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Improved cortical entrainment to infant communication calls in mothers compared with virgin mice

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Abstract

There is a growing interest in the use of mice as a model system for species-specific communication. In particular, ultrasonic calls emitted by mouse pups communicate distress, and elicit a search and retrieval response from mothers. Behaviorally, mothers prefer and recognize these calls in two-alternative choice tests, in contrast to pup-naïve females that do not have experience with pups. Here, we explored whether one particular acoustic feature that defines these calls – the repetition rate of calls within a bout – is represented differently in the auditory cortex of these two animal groups. Multiunit recordings in anesthetized CBA/CaJ mice revealed that: (i) neural entrainment to repeated stimuli extended up to the natural pup call repetition rate (5 Hz) in mothers; but (ii) neurons in naïve females followed repeated stimuli well only at slower repetition rates; and (iii) entrained responses to repeated pup calls were less sensitive to natural pup call variability in mothers than in pup-naïve females. In the broader context, our data suggest that auditory cortical responses to communication sounds are plastic, and that communicative significance is correlated with an improved cortical representation.

Introduction

The plasticity of auditory cortex has been well demonstrated through conditioning, training and electric stimulation experiments in animals (Weinberger, 2004; Ma & Suga, 2005; Ohl & Scheich, 2005). However, whether natural communication sounds induce similar plastic changes in the auditory cortex as their behavioral significance is acquired is not clear. Unlike laboratory training situations where specific sounds are chosen as targets, many physical acoustic waveforms can correspond to the same communicative message, as when a speech phoneme is pronounced by different individuals (Peterson & Barney, 1952; Lisker & Abramson, 1964). Moreover, communication processing may require simultaneous detection, discrimination and categorization of acoustic parameters, as when deciphering speech in a noisy background. However, animal cortical plasticity studies involving behavioral training have generally required only a single psychophysical task to obtain a reward or avoid punishment (Beitel *et al*., 2000; Ohl *et al*., 2001; Witte & Kipke, 2005), leaving open the question of how plasticity proceeds in more natural, social situations.

It is therefore of interest to explore cortical plasticity in natural communication. We pursue this in the mouse – a growing animal model for communication studies (Ehret & Riecke, 2002; Liu *et al*., 2003; Ehret, 2005; Holy & Guo, 2005). One such vocalization is produced during the pup–mother interaction. Pups emit bouts of ultrasonic (> 25 kHz) isolation calls (Fig. 1A) when isolated away from the nest (Noirot, 1966; Sewell, 1968). This alerts a mother, and prompts a search for and retrieval of the pup to the nest (Sewell, 1970; Haack *et al*., 1983). As expected for communication sounds, pup calls are variable along several acoustic dimensions, such as frequency, duration and repetition period (Noirot & Pye, 1969; Elwood & Keeling, 1982; Roubertoux *et al*., 1996; Branchi *et al*., 1998; Hahn *et al*., 1998; Liu *et al*., 2003). Some sound parameters, like ultrasound bandwidth and duration, are even perceived in a categorical fashion by mothers (Ehret & Haack, 1981, 1982; Ehret, 1992). In two-alternative choice experiments, mothers preferentially approach pup-like ultrasounds compared with a neutral, non-communicative sound; while pup-naïve, virgin females do not (Ehret *et al*., 1987). This suggests that mothers, but not virgins, recognize the communicative significance of these ultrasound calls (Ehret, 2005).

Does this behavioral distinction manifest in the cortical coding of ultrasonic pup calls? Immunohistochemical studies of c-FOS activation indicate differences between mothers and pup-naïve females among auditory cortical fields after sound exposure to repetitive pup calls (Fichtel & Ehret, 1999). We now use multiunit electrophysiology to determine whether the auditory cortical representation of one particular acoustic parameter of the natural pup calls – the repetition rate of calls (Fig. 1B) – is plastic. Acoustically, this parameter discriminates pup calls from a different ultrasound vocalization in the mouse repertoire produced by adult males (Liu *et al*., 2003), and might

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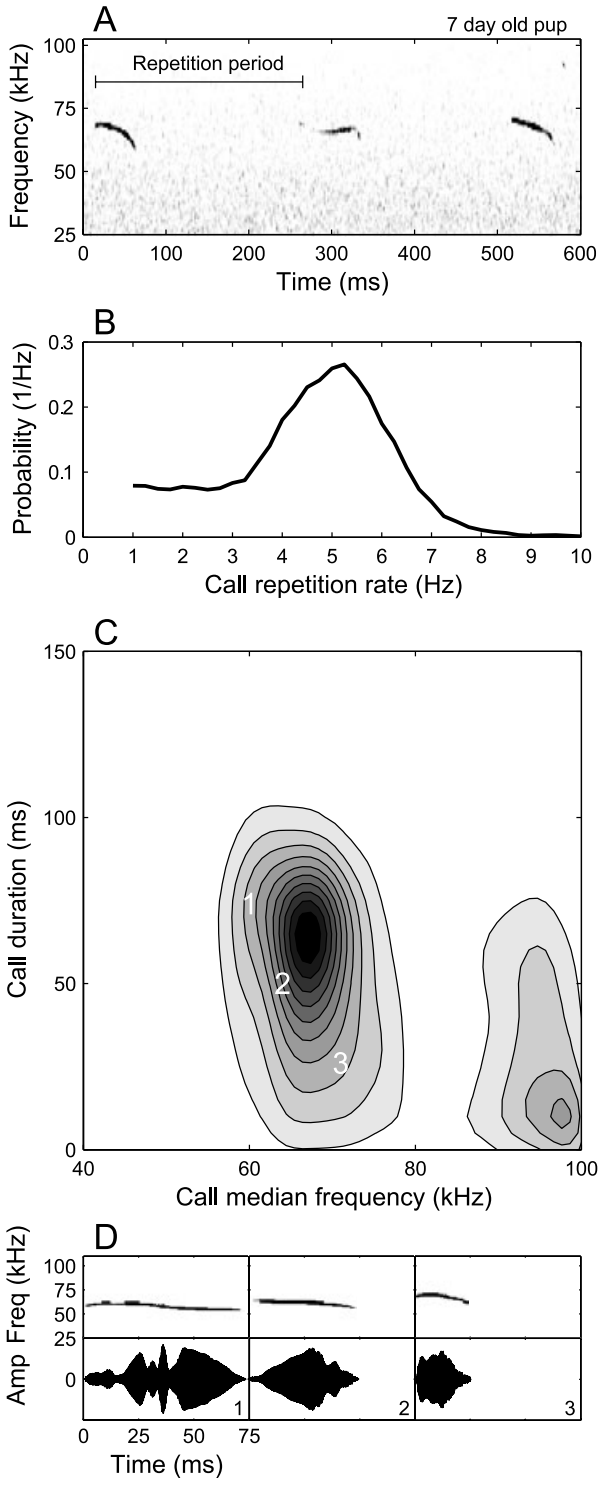

FIG. 1. Mouse pup ultrasound isolation vocalizations. (A) Spectrogram of a pup call bout. Most calls were simple whistles with some frequency modulation. The repetition period measures the interval between onsets of consecutive calls. (B) Distribution of pup call repetition rates [1/(repetition period)]. Call bouts were most often emitted at a rate of about 5 Hz. (C) Contour plot of the joint distribution of pup call median frequency and duration. Pup calls formed two clusters around 67 kHz/59 ms and 94 kHz/30ms.The numerical labels indicate the location of sample calls used to test neural responses. (D) Frequency trajectories and amplitude envelopes as a function of time for the sampled calls. The numerical labels correspond to those in C. Pup calls exhibited a variety of amplitude modulations, and subtle frequency modulations.

be used for recognition, as it is for wriggling calls in mice (Geissler & Ehret, 2002). Our underlying hypothesis was that the auditory cortex should be better tuned to this temporal parameter in animals for which the calls are behaviorally relevant.

Materials and methods

General

The University of California, San Francisco's Committee on Animal Research approved all animal procedures. Eighteen adult CBA/CaJ mothers and 10 pup-naïve female mice (12–20 weeks) were included in this work. Mice of the CBA strain have good hearing and do not show significant age-related hearing loss until nearly 2 years old (Willott *et al*., 1991; Walton *et al*., 1998). Animals were housed under a reversed light cycle, and accessed food and water *ad libitum*. At the time of experiments, mothers had weaned a litter of pups within the prior week. Naïve females were never housed with males or pups after they had been weaned, although their cages were located in the same room of the vivarium as those for mothers. Details of the surgery were described earlier (Linden *et al*., 2003). Briefly, mice were maintained under anesthesia with a combination of ketamine (100 mg/kg initial dose, 65 mg/kg maintenance) and medetomidine (0.3 mg/kg). A nose clamp secured the animal's head during both the craniotomy and recording stages of the experiment. A $\sim 4 \times 3$ mm hole in the skull was opened over the left auditory cortex (Stiebler *et al*., 1997).

Acoustic stimulation

After surgery, animals were repositioned in front of free-field speakers in an anechoic chamber (Industrial Acoustics, New York, NY, USA). In most experiments, we employed a low- (4–40 kHz, D-21/2, Dynaudio North America, Bensenville, IL, USA) and a high- (20–100 kHz, Ultrasound Loudspeaker, Ultrasound Advice, London, UK) frequency speaker to present stimuli. The transfer functions for each speaker inherently varied within a range of 12 dB; we improved on this by normalizing stimuli with the transfer functions to achieve a calibration that was flat to within 1 dB, with better than −44 dB total harmonic distortion (THD). However, because of the additional time required to obtain overlapping frequency tuning curves for both ranges (see below), we turned in later experiments to a single wide-bandwidth ribbon tweeter (High Energy EMIT-B, Infinity, Woodbury, NY, USA). After normalization to within 1 dB, this speaker had a THD better than −63 dB at frequencies from 11 to 100 kHz. Unfortunately, below 11 kHz, the THD varied up to −35 dB, thereby limiting its use at high amplitudes and low frequencies. This was not considered a serious problem because we focused on higher frequency ultrasonic sounds. The sound delivery system was calibrated by Tucker Davis Technology's (TDT, Alachua, FL, USA) SigCal software before every experiment, using a Brüel and Kjær (B & K, Norcross, GA, USA) 1/4′ free-field microphone coupled to a B & K 2669 pre-amp and 2690 amplifier. In some experiments, an acoustic horn (Mini-3 Detector accessory, Ultrasound Advice) placed in front of the mouse's ear boosted the overall sound level.

Recording procedure

Once the animal was positioned, the exposed cortical area was photographed to record penetration locations. Epoxylite-coated tungsten microelectrodes (1–2 MΩ, Fred Haer and Company, Bowdoinham, ME, USA) were introduced perpendicularly into the cortex, and

advanced 400–600 microns below the surface. Stimuli were generated using System II or 3 hardware and software from TDT. All stimuli were formatted by the SigGen32 software, and presented through the TDT Brainware software, which also served to collect and save to disk thresholded action potentials. Noise bursts and frequency sweeps were used as search sounds to assess the multiunit response to acoustic stimulation. Recording locations were usually chosen by looking for areas that had time-locked responses to at least one of these stimuli, and large spike amplitudes (a spike threshold was placed well above the peaks in the background noise level). While a few locations had a clearly distinguishable single unit, most recording sites likely contained on the order of two–five single units [based on offline spike sorting analysis of similar data collected with the same type of electrodes (personal communication, JFL)]. Our single unit population was small, and their inclusion in our analyses did not affect our conclusions as we tried to use measures that would be less sensitive to the number of neurons in a recording. We therefore occasionally use the term unit to refer to both single and multiunit recordings. While conclusions drawn from multiunit data may not always apply to single units, our approach can nevertheless be compared with other multiunit auditory entrainment studies (Eggermont, 1991; Kilgard & Merzenich, 1998b).

Online visualization in Brainware facilitated an initial characteristic frequency (CF) estimate from the driven responses to tonal mapping stimuli (described in detail below). The first penetration was normally near the center of the craniotomy; the subsequent four–eight penetrations were used to identify the reversal of tonotopy between primary (A1) and anterior auditory (AAF) fields. Further penetrations attempted mainly to target the ultrasound field (UF) (Stiebler *et al*., 1997).

Basic unit characterization by tones

At every recording location, tonal mapping stimuli were used to determine the frequency–amplitude response area (FARA) maps. Sixty-millisecond tone pips that included 5 ms $\cos^2$ onset and offset ramps, were played out at various frequencies and amplitudes. Coarse ($\sim$ 0.14 octave, 10-dB steps) or dense ($\sim$ 0.1 octave, 5-dB steps) sampling densities were used depending on whether a quick or more detailed map was desired. In experiments where both a low- and a high-frequency speaker were used, separate (but overlapping) FARA maps were obtained at each recording site for both frequency ranges.

After an experiment, FARA map files were analysed offline by custom MATLAB (Mathworks, Natick, MA, USA) functions. Data collected from low- and high-frequency speakers for the same multiunit were combined to produce a single FARA. Because it was necessary to cover a wide range of frequencies and amplitudes, each pair of frequency/amplitude parameters was only presented once. We therefore had to implement steps in our FARA analysis to reduce the noisy effects of trial variability; these measures applied only to this basic characterization, and not to the entrainment analysis, which is discussed below.

First, to attempt to isolate spikes that were well time-locked to the tone presentation, we selected a window around the peak response in the overall peristimulus time histogram (PSTH, binned in 5-ms bins) by eye for each file. This window started at the earliest driven response as viewed in the trial-by-trial rasters, and extended to where the overall PSTH dropped to about 1/4 of the amplitude between the spontaneous level and the peak (30 ± 9 ms, mean ± standard deviation window size across units). Next, the two-dimensional maps were smoothed with a Gaussian. The threshold and CF were then estimated by drawing a contour line in the image at approximately 40% of the maximum spike count across all frequency/amplitude combinations. The minimum amplitude point was selected as the threshold; the frequency at this point was picked as the CF.

After obtaining offline CF estimates from all recording sites in an animal, we attempted to assign each site to a specific auditory field by matching its response characteristics to the known properties of each field. In particular, the range of CFs within, and the spatial arrangement between, fields contributed significantly to our decision. The presence of multiple tuning peaks, high levels of bursting spontaneous activity, habituating responses and preference for modulated frequencies also influenced the designation (Stiebler *et al*., 1997). By these criteria, we discriminated between primary (A1 and AAF), UF and other/uncertain locations (which includes the dorsal posterior and secondary auditory fields). FARAs were derived for 272 (167) units in mothers (naïves), which included 105 (46) primary, 31 (16) UF and 136 (105) other/uncertain units.

Pup call stimulation

Natural pup isolation calls are generally single-frequency whistles, with durations up to $\sim$100 ms and frequencies between $\sim$50 and $\sim$100 kHz, as shown in Fig. 1C. Three calls (Fig. 1D) representative of the variability in isolation calls were pseudo-randomly selected from a call library (Liu *et al*., 2003), extracted from recordings, and denoised (Liu *et al*., 2003) for playback at equalized root-mean square voltages. The selection was pseudo-random because we tried to ensure that the resulting set did not include sounds that had obvious recording artifacts (e.g. clicks, saturated amplitude or high background noises). Call #2, near the center of the pup call distribution in frequency and duration, was selected as the basis for synthetic model calls. The amplitude envelope for this call was extracted by Hilbert transformation, and then applied to: (1) a tone at 64 kHz (the same frequency as the median frequency of the call); and (2) a tone at 24 kHz.

Throughout the initial mapping and later targeting stages, whenever neurons appeared to be driven by high frequencies, responses to natural and/or model pup calls were recorded. We routinely presented 12–24 trials of each sound in a stimulus set in random order, with at least 1200 ms between the start of each trial. Recordings to pup call stimulus sets were also occasionally made at locations that did not obviously respond to high-frequency tones, in order to see whether pup call responses might still be induced. The playback amplitudes across experiments were varied; in this work, only responses to calls presented between 60 and 80 dBSPL (corresponding to the behaviorally realistic range) were analysed.

Call bout and entrainment analysis

Neural following of a bout of two pup calls at the naturally occurring 5 Hz repetition rate was tested using call #2 (Fig. 1D), and amplitude-envelope matched 64 kHz and 24 kHz tone models of call #2. For the natural call, 104 (98) multiunits contributed to the 5 Hz bout analysis for mothers (naïves). This population included 23 (17) primary, 10 (12) UF and 71 (69) other/uncertain units. For the 64-kHz model, 103 (96) units contributed: 23 (16) primary, 10 (12) UF and 70 (68) other/uncertain units. For the 24-kHz model, 76 (71) units contributed: 18 (12) primary, 8 (5) UF and 50 (54) other/uncertain units.

To investigate pup call following at other repetition rates, entrainment functions were derived using call #1 and #3 (Fig. 1D). Three identical stimuli were played back at repetition intervals of 83, 100, 133, 150, 200, 300 and 400 ms. For call #1, 32 (48) units contributed

to the entrainment analysis for mothers (naïves). This population included 9 (18) primary, 9 (5) UF and 14 (25) other/uncertain units. For call #3, 74 (81) units contributed: 23 (31) primary, 11 (6) UF and 40 (44) other/uncertain. In all cases, the first stimulus in a sequence produced a driven response above the spontaneous rate.

For simplicity, we used a consistent 75-ms window, triggered 6 ms after the onset of each stimulus (to coincide with the earliest response), to count spikes for all pup call analyses (5 Hz bout, and entrainment). This window length was equal to the duration of the longest call tested, and allowed us to capture the full response of most neurons. Changing this window over a range from 50 to 100 ms, or shifting the window by ±5 ms did not greatly affect the shape of the entrainment functions or population measures, and did not alter our conclusions. This particular choice allowed us to compromise between measuring the entrainment at higher repetition rates and capturing the response to longer stimuli.

The mean and 95% confidence intervals on the spike counts were computed by bootstrap (Efron & Tibshirani, 1993). For the 5-Hz bout analysis, the spike count elicited by the second stimulus was directly compared with the first stimulus response. For entrainment, which quantifies the average *per stimulus* response, the entrained response (averaging over the responses to the second and third stimulus for all trials with the same interstimulus separation) was compared with the first response (averaging responses to the first stimulus over *all* trials). The best entrained rate was simply the one corresponding to the peak entrained activity. The average spontaneous rate was estimated over the last 75 ms of a trial.

Results

Response to ultrasonic tones

Acute, anesthetized experiments were conducted on two groups of mice: recent mothers and pup-naïve females. Previous studies indicate that these groups have different behavioral preferences for natural pup communication calls (Ehret *et al.*, 1987). To determine whether cortical responses to ultrasound calls in these two animal groups differ, we first looked at the response to ultrasonic frequencies. This was assessed by presenting pure tones to derive FARA maps. Examples (roughly matched for CF and tuning shape) are plotted in Fig. 2A–C for naïve females, and Fig. 2D–F for mothers. These gray-scale images show the actual spike counts in response to particular combinations of tone frequency and amplitude, as well as the smoothed border (see Materials and methods). For both mothers and naïve females, these multiunit maps were spectrally broad, especially in the behaviorally realistic amplitude range for pup calls (60–80 dBSPL).

Mothers and naïve females did not show significant differences in terms of their relative responsiveness to the dominant, ~65 kHz frequency of pup calls. This was assessed by using the smoothed FARA maps to predict the response to a pure tone at 65 kHz/70 dBSPL and compare it with the response to a tone at CF/70 dBSPL. This ratio is plotted in Fig. 2G as a function of a unit's CF, for both mothers (light gray) and naïve females (dark

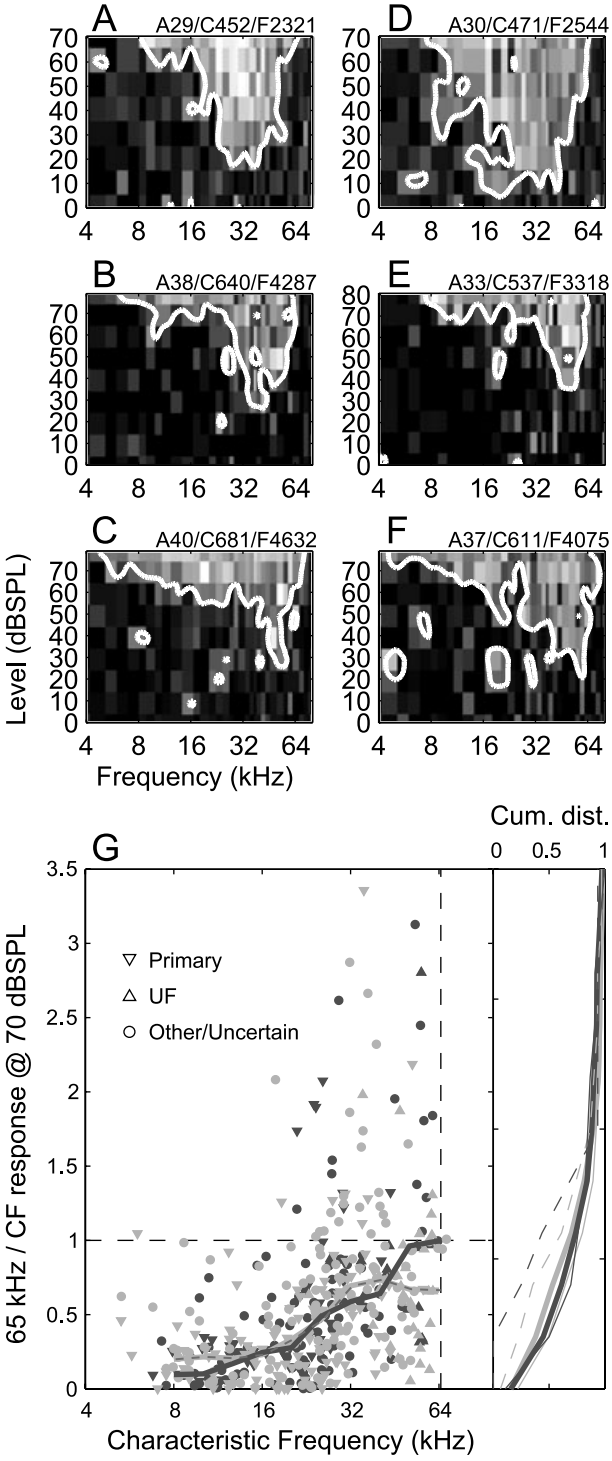

FIG. 2. Examples of the FARA maps from naïve females (A–C) and mothers (D–F). Grayscale images show raw spike counts in windows around each unit's PSTH peak. Thick white line outlines the contour line at 40% of the maximum spike count. (A) Primary, 37 kHz CF, maximum firing rate (white) of 503 spikes/s. (B) Other/uncertain, 42 kHz CF, 400 spikes/s. (C) UF, 55 kHz CF, 778 spk/s. (D) Other/uncertain, 21 kHz, 824 spikes/s. (E) Other/uncertain, 53 kHz CF, 598 spikes/s. (F) UF, 60 kHz CF, 590 spikes/s. (G) (Main) Ratio of the response magnitude at 65 kHz to that at its CF, obtained from a neuron's FARA at 70 dBSPL. Units from mothers (272) are in light gray; units from naïve females (166) are in dark gray. The thick solid lines in light and dark gray indicate the sliding median (2/3 octave window) of the ratio across the data for mothers and naives, respectively (for clarity, a darker, thin dashed line is superimposed over the light gray line for mothers). (Right) Cumulative distribution of response ratios. The thin solid lines correspond to Primary units (mothers, light gray; naives, dark gray); dashed lines, UF units; thick lines, all units. Across the population, the response to an ultrasonic tone at the pup call frequency gradually falls off with decreasing CF.

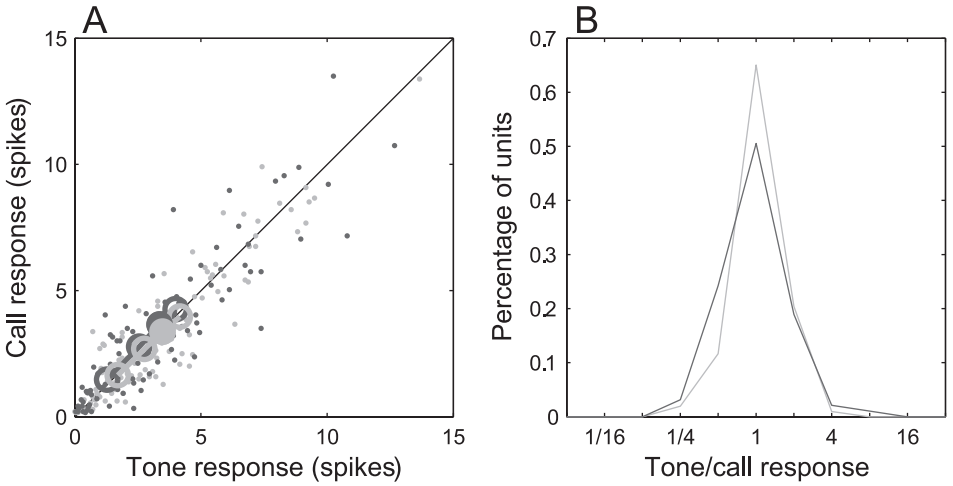

FIG. 3. Response to natural call #2 versus response to a 64 kHz tone model with the same amplitude envelope modulation, but no frequency modulation. (A) The small points indicate the individual unit responses measured in a 75 ms window, plotted for both mothers (light gray) and naïve females (dark gray). Large, filled circles indicate the population means for the 75 ms window for mothers (light gray) and naives (dark gray). Large open circles indicate the population means for 25, 50, and 100 ms windows. Regardless of the window size used for counting spikes, the average response to the tone model tracked that to the natural call, in both animal groups. (B) Distribution of the tone to call response ratio. The ratio was distributed symmetrically, and similarly for mothers (light gray) and naives (dark gray), suggesting that neurons in both animal groups were not sensitive to the mild frequency modulation found in natural pup isolation calls.

gray). The thick solid lines indicate the sliding window medians of the ratios (mothers in light gray with dashed highlight line, pup-naïve females in dark gray) across CF; 50% of the units had ratios above this line. For both animal groups, the population showed a gradual decline in the ratio as the CF decreased from 65 kHz. Some deviation between the curves is apparent at the highest frequencies, where our sample was thinnest. Nevertheless, between the two animal groups, the cumulative distributions of the ratios were not significantly different ($P = 0.36$, two-sample Kolmogorov–Smirnov test, used for all statistical comparisons, unless otherwise noted), even when only primary ($P = 0.29$) or UF (i.e. high-frequency; $P = 0.36$) sites were considered.

Mothers and naïve females also showed no significant differences between the spike count responses (in a 75 ms window) to a natural 64-kHz call ($P = 0.38$) and a tonal model of that call with the same amplitude envelope ($P = 0.37$). Moreover, the correlation between natural and model calls (Fig. 3A) was high within each animal group ($r = 0.92$ for both mothers and naïve females). Thus, the population-averaged spike counts (large circles) fell close to the diagonal in Fig. 3A, which was true even for different spike integration windows. Hence, the ratio of the tone model to call response was distributed symmetrically around 1 (Fig. 3B). This indicates that the subtle frequency modulation of the natural call was not important, on average, in driving the multiunit spike count for either mothers or naïve females.

Response to call bouts

We next played back a sequence of two identical pup calls (#2 in Fig. 1C and D), spaced by 200 ms between call onsets, to simulate the typical periodicity of natural pup call bouts. Example responses for two multiunits from a mother and naïve female are plotted as both rasters and PSTHs in Fig. 4A and B, respectively. Each call usually elicited an onset response followed by a suppression below the spontaneous rate.

To assess the ability of small clusters of neurons to follow each call presentation, we compared the average response to the second call in a bout with that of the first. Figure 4C plots these absolute spike counts (75-ms window, see Materials and methods) for each of the 104 (98) multiunits from mothers (naïve females) in light (dark) gray. The data for both groups tended to lie below the diagonal, indicating that at the time of the second stimulus, most multiunits were still recovering from the suppression in activity induced by the first sound presentation.

The ratio of the second to first response was significantly different between mothers and naives (Fig. 4D, $P = 0.004$), with the latter group offset towards smaller values. When the 64-kHz tonal model of a pup call (see Materials and methods) was used instead of a natural call, the two distributions remained significantly different ($P = 0.008$). For mothers, response ratios were narrowly distributed close to 1, while response ratios for naïves were shifted towards smaller values. The population differences observed for this communication sound and its tonal model were not found for a behaviorally irrelevant 24-kHz tone with the same amplitude modulation as the natural call (Fig. 4E and F). The ratio of second to first responses for this stimulus were closely distributed around 0.5–1, and the distributions for mothers and naïves were not significantly different ($P = 0.26$).

Entrainment sensitivity to call variation

The above results focused on auditory cortical entrainment to a specific (albeit typical) pup call at the natural repetition rate of 5 Hz. We next investigated the following capabilities to other natural calls over a wider range of repetition rates. In this study, responses to a series of three identical calls were recorded, and entrainment functions were computed by averaging the spike count for the second and third calls as a function of the repetition rate. Because an animal must contend with the natural pup calls' variability, we tested whether two acoustically distinct ultrasound vocalizations would yield similar following: a 60-kHz/75-ms call with a gradual onset (#1 in Fig. 1C and D); and a 70-kHz/27-ms call with a faster onset (#3).

Example responses from both mothers and naïve females are shown in Fig. 5, which displays both the raster plots from individual trials as well as the entrained spike count vs. the repetition rate. The first two entrainment functions (Fig. 5B and D) were collected from the same multiunit using calls #1 and #3, respectively. Both vocalizations

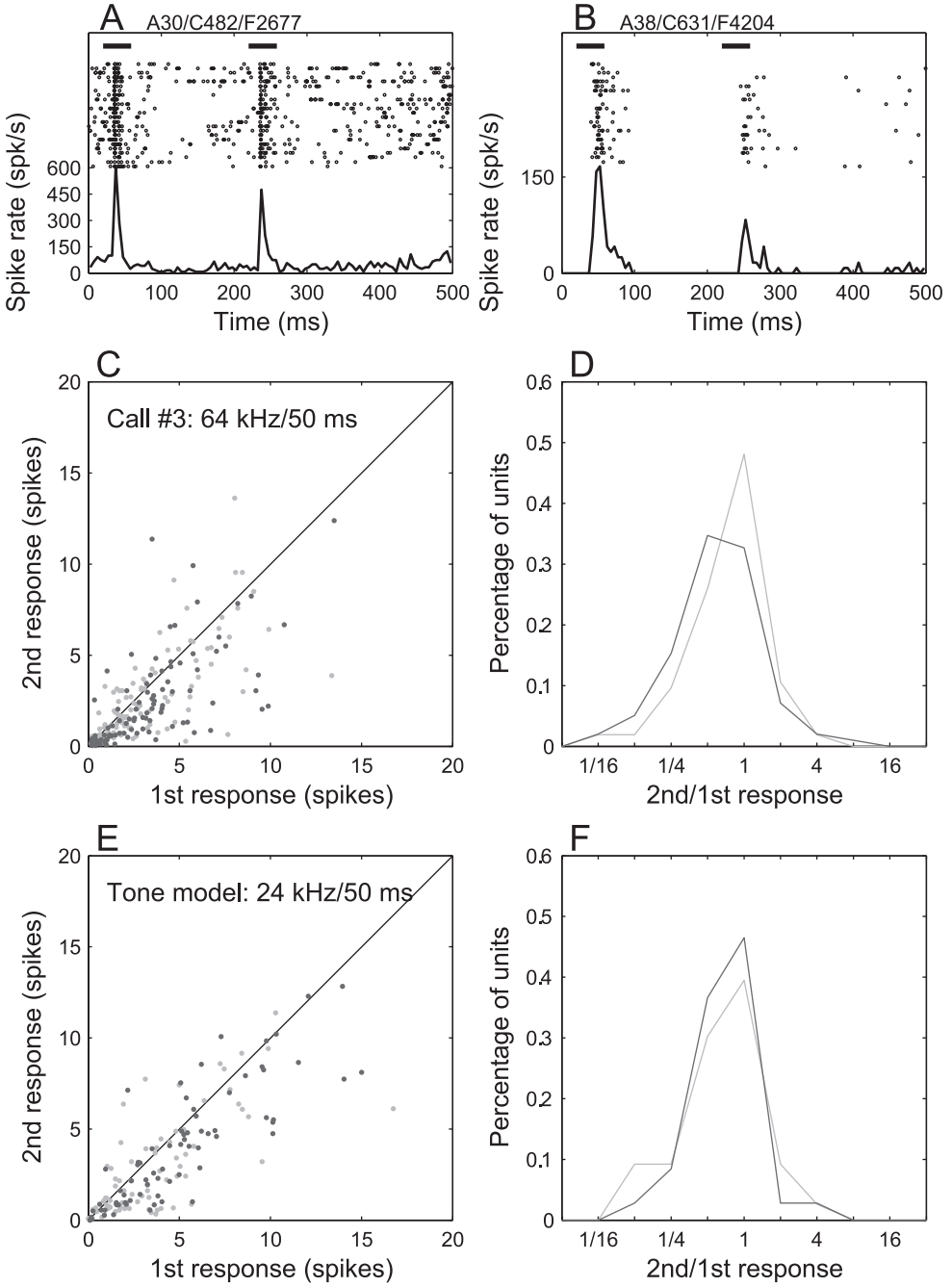

FIG. 4. Comparison of response to 5 Hz pup call bouts. (A) Example raster and PSTH (5 ms bins) from a mother to a sequence of 2 natural pup calls (#2) spaced by 200 ms. (B) Same for naïve female. (C) The response to the second stimulus in a sequence is plotted against the response to the first stimulus, for both mothers (light gray) and naïve females (dark gray). (D) The distribution of the ratios of the second to first responses for mothers (light gray) and naïve females (dark gray). (E and F) Same as C and D, but for a 24 kHz, 50 ms long tone model of call #2 that uses the same amplitude envelope (mothers, light gray; naïve females, dark gray). Responses to the second stimulus in a bout were generally suppressed compared to the first stimulus, so that more points were below the diagonal than above for both types of stimuli, and the means were less than 1. For the natural call, there was a significant difference between mothers and naives (D) in the distribution of the ratio of the second to first response; mothers had a higher average ratio than naives. No significant difference between the groups was found for the 24 kHz model, which has no analog in the mouse communication repertoire (F).

produced similar functions, responding well to low rates of repetition, but rolling off after 5 Hz. This behavior likely arose from the post-excitatory suppression that prevents neurons from spiking again soon after a response. The duration of this suppression can vary for different neurons, as shown by two other multiunits in Fig. 5F and H. The first, taken from a naïve female rolled off around 3 Hz; while the second, from a mother, followed well up to 10 Hz.

To compare the response to call #1 with call #3 across the population of multiunits, we pooled individual entrainment functions after dividing the spike count evoked by later calls in a series by that of the first call. This normalized out the absolute spike rate, which was higher on average for call #3 compared with call #1, probably due to the former call's rapid amplitude-envelope onset. Figure 6A shows that for mothers, the normalized population entrainment for the

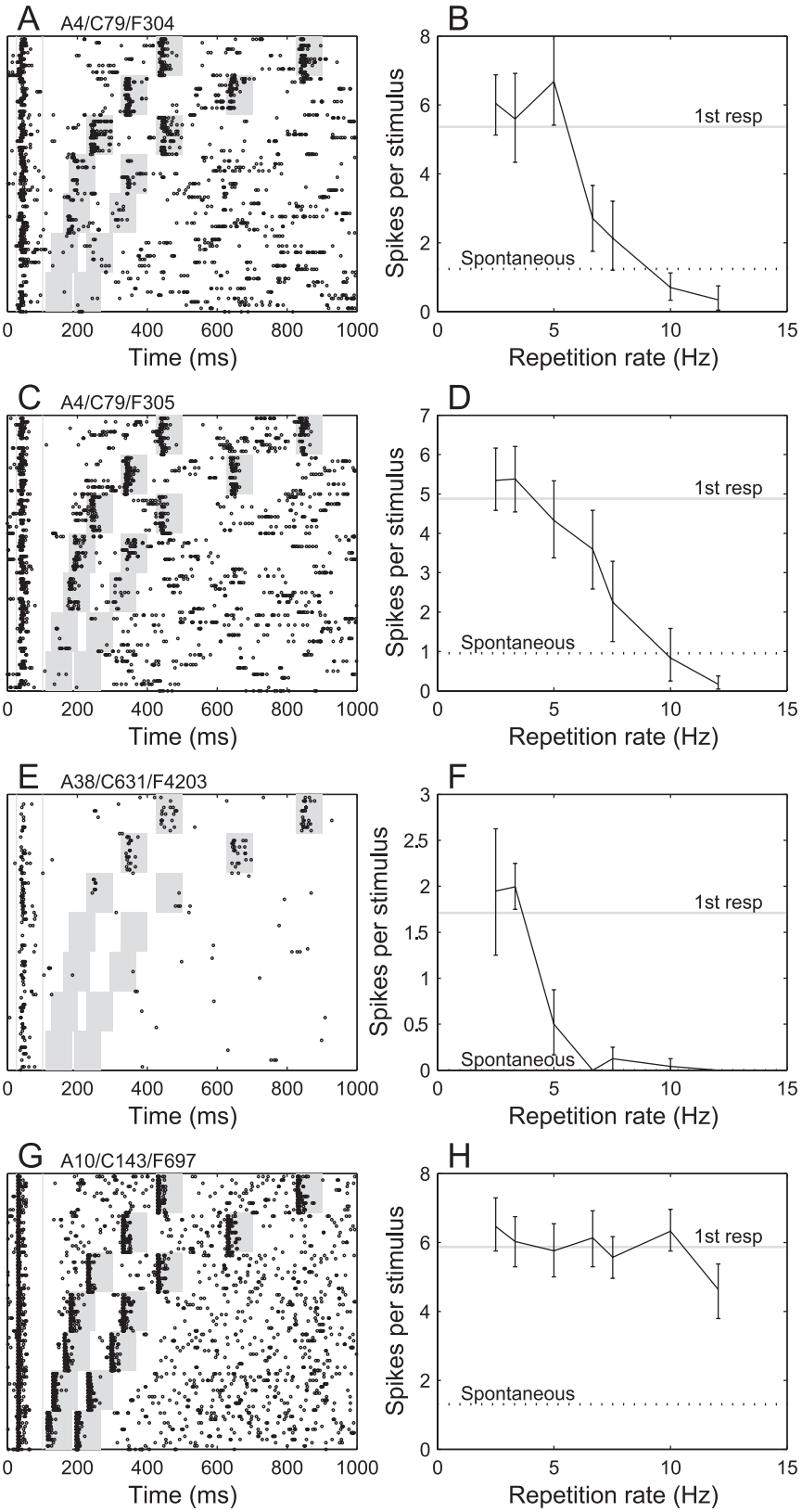

FIG. 5. Entrainment functions for natural pup calls. (A, C, E and G) Individual rasters of all trials. Vertical gray lines indicate the 75 ms window over which spikes were counted to estimate the first response (see Methods). Gray boxes mark the location of the 75 ms windows for counting spikes in response to the second and third presentations of the pup calls. (B, D, F and H) Average entrained response per stimulus, as a function of repetition rate. Error bars indicate the 95% confidence interval on the mean spike count. Solid gray horizontal line designates the average response to the first pup call. Dotted black horizontal line marks the spontaneous rate. A and B was an Uncertain/Other cluster from a mother, with a CF of 26 kHz, in response to call #1 at 80 dBSPL. C and D was the same cluster, in response to call #3 at 67 dBSPL. E and F was a likely UF cluster from a naïve female, with a CF of 55 kHz, in response to call #1 at 66 dBSPL. G and H was a likely UF cluster from a mother, with a CF of 58 kHz, in response to call #3 at 66 dBSPL.

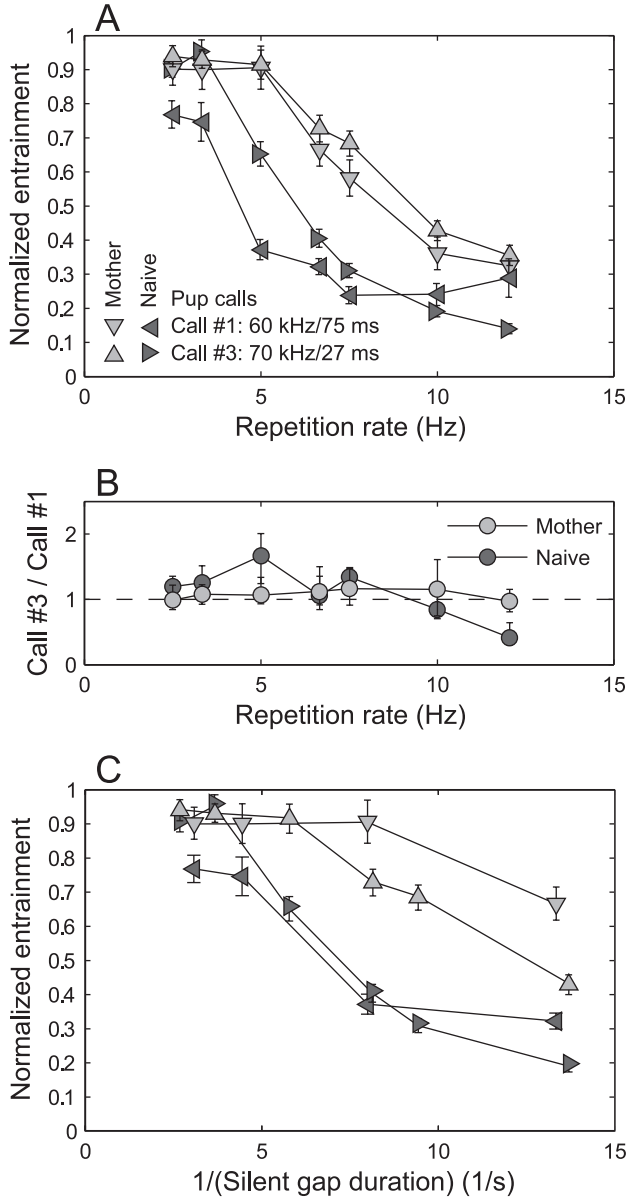

FIG. 6. Comparison of population entrainment data for different calls. (A) Normalized pup call entrainment functions for mothers (light gray) and naïve females (dark gray). Those derived using a 60 kHz/75 ms call ($n = 29$ mothers; $n = 20$ naives) were pooled separately from those derived using a 70 kHz/27ms call ($n = 57$ mothers; $n = 28$ naives). Entrainment in mothers was similar for both calls, but dissimilar for naïve females. (B) Mother versus naïve female comparison of entrainment sensitivity to acoustic differences. This panel plots the ratio at each repetition rate (between 2.5 and 10 Hz) of the normalized entrained response to call #3 over call #1. This was taken from the $n = 19$ multiunits in mothers (and $n = 18$ in naives) where both calls were presented. Error bars show 95% confidence intervals around the median. The following abilities of multiunits in mothers were not as sensitive as those in naïve females to the acoustic structure of the calls. (C) Same data as in A, plotted as a function of the inverse silent gap duration. If the duration of the silent interval between calls is primarily responsible for limiting entrainment in naïve females, then the entrainment functions for the two different calls should overlap when plotted against this parameter. In the region from 4 to 10 Hz, this was the case for naïve females.

longer, more slowly modulated call #1 tracked that for the shorter, more quickly articulated call #3, across a wide range of rates. On the other hand, for naïve females, the normalized entrainment to call #1 was generally weaker than to call #3. To highlight this difference, the ratio of the normalized entrained rate for call #3 to call #1 was computed for each of the multiunits in mothers and naïve females where both calls were presented (subset of the total population). A ratio of 1 for a particular repetition rate implies that the unit followed equally well for the two different calls. Figure 6B plots the median ratios across units, with 95% confidence intervals calculated by bootstrap. This ratio for mothers did not differ significantly from 1 over the range of rates (except at 3.3 Hz, $P = 0.03$, two-tailed t-test), suggesting that their entrainment was not greatly affected by acoustic differences. For naïve females, the ratio was significantly different from 1 at all rates except 6.7 Hz ($P = 0.07$) and 10 Hz ($P = 0.3$). In particular, at the naturally occurring pup repetition rate of 5 Hz, the largest entrainment difference for the two acoustically distinct calls was observed.

For a fixed repetition rate, the interval between each presentation of the longer call #1 was shorter than that for call #3. This time-since-sound-offset can influence subsequent cortical responses (especially for intervals up to 100 ms), as has been shown in the cat using noise stimuli as forward maskers for tones (Phillips, 1985). To see if this acoustic parameter might explain the differences in following for naïve females, the population data in Fig. 6A were replotted in Fig. 6C as a function of the inverse silent gap duration. The naïve female functions now overlapped in the 4–10 (1/s) range, suggesting that the silent gap duration rather than the repetition period may constrain the following. This was not the case for mothers, whose normalized entrainment began to diverge above ~ 6 (1/s). At least for these two calls, repetition rate entrainment was apparently sensitive to call duration in naïve females but not in mothers.

Improved entrainment in mothers

To summarize entrainment differences, Fig. 7A compares the overall entrainment between mothers and naïve females by combining the results for call #1 and call #3. Entrainment to pup calls declined rapidly for naïve females above ~ 3 Hz. In contrast, following to pup calls in the maternal cortex is enhanced compared with naïves. In particular, the population entrainment was still near maximum at the peak in the natural pup call repetition rate distribution (Fig. 1B). Additionally, there was a shift in the best-entrained rates between naïves and mothers so that a larger fraction of units in mothers responded well at higher repetition rates, as shown in Fig. 7B. These results indicate an overall improvement in pup call entrainment in the maternal auditory cortex.

Discussion

We found that the ability of the neural population to follow repeated pup calls was better matched to the calls' rhythmic characteristics in mothers than in naïve females. Compared with naïve females, the entrainment was stronger and less sensitive to significant natural variations in the acoustic details of the calls.

Technical considerations

First, our data consist of predominantly multiunit spiking activity. We therefore refrained from making concrete statements about how auditory cortical neurons encode individual calls. Instead, we concentrated on the question of how well these small clusters of neurons respond to sequences of identical calls, using a normalized entrainment function to quantify the response in a manner that would be less sensitive to the number of contributing single units.

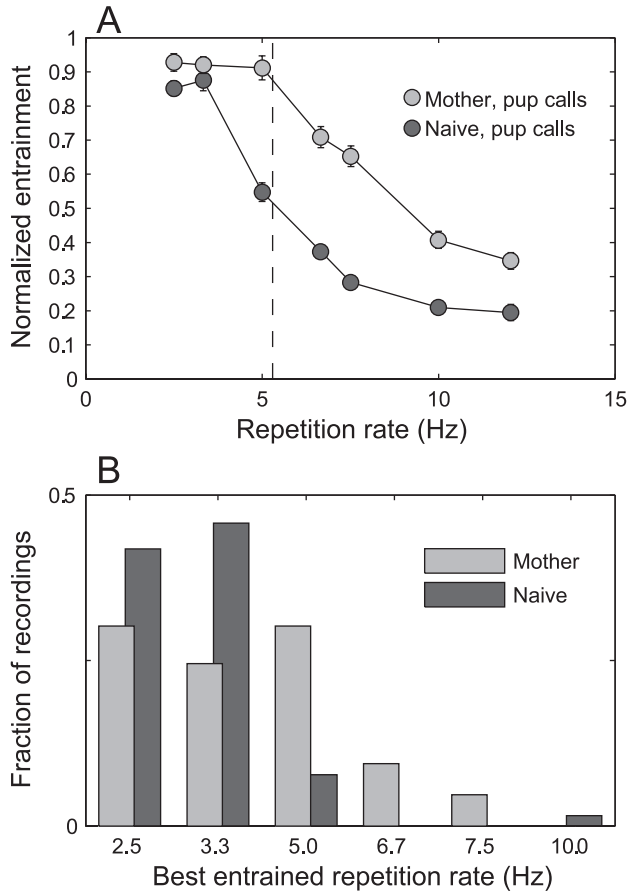

FIG. 7. Comparison of entrainment data between mothers and naïve females. (A) Normalized entrainment functions for mothers (light gray, $n = 86$) and naïve females (dark gray, $n = 48$) after combining responses to both calls. Entrainment in mothers extended out to higher repetition rates than in naïve females, and was still near unity at the behaviorally-important rate of 5 Hz, the dominant repetition rate in natural pup call bouts (dashed vertical line). (B) Distributions of best entrained rates for mothers (light gray, $n = 86$) and naïve females (dark gray, $n = 48$). A multiunit's best entrained rate is the repetition rate that gives the maximum entrained response; data shown combines recordings for both types of calls. Recordings from naïve females were mostly best entrained at low repetition rates (3.3 Hz). Mothers had rates shifted towards 5 Hz.

Second, pup isolation ultrasounds are at the upper end of the hearing range of mice; it might therefore be argued that these stimuli do not drive auditory cortical neurons sufficiently well, leading to low overall entrainment rates. Two controls suggest that this is not the case. When ultrasounds are presented at behaviorally realistic amplitudes (such as 70 dBSPL), multiunits with CFs as low as 20 kHz can still respond to pup call frequencies about half as well as they do to a tone at CF (Fig. 2G). This also justifies including recording sites outside of the UF in our study. Furthermore, entrainment rolls off around 3 Hz to a short 24 kHz pure tone (27 ms long, $N = 44$ in naïve females, data not shown), indicating that the low entrainment in naïve females is not frequency specific.

Third, because complete CF maps were not obtained during experiments, we did not assess the possibility of an areal expansion in the cortical representation of pup call frequencies in mothers compared with naïve females. Our data do suggest that, at the multiunit level, the median responsiveness of cortical neurons to pup call frequencies (i.e. 65 kHz) does not differ significantly between mothers and naïve females (Fig. 2G). Therefore, a spectral processing difference between animal groups probably does not account for the entrainment differences we observed.

Fourth, because the sample of identified UF recording sites for naïve females was small, we did not draw conclusions about differential plasticity between the primary and UF fields. We note though that when the entrainment data for call #1 and #3 were combined for mothers (data not shown), the population entrainment began to roll off slightly earlier (after 3 Hz) in primary ($N = 32$) compared with UF recordings ($N = 20$, roll off after 5 Hz). This would be consistent with a more central role for UF in processing ultrasonic pup call bouts.

Pup call perception

The playback of ultrasonic signals can produce a positive phonotaxic response in adult females, even if those ultrasounds are not acoustically similar to pup calls (Smith, 1976; Ehret *et al*., 1987; Ehret, 2005). However, the recognition of an ultrasound as a behaviorally important pup call occurs only for pup-experienced animals (Fichtel & Ehret, 1999). For example, when a 50-kHz pup call model is compared with a 20-kHz neutral ultrasound in two alternative choice experiments, mothers and adult females that co-care for a litter of pups show a significant preference for the pup-like sound (Ehret *et al*., 1987; Ehret & Koch, 1989). Pup-sensitized female mice also approach ultrasound models with frequencies similar to natural calls significantly more often than models with higher or lower frequencies (Smith, 1976). In contrast, pup-naïve females do not exhibit such differential preferences (Ehret *et al*., 1987; Ehret & Koch, 1989).

This paper presents the first electrophysiological evidence that the differences in behavioral preference manifested by these animals groups are correlated with changes in the population activity of auditory cortical neurons to the acoustic structure of these vocalizations. Instead of frequency, we looked at the representation of call repetition period − another parameter that can in principle be used to recognize these vocalizations (Liu *et al*., 2003). Our results predict that mothers would have a higher preference for 5-Hz call bouts, in contrast to naïve females, who would not follow these calls as effectively.

Auditory entrainment in mice

Central auditory coding of periodic stimuli in the mouse has only been pursued in the inferior colliculus (IC) using sinusoidally modulated noise (Walton *et al*., 2002). IC neurons were found to synchronize their spiking up to modulation rates as high as 100–200 Hz. The 5–7 Hz cortical entrainment rates measured here are far below this, even if possible differences between synchronization (vector strength) and entrainment measures are taken into consideration (Eggermont, 1991). This fact supports the assumption that our results reflect cortical rather than subcortical processing. Moreover, the mismatch between IC and cortex is not unexpected; best modulation rates progressively decrease from the brainstem on up (Creutzfeldt *et al*., 1980; Eggermont, 2001). However, why are rates reduced to the extent observed? After all, in rats, cortical population entrainment does not begin to roll off until 9 Hz (Kilgard & Merzenich, 1999); and in owl monkeys, best entrained rates average about 11–12 Hz (Beitel *et al*., 2003).

Temporal processing in mice appears to be limited to slower rates. Correspondingly, durations of mouse A1 and AAF spectrotemporal receptive fields (i.e. neural linear filters for sound spectrograms) (Linden *et al*., 2003) are longer than observed in rats under the same experimental conditions (J.F. Linden, unpublished results). Yet

evidence suggests that cortical temporal processing is plastic (Kilgard & Merzenich, 1998b; Beitel *et al*., 2003), and the differences we see between mothers and naïve females support this idea. Thus, we argue that the reduction in entrainment rates reflects processing strategies attuned to the temporal structure of behaviorally relevant pup calls (Schreiner & Urbas, 1988). Perhaps following high modulation rates is not necessary in these animals, but detecting bouts of 5-Hz pup calls is very important, at least for mothers. Auditory cortex, whose role may well be to extract information-bearing parameters of communication calls (Suga, 1995), should therefore at least be able to entrain to pup calls at this dominant rate. This was indeed our finding in mothers.

Entrainment plasticity in a natural context

Our results are the first to demonstrate plasticity in auditory cortical responses that is correlated with the behavioral relevance of a natural communication call perceived by non-conditioned animals. These findings are consistent with a study of cortical plasticity in the maternal rat's primary somatosensory cortex associated with pup suckling (Xerri *et al*., 1994). Large changes in the size of cortical receptive fields representing the ventrum skin were observed in postpartum, lactating mothers, but not in virgins and postpartum females that have had their litter removed (and thus have not been stimulated by pups).

The plasticity observed here might be due to a stimulus-specific change associated with pup call experience, and a 'memory' of their acoustic structure (Weinberger, 2004). In support of this is our finding that the sequential response to a behaviorally irrelevant, 24-kHz tone bout is not statistically different between mothers and naïves, in contrast to the behaviorally relevant pup calls. Furthermore, several mothers were observed retrieving ultrasound-emitting pups in their home cages. The number of pup calls that an individual mother experienced likely varied, leaving open the issue of how much exposure is necessary for such cortical changes to occur.

Finally, because naïve females were not housed with either pups or adult males, they were not exposed to direct, behaviorally relevant acoustic stimulation that mothers obtained by caring for pups. Thus, a difference in the level of environmental enrichment (Engineer *et al*., 2004) rather than specific interactions with pups might account for the cortical changes.

Potential mechanisms for plasticity

Cholinergic and/or dopaminergic neuromodulatory systems may be involved in this kind of plasticity. For example, acetylcholine is hypothesized to mediate both spectral receptive field changes in auditory cortical neurons (McKenna *et al*., 1989; Metherate & Weinberger, 1989, 1990; Kilgard & Merzenich, 1998a; Ma & Suga, 2005), as well as temporal receptive field (i.e. entrainment function) changes (Kilgard & Merzenich, 1998b; although see Kamke *et al*., 2005). In mice, a knockout of the gene that encodes the M1 muscarinic acetylcholine receptor prevalent in the cortex decreases the stimulus-specific plasticity of auditory cortical neurons after electrical stimulation of the nucleus basalis (Zhang *et al*., 2005). Furthermore, stimulating dopaminergic projections from the ventral tegmental area (VTA) in conjunction with tone exposure can enhance the cortical representation of that tone frequency (Bao *et al*., 2001). Although we did not evaluate the possible cortical map expansion of ultrasound frequencies, dopamine might still be relevant because the VTA receives input from the medial preoptic area (MPOA), a critical nucleus in the maternal circuitry (Numan & Insel, 2003).

Besides experience-dependent mechanisms for plasticity, hormonal mechanisms may also contribute to the sensory processing changes observed, as has been reported at the auditory periphery in the midshipman fish (Sisneros *et al*., 2004). Beyond the periphery, hormones can induce morphological plasticity in the mammalian maternal circuit, as well as brain areas not usually associated with reproduction (Woolley & McEwen, 1993; Kinsley *et al*., 2006; Woodside, 2006). Hormone-related improvements in sensory behavior have also been reported, with food-deprived, mother rats able to capture prey more quickly than virgins (Kinsley & Lambert, 2006). A possible pathway for hormones like estradiol to influence cortical plasticity may be through modulating the function of cholinergic basal forebrain neurons, although this process is still not well understood (Luine, 1985; Singh *et al*., 1994; McEwen & Alves, 1999; Bora *et al*., 2005). In order to dissect the roles of hormones and experience on the mouse communication behavior described here, future experiments may contrast entrainment in ovariectomized females that co-care for a litter (no hormones, but gain pup experience) with postpartum females that have had their litters removed (undergone hormonal changes, but no pup experience).

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Abbreviations

A1, primary auditory field; AAF, anterior auditory field (grouped with A1 to form the primary group); CF, characteristic frequency; FARA, frequency–amplitude response area; IC, inferior colliculus; MPOA, medial preoptic area; PSTH, peristimulus time histogram; THD, total harmonic distortion; UF, ultrasound field; VTA, ventral tegmental area.

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