4/10 significant results ($p < 0.05$) for both CF and BF30 (BF10 was not tested), indicating that four recording sites exhibited nonrandom tuning over days. However, in no case did tuning systematically shift over days; rather, the CF and BF10 values were generally the same over days. For example, the CFs of these four probes were the same on 11/12, 12/12, 10/10, and 9/10 days, respectively. The other six sites also exhibited predominantly identical tuning to the CF that was obtained on their first recording day: 9/11, 10/11, 8/11, 10/11, 6/10 and 9/10, respectively. Overall, 94/108 (87%) of the CFs had the same values within a recording site across days. A parallel tally revealed more variability of tuning for BF30, but still 80/108 (74%) were the same.

In addition, the absolute tuning differences were calculated for the first and last days of recording for these ten sites. For CF, 9/10 recordings had identical values: median = 0, mean = 0.075 octave (±0.24 SD). For BF30, 7/10 were identical: median = 0, mean = 0.10 octave (±0.18 SD). The tendency for increased


A.
P1
P2
N1
200 μV
40 ms
B.
80
70
60
50
40
30
20
10
0
−10
Intensity (dB)
BF30
BF10
CF
0.97
1.38
1.95
2.75
3.89
5.50
7.78
11.0
15.56
22.0
30.0
Frequency (kHz)
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100 ms

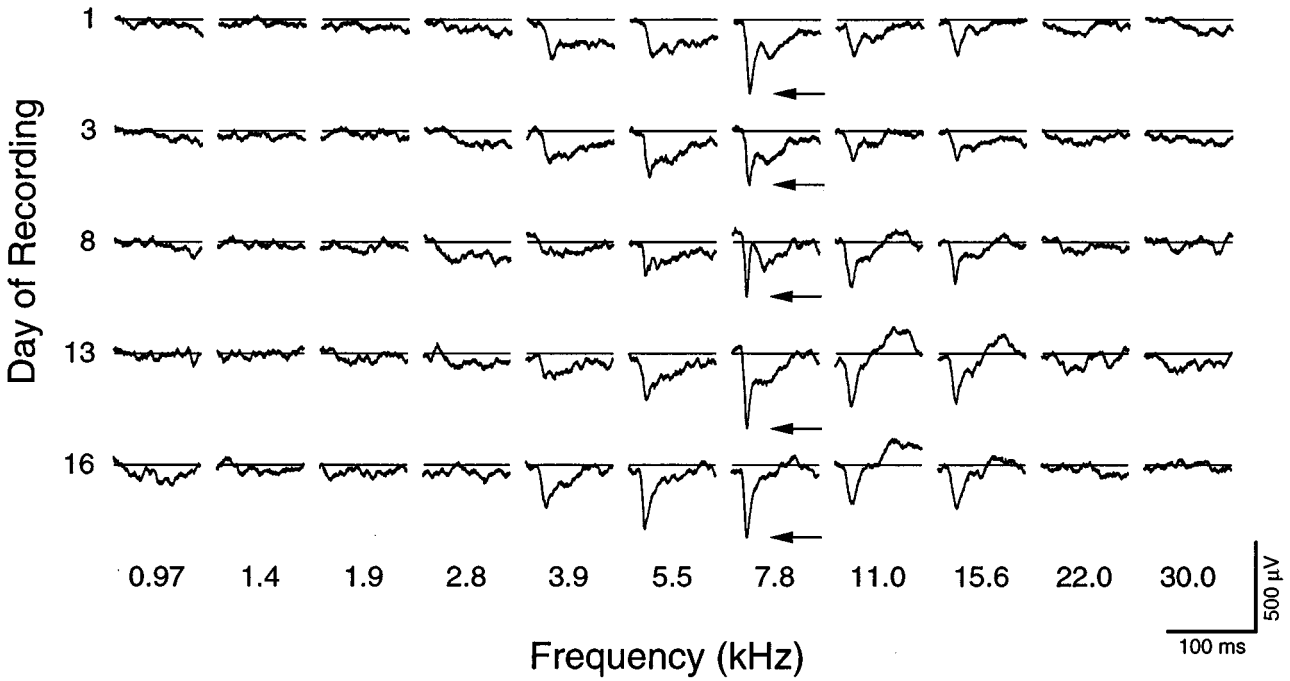


FIG. 2. Example of average LFPs from one recording site at one intensity (20 dB) across 16 days. The BF (7.8 kHz) remained the same from Day 1 to Day 16, and the response range was highly similar (3.9–15.9 kHz) across days. Arrows indicate BF.

first-to-last day variation from CF vs. BF30 was not significant (Wilcoxin test, $p > 0.05$).

Daily variability in tuning. Although tuning exhibited no significant trends, it did exhibit considerable day-to-day variability. To quantify this variability, we calculated the octave differences in tuning between each recording day and the preceding recording day for CF, BF10, and BF30 and for every recording site. The resultant unsigned differences are referred to as "daily tuning differences" (DTD). The mean DTDs for CF, BF10, and BF30 were 0.164 (±0.031 SE), 0.162 (±0.026 SE), and 0.152 octave (±0.025 SE), respectively. The medians were all 0.0. To determine if the magnitudes of DTDs were significantly different across the 16 days of recording, successive DTDs were compared, e.g., DTDs for Day 2 minus Day 1 with DTDs for Day 3 minus Day 2, etc. There were no statistically significant effects (Wilcoxin test, all $p > 0.05$). That DTDs ranged from 0.164 to 0.152 octave indicates that daily tuning variation is of considerable magnitude, about one-sixth of an octave. As all medians were zero, the majority of cases for CF, BF10, and BF30 had the same tuning from day to day.

Quarter-octave group

Evaluation of tuning trends. The use of 0.5-octave steps might have failed to reveal tuning drift or minimized tuning variability. Data from the quarter-octave group might be more sensitive. Figure 7 presents an example of LFPs over a period of 12 days from this group. In this case, the BF (6.20 kHz) remained the same across time; bandwidth narrowed somewhat across days while the range of response was essentially the same (3.2–21.0 kHz). As suggested by these data, tuning can be quite stable using a 0.25-octave frequency resolution. Figure 8A–C present data obtained over a period of 12 days. Note that the CF and BFs are the same across days, except for CF at Day 8, which is 0.25 octave lower; frequencies above and below the CF and BF10 and BF30 exhibit considerable day-to-day fluctuations. However, such low CF and BF variability was not the dominant finding. Figure 8D–F show examples of high variability in which the CF varied by as much as 0.5, BF10 by 0.75 and BF30 by more than 1.0 octave.

Quarter-octave group data are presented in Figures

FIG. 1. Example of average LFPs exhibiting frequency tuning. **A**. An average potential indicating the N1 component that is tuned to frequency, and the smaller, more variable P2 component which is not tuned. **B**. Average potentials across frequency and intensity. Note the decreasing bandwidth as stimulus level is reduced from 80 dB. The threshold was 0 dB and the characteristic frequency was 7.78 kHz. The best frequencies (BF) at 10 and 30 dB above threshold are denoted and were also 7.78 kHz.

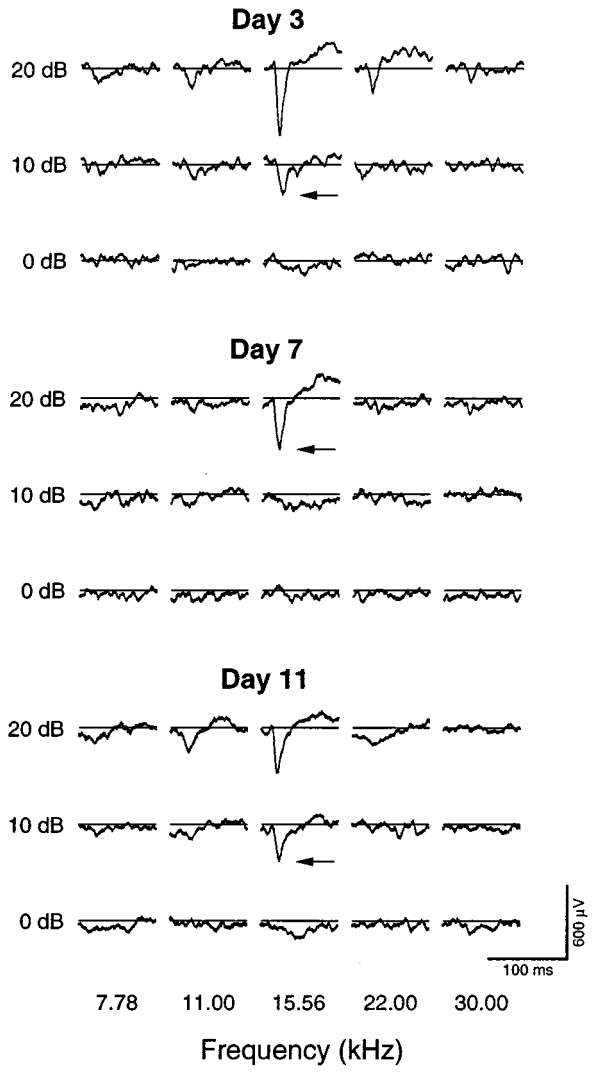


FIG. 3. Example of LFPs at threshold from one recording site. Data are shown for three days at 0–20 dB. The characteristic frequency (15.56 kHz) was the same across this time period, although the threshold intensity varied between 10 and 20 dB. The large magnitude at the CF on Day 7 may suggest that the actual threshold intensity was between 10 and 20 dB. Arrows indicate BF.

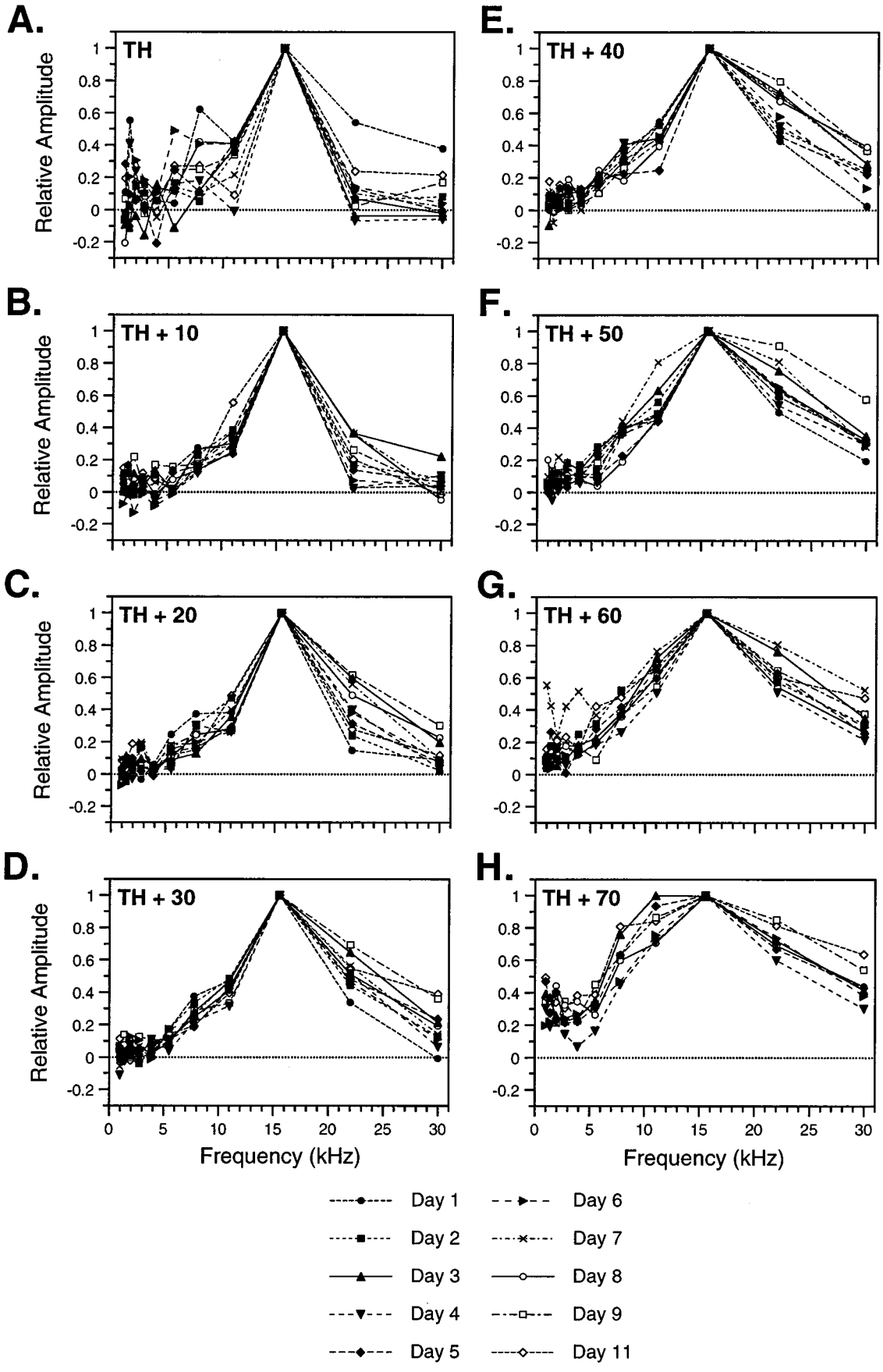
9A–E. There were no significant differences from the mean across days for CF, BF10, BF30, and BW (Friedman test, all $p > 0.5$). However, the threshold was greater on Day 10 than on Day 1 (Wilcoxin, test, $z = -2.121$, $p = 0.034$). There were no significant trends across days for any parameter, CF, BF10, BF30, TH, or BW (Page test, all $p > 0.05$).

The failure to find significant trends in tuning over days might be explained by the averaging of individual changes of opposite signs at different recording sites across the group. Therefore, we examined all individual tuning functions for CF, BF10, and BF30 (Fig. 10). Tuning variability was evident: Only two recording exhibited the same tuning values over 12 days (Fig. 10G, CF; Fig. 10H, BF10, BF30). Despite variation, trends of opposite signs were not evident. A Runs test could not be performed because the number of recording days ($n = 6$) was too small. The number of days with tuning identical to that of the first recording day was tallied, similar to the analysis for the half-octave group. For CF the value was 35/54 (65%), for BF30 it was 23/54 (43%). The degree of resolution is ±0.25 octave and a smaller-frequency step might have revealed a trend of smaller magnitude.

In addition, the tuning differences from the mean were calculated for the first and last days of recording (Days 1 and 12). For CF, 5/9 recordings had the same values; the mean difference = 0.19 octave (±0.27 SD) and the median difference = 0. For BF 30, 3/9 were identical; mean difference = 0.25 (±0.22 SD) and median difference = 0.25 octave. Although the value for BF30 was larger than for the CF, the difference was not statistically significant (Wilcoxin test, $p > 0.05$).

Daily variability in tuning. Mean DTDs ranged from 0 to 0.472 octave (BF30, Day 8). While the mean differences could be substantial, the median DTDs were zero, with the exception of BF30, Day 12, whose median difference = 0.25 octave. Therefore, the majority of cases had the same tuning on successive days. The grand mean DTDs for CF, BF10, and BF30 were 0.228 (±0.043 SE), 0.211 (±0.045 SE), and 0.250 octave (±0.059 SE), respectively. These DTDs are each larger than the corresponding values of the half-octave group (0.164, 0.162, and 0.152 octave, respectively), indicating that the 0.25-octave frequency step is more sensitive to tuning variability. The grand medians were 0.25, 0, and 0 octave for CF, BF10, and BF30, respectively. Given the substantial mean DTDs and zero medians (for BF10 and BF30), the findings indicate that while a minority of electrodes exhibited daily tuning differences, their changes could be large. There were no significant differences between individual days for

FIG. 4. Example of normalized tuning function from one recording site. Each panel presents tuning function relative to threshold (TH) across 11 days. **A–E**. Tuning function at low intensities show tuning stability at the BF (15.56 kHz) and neighboring frequencies. **F, G**. As intensity increases, more variability is seen at sideband frequencies. **H**. At the highest intensities, saturation is reached and there is much greater variability at sideband frequencies. **A–H**. The BF remained the same for all days and all intensity levels except TH + 70 dB on Day 3, which is lower. To facilitate comparisons of tuning irrespective of absolute amplitude differences, normalizations consisted of dividing the amplitude of each average LFP by the maximum amplitude within a tuning function.


A.
TH
B.
TH + 10
C.
TH + 20
D.
TH + 30
E.
TH + 40
F.
TH + 50
G.
TH + 60
H.
TH + 70
Relative Amplitude
Frequency (kHz)
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Day 9
Day 11

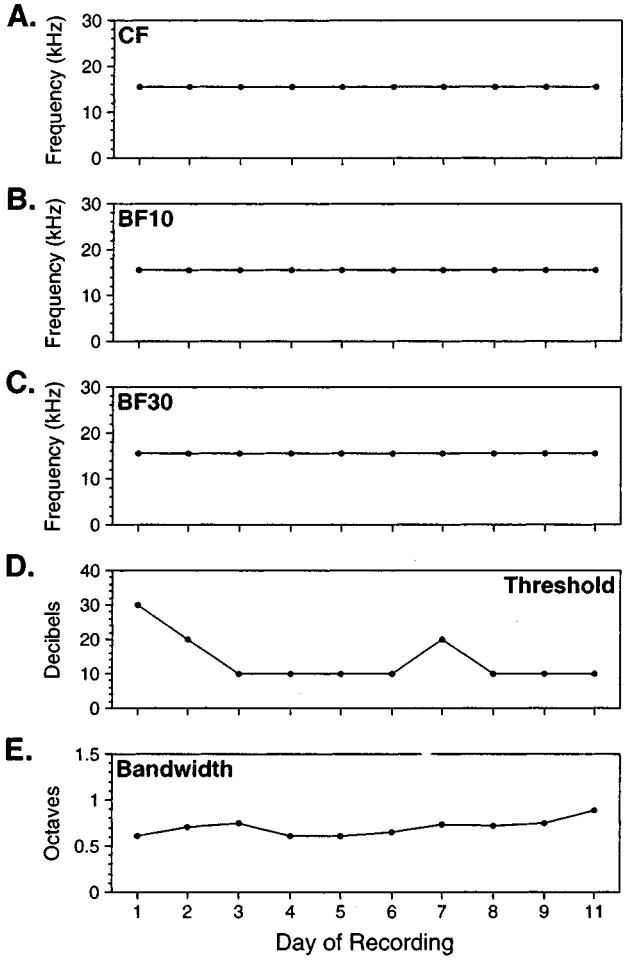


FIG. 5. Tuning function tuning values from a single recording site across 11 days. **A–C**. CF, BF10, and BF30 dB were the same across all days of recording. **D**. Threshold intensity was higher the first two days of recording and stabilized thereafter. **E**. Bandwidth (at 10 dB above threshold) varied from 0.6 to 0.9 octave across 11 days.

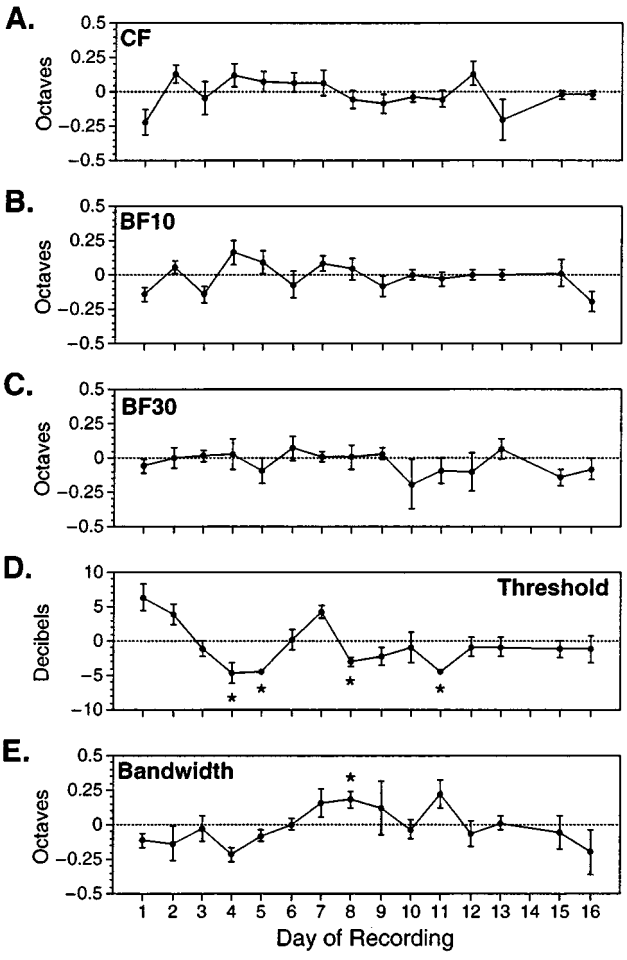


FIG. 6. Half-octave group tuning function parameters (mean ± SE). Shown are the average daily deviations from the mean of the parameter across all days. **A**. CFs for Day 1 and Day 13 were ~0.21 octave below the overall mean. CFs for all other days were less than 0.15 octave from the overall mean. **B**. All daily BF10s were less than 0.17 octave from the overall mean, except Day 16 (0.18 octave). **C**. BF30s varied slightly around the overall mean (±0.14 octave), except Day 10 (0.18 octave). **D**. Threshold was 6.5 dB higher than the overall mean on Day 1 and varied ±4.5 dB thereafter. **E**. Bandwidth varied ~0.22 octave from the mean across 16 days. Asterisks (*) denote significant differences from Day 1 (Wilcoxin test, $p < 0.05$).

CF, BF10, or BF30 (Friedman test, all $p > 0.05$). Neither were there any significant trends across days in the magnitudes of DTDs for CF, BF10, or BF30 (Page test, all $p > 0.05$).

DISCUSSION

Overview of findings

This study examines two aspects of frequency tuning across 12 or more days: directional changes in tuning ("drifts") and random day-to-day tuning variability.

The present findings indicate that frequency tuning of local field potentials in the auditory cortex of waking guinea pigs does not drift significantly to either lower or higher frequencies across periods of 12 days or longer. Three measures of tuning were used: characteristic frequency at threshold (CF) and best frequency 10 and 30 dB above threshold (BF10 and BF30, respectively). Two degrees of frequency resolution were studied: 0.5 and 0.25 octave. There were virtually no significant differences between Day 1 and subsequent days and there were no significant trends across time for any of these three tuning parameters. There were some differences in bandwidth and absolute threshold. These are best considered separately for the half- and quarter-octave groups (below).

On the other hand, considerable day-to-day tuning variability was observed in both the half-octave and quarter-octave groups. As median values for the (unsigned) DTDs were almost all zero, the changes in tuning appear to be at a minority of electrode sites.

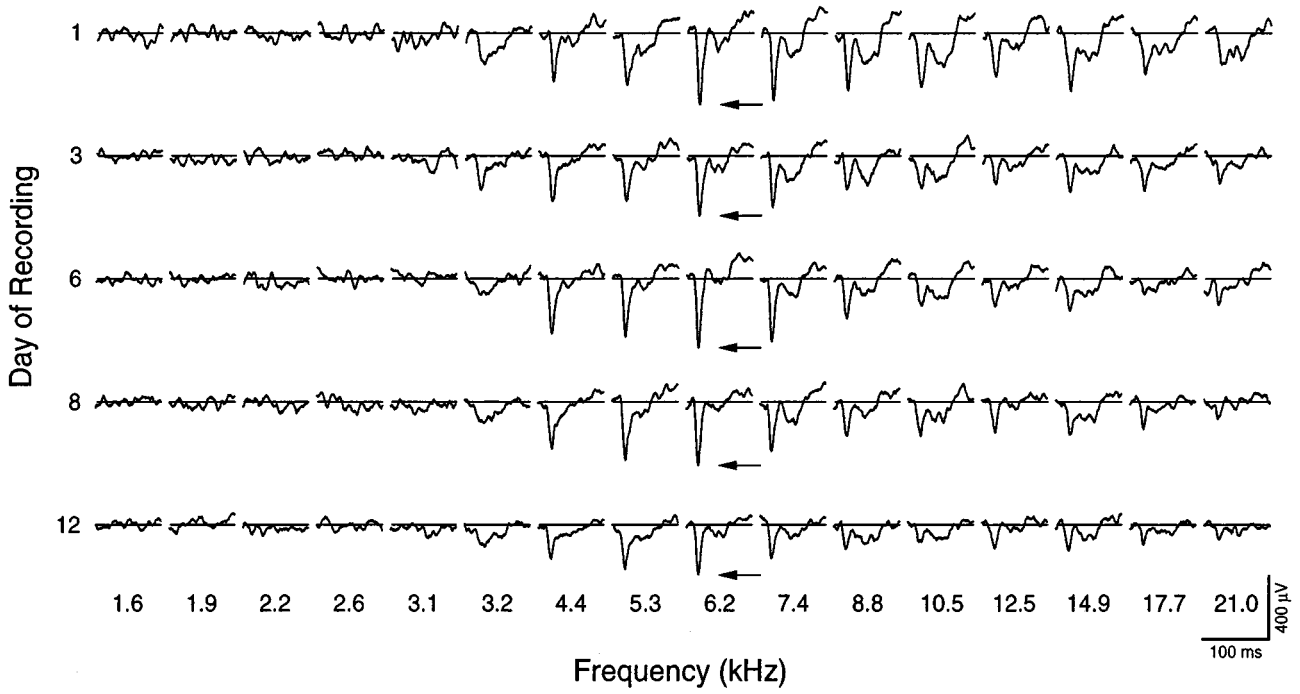


FIG. 7. LFPs from one recording site in the quarter-octave group (20 dB) across 12 days. The BF (6.2 kHz) remained the same and the response range was highly similar (3.2–21.0 kHz). In this case, the range of responsive frequencies appeared to decrease over days. Arrows indicates BF.

The amount of day-to-day tuning change also failed to show trends over days. Thus, although CF, BF10, and BF30 do not exhibit directional tuning drift, they do change randomly from day to day. Across the entire data set, maximum DTD values across days were 0.228, 0.211, and 0.250 octave (quarter-octave group).

Half-octave group

The half-octave subjects provided group data for 16 days plus data from two subjects for 17–27 days. While the latter also exhibited no trends in tuning, these observations are considered as ancillary only, as periods longer than 16 days lacked a sufficient number of recordings to permit statistical evaluation. As noted above, the half-octave group displayed no significant trends in the three measures of frequency tuning across 16 days. However, changes in bandwidth on one day (Day 8) were sufficient to manifest a difference when individual days were compared with Day 1.

Several significant differences were observed for deviations of absolute threshold from the parameter mean. In particular, the deviation of threshold for Day 1 was significantly greater than deviations for thresholds on many later recording days. The value for Day 2 was also larger. However, this particular finding need not indicate intrinsic variability because it is the single parameter that would be maximally affected by variations in effective stimulus levels at the cochlea. Two sources of such variation are placement of the speaker with respect to the long axis of the ear canal and middle-ear muscle contraction.

Regarding speaker placement, we attempted to be systematic in placing the opening of the speaker housing at the same distance and orientation from the entrance to the ear canal each time. In the absence of independent retrospective measurements of exact distance and angle, we cannot rule out the possibility that actual sound levels at the ear were lower on Day 1 and Day 2.

Contraction of the middle-ear muscles is a second potential source of reduced stimulus level. These contractions would be tonic, rather than phasic, in response to sound. Such tonic contractions are known to accompany general increased muscle tonus and could account for reduced stimulus levels as large as the 6.5 dB level observed on Day 1 (Fig. 6D) (Hugelin et al. 1960; Baust et al. 1964; Carmel and Starr 1964; Starr 1964; Irvine and Webster 1972). The most likely time for guinea pigs to be in such a state is during the first few days of recording, at which time they are least likely to have adapted to head and body restraint. This explanation is consonant with the lack of higher threshold in the quarter-octave group on their Day 1. As noted in the Methods section, these subjects underwent a preliminary day of recording before 0.25-octave steps were initiated. Hence, their Day 1 of 0.25-octave data was obtained after they had the opportunity to adapt to restraint on the previous day.

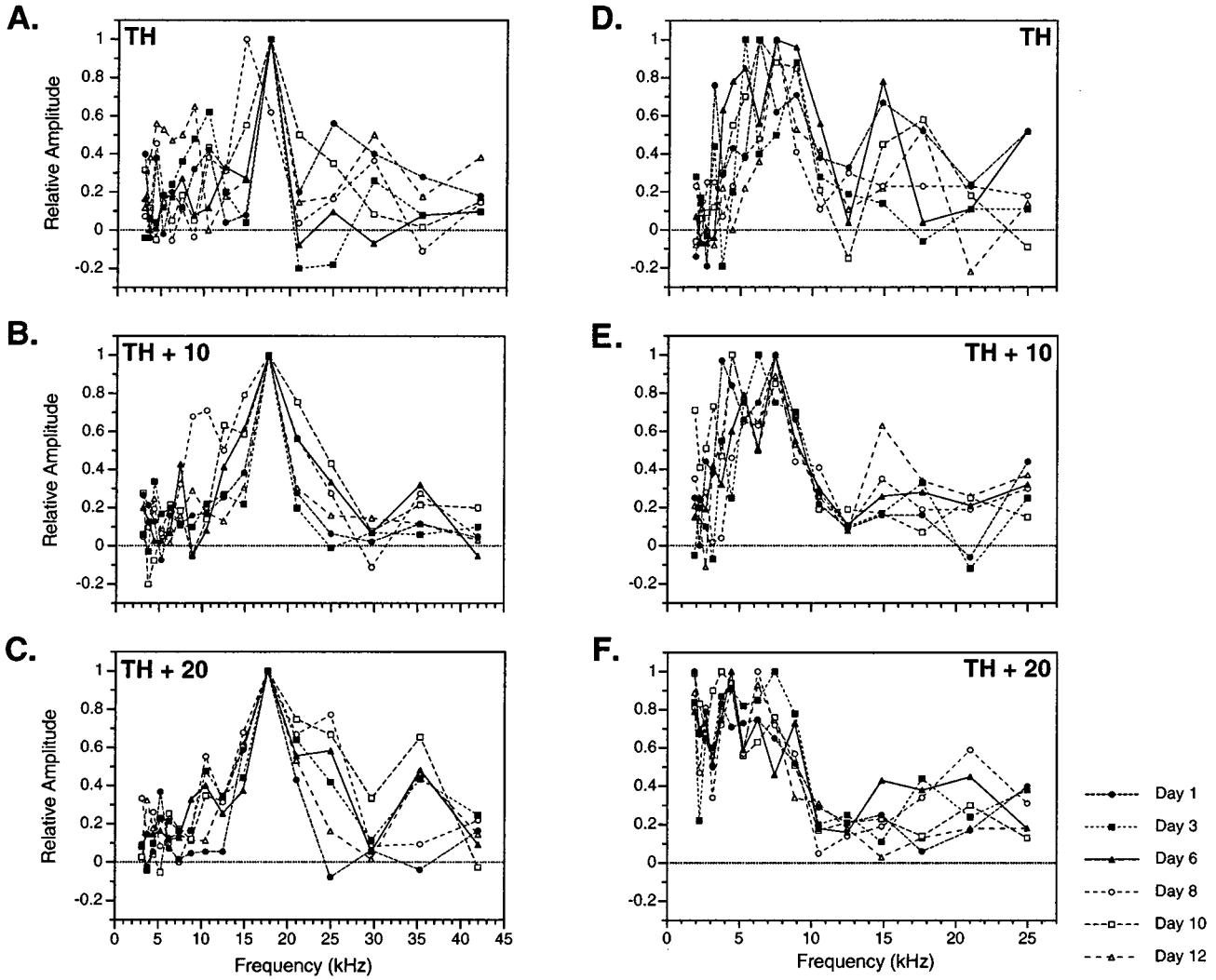


FIG. 8. Examples of normalized tuning curves across 12 days in two subjects from the quarter-octave group showing small (**A–C**) and large (**D–F**) daily tuning variations. **Subject 1: A**. The CF (17.65 kHz) was the same for all recordings at threshold except for a 0.25-octave shift to 14.84 kHz on Day 8. **B, C**. The BF (17.65 kHz) was the same for all recordings at 10 dB (TH + 10) and 20 dB (TH + 20) above threshold, respectively. Sideband frequencies exhibit greater variability. The greatest overall variability was on Day 8. **Subject 2: D**. The CF varied over 0.5 octave; CFs were either 6.25 or 7.42 kHz, with the exception of Day 3 (5.26 kHz). **E**. At 10 dB above threshold, the BFs varied over 0.75 kHz (7.43 on all days, except 6.25 kHz on Day 3 and 4.42 kHz on Day 10). **F**. At 20 dB above threshold, the daily tuning variation was greater; 1.86 kHz on Day 1 and 3.72–7.43 kHz thereafter.

Quarter-octave group

Data for the quarter-octave subjects were available for a period of 12 days. During this period, the animals exhibited no statistically significant trends in the tuning parameters or in bandwidth. One would have expected the smaller-frequency step of 0.25 octave to reveal more variability in BW. Thus, given the lack of change of BW, one cannot conclude that bandwidth is inherently unstable.

Deviations from the parameter mean for absolute threshold were higher on Day 10 than on Day 1. This difference cannot be explained by putative increased middle-ear muscle contraction because no effect on TH was observed on Day 1 in this group, and presumably the subjects were well-adapted by Day 10. The absence of higher thresholds on Day 1 might reflect the fact that the quarter-octave group had a day to adapt prior to starting. In any event, the source of the difference in threshold on Day 10 cannot be determined in this experiment.

Relation to learning-induced tuning plasticity

Previously, we have observed learning-induced frequency-specific changes in tuning of unit clusters, retained for periods as long as 8 weeks (Weinberger et al. 1993). Responses to the frequency of a conditioned stimulus (CS) increased while responses to the pretraining BF and other frequencies tended to decrease. These opposite changes were often sufficient to directionally shift tuning toward or even to the frequency

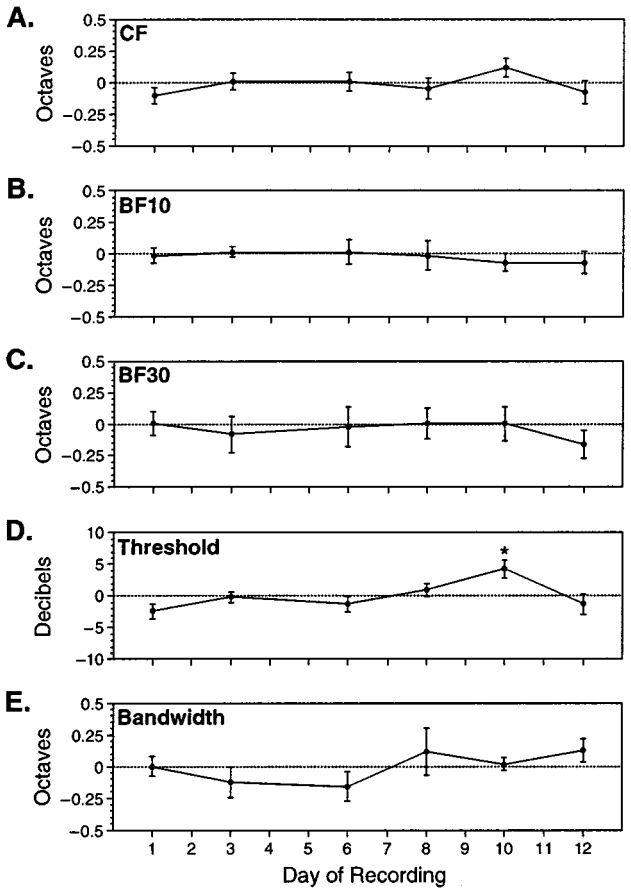


FIG. 9. Deviations of group tuning function parameters from the overall mean across 12 days for the quarter-octave group. **A**. CFs exhibited little deviation, the largest being ~0.12 octave on Day 10. **B**. BF10 showed less variation; the largest deviation was 0.06 octave. **C**. BF30 exhibited greater variation (±0.17 octave). **D**. Absolute threshold exhibited maximum deviation of 4 dB on Day 10, which was significant (Wilcoxin, $p < 0.05$). **E**. Bandwidth varied ±0.2 octave from the overall mean. There were no significant trends over days.

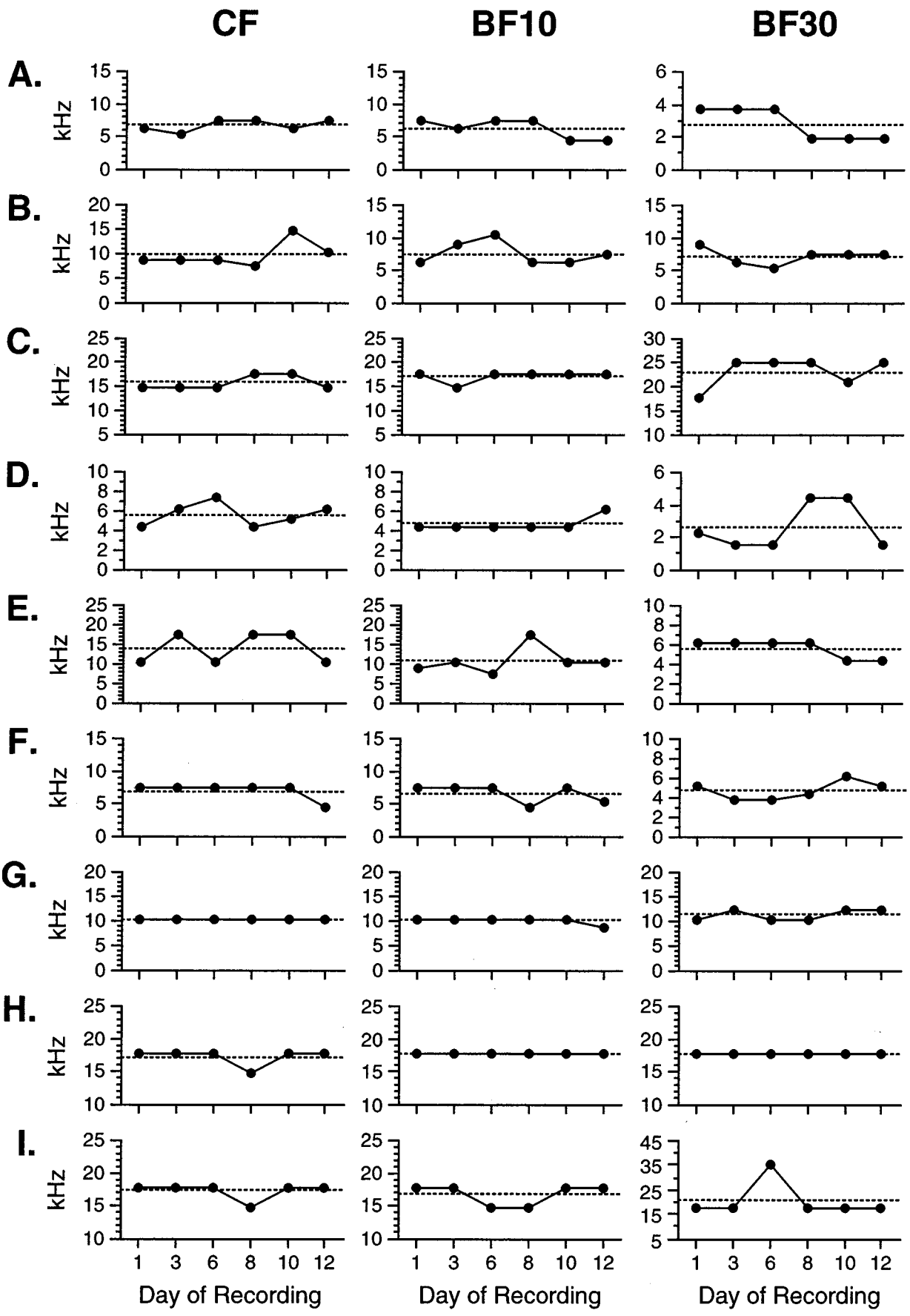
of the CS. Kisley and Gerstein (1999) have questioned these findings. They studied tuning in rats repeatedly across 7 days and reported "quite dramatic changes . . . including changes in best frequencies." Tuning was seen to exhibit continual increasing variability from day to day. Moreover, they stated that the changes were so great that they could "qualify as long term 'plasticity' (according to the criterion of Weinberger et al. PNAS, 90:2394–8, 1993)."

Their report raises two issues. First, was the long-term retention of conditioning-induced receptive field (RF) plasticity actually because of spontaneous changes of best frequencies rather than a result of associative learning? Second, why did Kisley and Gerstein find increasing tuning variability across days, whereas we failed to find such an outcome in this study?

With respect to the first point, spontaneous changes of tuning cannot account for long-term retention of RF plasticity. Long-term (tracked from 1 hour to 8 weeks) and shorter-term (tracked from 1 hour to 24 hours) RF plasticities have identical CS-specific characteristics. However, shorter-term RF plasticity cannot be caused by spontaneous tuning changes for at least three reasons (reviewed in Weinberger 1998, 2001a, b): (a) Nonassociative drift of tuning should lead to shifts away from as well as toward the frequency of the conditioned stimulus. However, the shifts overwhelmingly develop toward the CS frequency. (b) Nonassociative spontaneous changes should be observed in animals undergoing sensitization training. However, sensitization subjects do not develop tuning shifts but only exhibit increased responses across all frequencies. (c) In discrimination training, nonassociative shifts of tuning should occur to a nonreinforced (CS−) tone as well as to a reinforced (CS+) tone. But tuning shifts only toward the CS+, while responses to the CS− decrease. Since RF plasticity observed over shorter periods is associative, and it has the same characteristics as long-term plasticity, what is the rationale for asserting that long-term plasticity is nonassociative?

To accept nonassociative, spontaneous tuning drifts as an explanation of very long-term retention of receptive field plasticity, one would have to accept three conjoint assumptions: First, that the associative RF plasticity observed upto 24 hours or the first few days has no relation to that observed over periods of weeks. Second, that spontaneous shifts somehow manage to seek out the frequency of the conditioned stimulus. Third, that the long-term spontaneous tuning shifts do not begin for 24 hours or a few days. In other words, the CS-specific RF plasticity obtained at 1 hour after conditioning, which was maintained within the same recording site at 24 hours, 1 week, and up to 8 weeks (see Fig. 1 and Table 2 in Weinberger et al. 1993) actually would have to be caused by two independent processes. Short-term RF shifts are associative; but then the associative effect disappears, to be replaced by a spontaneous shift of tuning that is identical to that previously induced by association. The alternative is that the RF plasticity, known to develop rapidly during learning, simply is maintained. In fact, it has now been tracked from 1 hour to 10 days after a single conditioning session, even exhibiting systematic consolidation (i.e., increased strength) over 7 days (Galván et al. 1998). Therefore, spontaneous drift of tuning cannot account for long-term retention of frequency RF plasticity.

With reference to the second issue of increased variability of tuning over days, which would result in directional drifting of the BF itself, we could find no significant trends. However, our findings actually may be compatible with the data obtained by Kisely and Gerstein. They did not track changes in CF or BF over days but rather correlated entire tuning curves from


CF
BF10
BF30
A.
B.
C.
D.
E.
F.
G.
H.
I.
kHz
Day of Recording
1 3 6 8 10 12

one day with tuning curves from the next (and successive) days. They found decreased correlation coefficients as a function of days, hence concluding that frequency tuning exhibits directional drift (Kisely and Gerstein, personal communication). However, such correlations give equal weight to all frequencies, both those that elicit strong responses (e.g., to the BF) and those that elicit moderate or weak responses at increasing frequency distances from the BF. Therefore, reduced correlations could reflect increased variability of weak response to these frequencies even if the BF shows no directional drift. In fact, correlations would decrease if BF were constant while bandwidth increases over days. Therefore, the CF and BF can exhibit no tuning drift while correlations across days may decrease.

Relation to previous findings

Local field potentials are thought to represent extracellularly recorded, synchronous, excitatory, postsynaptic potentials (EPSPs) rather than spike activity (Creutzfeldt et al. 1966; Mitzdorf 1985). The "N1" potential recorded here from cortical depths is comparable to the positive potential of the same latency range that is recorded on the surface of the brain, which reverses polarity near the Layer III–IV border (Borbély 1970). This is thought to index current sinks associated with depolarization of radially oriented pyramidal cells, probably by thalamocortical input from the ventral medial geniculate nucleus (Borbély 1970; Wolpaw 1979; Kaga et al. 1980; Barth and Di 1990; Di and Barth 1992). As LFPs and unit discharges in the auditory cortex that are elicited by acoustic stimuli index are related but separable physiological processes (Eggermont and Smith 1995; Eggermont 1996; Galván et al. 1997; see also Bullock 1997), it would be of interest to determine tuning of both simultaneously over days. While this might be difficult because single-unit recordings appear to be more susceptible to slight changes in electrode position over time than LFPs, long-term single-unit recordings have been accomplished. For example, Williams et al. (1999) reported stable recordings from the same cells for more than six weeks in the auditory cortex of the waking guinea pig. This group also has obtained highly stable tuning in multiple-unit recordings over periods of five days in the waking cat (Witte et al. 1999). Thus, it should be possible to determine tuning variability for units and LFPs simultaneously, over weeks.

Given the report of Kisely and Gerstein (1999) and the present findings, comprehensive analyses of spontaneous changes in tuning, in the absence of behavioral learning protocols or similar manipulations, remain to be accomplished. These analyses should include tracking of not only correlations between tuning curves or the frequency of peak response (CF and BF), but also all frequencies within a tuning curve. Moreover, it would be preferable to do so at a finer frequency resolution, e.g., eighth octave or less. Random tuning variation over days may differ as a function of octave distance of each frequency from the BF or as a function of strength of response (which is generally weaker with increasing frequency distance). Furthermore, such analyses should be performed for all stimulus levels, e.g., from threshold to 80 dB.

Spontaneous tuning variability is of both practical and theoretical interest. From a practical point of view, it must be taken into account in long-term studies. Such variability does not account for the CS-specific effects of learning because the latter do not merely involve a magnitude of tuning shift but rather also entail an *a priori* direction of tuning change, i.e., toward or to the frequency of the CS (Weinberger 1998). There are many other types of investigations of chronic, long-term studies, in particular, there is an increasing amount of imaging studies of human auditory cortex (e.g., Rauschecker 1998; Griffiths 1999; Lambe 1999; Pantev and Lutkenhoner 2000; Simos et al. 2000). From a theoretical point of view, there are many questions concerning the source of variability. It might be cortical, subcortical, or both. At a subcellular level, tuning variability might be caused by shifting synaptic weights. Another issue concerns its functional significance. Variability might reflect a normal, dynamic state, within which frequency information is processed, a state that may subserve auditory perception more effectively than would a static system.

At present, the current observations provide an initial guide to spontaneous tuning variability. They indicate that LFP tuning at threshold and 10 and 30 dB above threshold does not systematically drift over periods of 12–16 days. Selectivity of tuning, as measured by bandwidth, is also stable using a 0.25-octave frequency resolution, however, it also may exhibit increases, as seen in the half-octave group. The majority of recording sites exhibited no daily tuning changes, but considerable daily variation was evident in other recordings. Therefore, as a group, long-term LFP tuning in the auditory cortex of waking animals, at or within 30 dB of threshold, might best be considered to have a central tendency with a preferred range,

FIG. 10. Individual tuning data for the quarter-octave group across 12 days of recording. Functions present the daily deviation from the mean (dotted line) for CF, BF10, or BF30 tuning values. **A–I** denote each of the nine recording sites. Tuning was identical over days in a few cases (i.e., **G**, CF; **H**, BW10, BW30). Daily variations were evident but these rarely consisted of trends (i.e., **A**, BF30).

rather than a fixed frequency value. The assumption that CF and BF tuning are stable in the absence of discrete manipulations, such as changes in state, attention, or learning, appears valid regarding directional drift but must be qualified by nonsystematic tuning variability, which in the present case maximally averaged about 0.20–0.25 octave.

ACKNOWLEDGMENTS

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