LETTERS

Sustained firing in auditory cortex evoked by preferred stimuli

Xiaoqin Wang[1], Thomas Lu[1], Ross K. Snider[1]† & Li Liang[1]

It has been well documented that neurons in the auditory cortex of anaesthetized animals generally display transient responses to acoustic stimulation, and typically respond to a brief stimulus with one or fewer action potentials[1–5]. The number of action potentials evoked by each stimulus usually does not increase with increasing stimulus duration[1,5–7]. Such observations have long puzzled researchers across disciplines and raised serious questions regarding the role of the auditory cortex in encoding ongoing acoustic signals. Contrary to these long-held views, here we show that single neurons in both primary (area A1) and lateral belt areas of the auditory cortex of awake marmoset monkeys (*Callithrix jacchus*) are capable of firing in a sustained manner over a prolonged period of time, especially when they are driven by their preferred stimuli. In contrast, responses become more transient or phasic when auditory cortex neurons respond to non-preferred stimuli. These findings suggest that when the auditory cortex is stimulated by a sound, a particular population of neurons fire maximally throughout the duration of the sound. Responses of other, less optimally driven neurons fade away quickly after stimulus onset. This results in a selective representation of the sound across both neuronal population and time.

The phenomenon that neurons in the auditory cortex under anaesthesia respond to sounds with phasic discharges irrespective of stimulus duration has been observed in a variety of mammalian species[1–7] with varying rates of discharge depending on the anaesthetic type and concentration[8–11]. The transient nature of auditory cortical responses and the lack of neural firing throughout stimulus duration have prompted researchers to propose various theories to explain neural coding strategies. For example, it has been suggested that neurons in the primary auditory cortex (A1) are specialized to respond to brief stimulus events[12]. A recent study suggested that A1 neurons discharge in a 'binary mode' in response to brief tone stimulation[5]. Researchers have also suggested that correlated firing between neurons, instead of the firing rates of individual neurons, signals the presence of steady-state sounds that fail to evoke continuing neural activity in A1 of anaesthetized marmosets[6] or cats[7]. On the other hand, accumulating evidence suggests that neurons recorded from the auditory cortex of awake animals exhibit both onset and sustained discharges in response to continuous acoustic stimulation[13–19]. However, the extent of sustained discharges in awake animals and their role in cortical coding of acoustic information remains unclear. Furthermore, as often encountered by experimenters, phasic responses are commonly observed even in the auditory cortex of awake animals.

In this report, we have addressed three specific questions regarding sustained firing in the auditory cortex of awake marmoset monkeys. First, can auditory cortex neurons discharge continuously over a prolonged period of time in response to continuous acoustic stimulation? Second, what are the stimulus conditions under which neurons in the auditory cortex are likely to discharge in a sustained manner? Third, do well-isolated single neurons in the auditory cortex discharge more than one action potential for each brief stimulus?

In contrast to observations from the auditory cortex of anaesthetized animals[6–7], we found neurons in both A1 and lateral belt (LB) areas of awake marmosets that were capable of firing throughout the duration of a tone or noise stimulus, over a prolonged period of time. Figure 1a shows an example of a single neuron responding to a pure tone at the neuron's best frequency. The tone was unmodulated and had a long duration (5 s) and slow rise and fall times (1 s). Such a stimulus generally produces the greatest adaptation in responses of auditory cortical neurons. In A1 of anaesthetized marmosets, this type of stimulus was shown to evoke only a brief response after stimulus onset[6]. In sharp contrast, the A1 neuron shown in Fig. 1a, which was recorded from an awake marmoset, gave strong, sustained discharges over the entire stimulus duration. As was typical of many A1 neurons we studied in awake marmosets, this single neuron was strongly driven by pure tones at its best frequency, but not by broadband noises. Neurons in the LB areas of marmosets, on the other hand, often responded more strongly to noise stimuli than to pure tones, similar to earlier observations in macaque monkeys[20]. Some LB neurons were found to respond continuously to unmodulated noise stimuli of long duration, as shown by the example in Fig. 1b to a 5-s broadband noise. Such prominent, sustained discharges have not been observed in the secondary auditory cortex of anaesthetized animals. In contrast to the A1 neuron shown in Fig. 1a, the LB neuron in Fig. 1b did not respond strongly to pure tones. Thus, the A1 and LB neurons shown discharged in a sustained manner when driven by their respective preferred stimulus (Fig. 1a, b).

The observations illustrated in Fig. 1 suggest that auditory cortex neurons can discharge in a sustained manner throughout stimulus duration if stimulated by their preferred stimuli. Pure tones and broadband noises were the extreme cases of a wide range of acoustic stimuli that could preferentially drive auditory cortex neurons in the awake condition. The majority of auditory cortex neurons we studied were preferentially driven by stimuli with intermediate spectral bandwidth and/or greater temporal complexity (for example, temporal modulations). We also studied neurons using stimuli with greater spectral and temporal complexity than pure tones and broadband noises. Most A1 neurons were more strongly driven by amplitude- or frequency-modulated tones than by pure tones, and typically showed preference for a particular, or 'best' modulation frequency (BMF). In contrast to anaesthetized animals, many A1 neurons in awake marmosets showed modulation frequency tuning without showing stimulus-synchronized discharges[19]. Similarly, neurons in LB areas often responded more strongly to amplitude-

[1]Laboratory of Auditory Neurophysiology, Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA. †Present address: Department of Electrical and Computer Engineering, Montana State University, Bozeman, Montana 59717, USA.

modulated noises at the BMF than to unmodulated noises. Neuron responses generally became weaker at modulation frequencies away from the BMF in both A1 and LB areas. Accompanying this reduction in the response magnitude was a change in temporal discharge pattern, from strong, sustained firing at the BMF to weakly sustained firing or onset firing as the modulation frequency moved away from the BMF. This trend was observed in both A1 (Fig. 2a) and LB areas (Fig. 2b). Note in Fig. 2 that although there is a large decrease in sustained firing between the preferred stimulus and non-preferred stimulus conditions, the change in onset firing between the two conditions is much smaller. In some neurons, off-responses emerged as the stimulus shifted from the preferred to non-preferred condition (Fig. 2b). Thus, when neurons in both cortical areas were driven by their preferred stimuli, they showed not only higher mean firing rates but also sustained firing patterns throughout the stimulus duration.

We further quantified the sustained and onset responses on a neuron-by-neuron basis (Fig. 3). We defined the first 100 ms of the response after the beginning of the stimulus as 'onset' (0–100 ms) and the remaining response as 'sustained' (from 100 ms until stimulus offset). Figure 3a compares the firing rates of the first and second halves of the sustained response at each neuron's BMF. The firing rates calculated from these two time intervals were similar, indicating that the sustained response of the neurons at their preferred stimuli indeed lasted throughout the stimulus duration. This property was observed for all three types of temporally modulated stimuli, regardless of whether or not neurons showed stimulus-synchronized firing patterns at the BMF (Fig. 3a). About 40% (45/113) of neurons showed discharges synchronized to the modulation envelope; the remaining ~60% of the tested neurons responded to temporally modulated stimuli at the BMF without showing stimulus-synchronized firing patterns. Note that such sustained firing differs from repetitive firing that results from entrainment to stimulus cycles; in the latter case, neurons would exhibit stimulus-synchronized firing patterns. We suggest that the

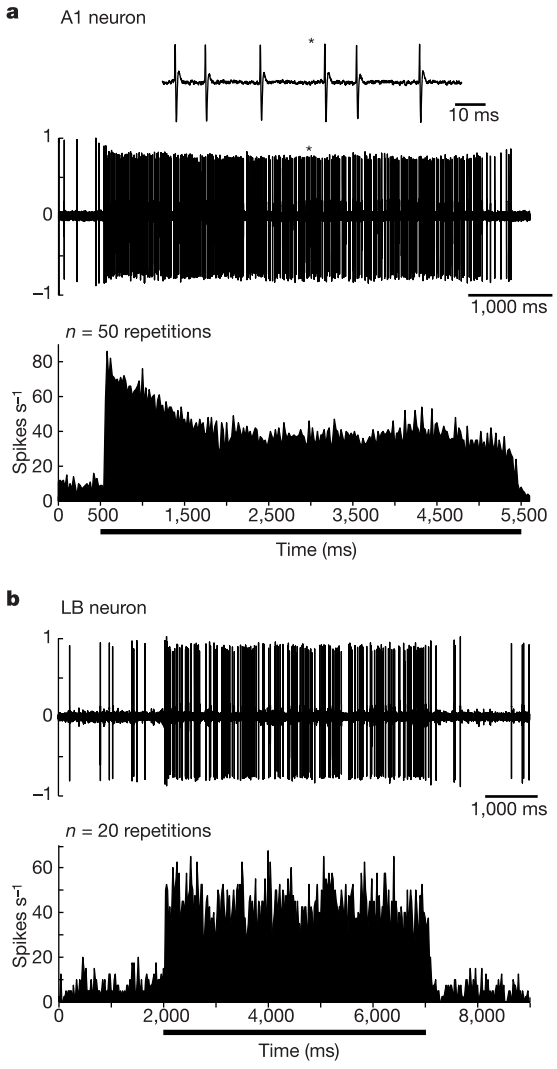

Figure 1 | Examples of sustained firing of single neurons evoked by long-duration stimuli. **a**, A1 neuron (unit M42M-171). Stimulus: unmodulated pure tone at the neuron's best frequency (9.3 kHz), 80 dB SPL, rise/fall time 1 s, duration 5 s. Upper panel, raw recording trace of the response to the 25th presentation of the stimulus. Inset shows an expanded view of a portion of the trace (2950–3050 ms). Asterisks mark the time at 3,000 ms. Lower panel, PSTH computed from responses to 50 repetitions of the same stimulus (bin-width, 20 ms). **b**, LB neuron (unit M60107-124). Stimulus: unmodulated broadband noise, 80 dB SPL, rise/fall time 5 ms, duration 5 s. Upper panel, response to 20th presentation of the stimulus. Lower panel, PSTH (20 repetitions; bin-width, 20 ms). The thick bar below the *x* axis in **a** and **b** (lower panels) indicates stimulus duration.

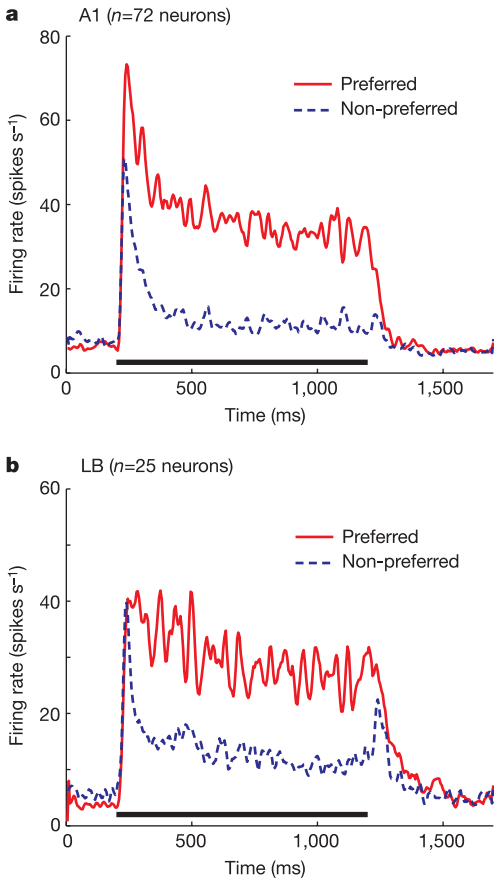

Figure 2 | Temporal firing patterns evoked by preferred and non-preferred stimuli. **a**, **b**, Mean PSTHs calculated from populations of A1 (**a**) and LB (**b**) neurons in response to each neuron's preferred stimulus (sAM, sFM or nAM) at preferred (red) and non-preferred (blue) modulation frequencies (10–20 repetitions at each modulation frequency). The preferred modulation frequency is equivalent to the best modulation frequency (BMF). The non-preferred modulation frequency corresponds to the minimum firing rate above the BMF. A similar trend is observed at the non-preferred modulation frequency below the BMF. PSTH bin-width, 5 ms (smoothed by a 5-point moving triangular window). The thick bar above the *x* axis indicates stimulus duration (1 s).

sustained firing observed in these conditions truly represents transformed representations of time-varying acoustic signals. Additional examples of sustained responses to 5-s tone or noise stimuli were analysed and are shown in Fig. 3a.

As shown by averaged population post-stimulus time histograms (PSTHs) in Fig. 2, the magnitude of onset response relative to sustained response was larger at the non-preferred than at the preferred stimulus condition. We analysed this property quantitatively on a neuron-by-neuron basis (Fig. 3b) using an onset response index, defined as the ratio of onset versus sustained firing rates. This index is much higher when measured at the worst modulation frequency compared to the best modulation frequency (Fig. 3b), indicating a greater extent of onset responses when neurons are less optimally driven.

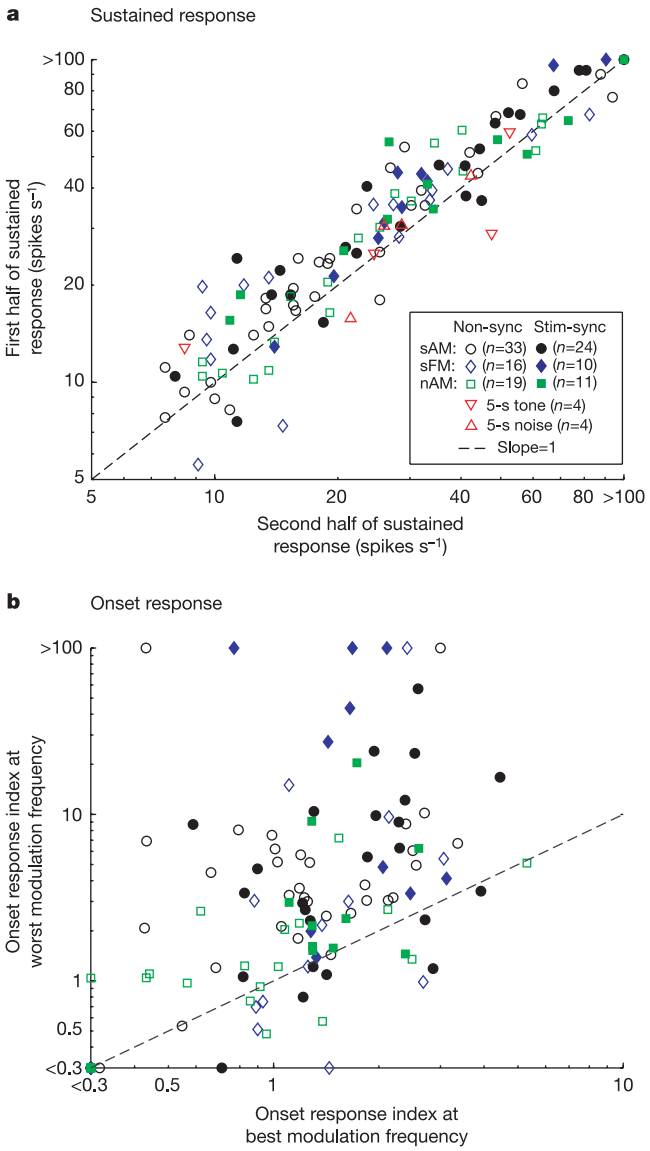

Figure 3 | Quantitative analysis of sustained and onset responses. Data include the 72 A1 neurons and 25 LB neurons analysed in Fig. 2, and an additional 16 neurons from the rostral and medial areas surrounding A1 (113 neurons in total), all tested with 1-s long, temporally modulated stimuli (sAM, sFM or nAM). Neurons showing stimulus-synchronized or non-synchronized discharges at BMF (quantified by the Rayleigh statistic) are marked with filled or open symbols, respectively. **a**, Mean firing rates of the first half (100–550 ms) and second half (550–1,000 ms) of the sustained response at each neuron's BMF are compared. Rates given as mean ± s.d. in spikes s^{-1} for the first half, second half: sAM, 36.3 ± 27.2, 30.7 ± 24.0 ($n = 57$); sFM, 35.7 ± 25.0, 29.9 ± 22.0 ($n = 26$); nAM, 37.3 ± 25.1, 33.5 ± 25.9 ($n = 30$). Sustained responses of 8 additional neurons to 5-s long, unmodulated best-frequency-tones or noises were also analysed (windows for first half: 100–2,550 ms; second half: 2,550–5,000 ms). **b**, The onset response index, the ratio of onset firing rate (0–100 ms) divided by the sustained firing rate (100–1,000 ms) is compared between the BMF and the worst modulation frequency for an individual neuron (corresponding to the minimum firing rate across all tested modulation frequencies above BMF). A larger index value indicates a greater onset response relative to the sustained response. Symbols used in **b** are defined in the key in **a**.

The complex stimuli used in the experiments described in Figs 2 and 3 had relatively long duration (1 s). Most previous studies of the auditory cortex have used brief, pure tone stimuli. We carried out additional experiments in awake marmosets to determine whether cortical responses evoked by short duration tones share the same or different properties with the responses recorded from anaesthetized animals. A recent study[5] using anaesthetized rats suggested that A1 neurons discharge in a 'binary mode', and the appearance of multiple action potentials per stimulus reported in previous studies could have resulted from multi-unit recording methods. The examples shown in Fig. 1 clearly demonstrate that prolonged, sustained firing can be observed in well-isolated single neurons from extracellular recordings in the awake condition. The majority of A1 neurons we studied did not discharge in a binary fashion in response to brief tones at a neuron's best frequency. Figure 4a shows the distribution of the number of action potentials per stimulus presentation for 50-ms best-frequency-tone stimulation. The majority of neurons discharged more than one action potential per stimulus presentation (median 2 per trial), and the distribution was well fit by a Poisson distribution. Furthermore, the number of action potentials per stimulus presentation generally increased with increasing stimulus duration. Figure 4b shows that A1 neurons responded to 100-ms best-frequency-tones with more action potentials per stimulus presentation (median 3 per trial) than to 50-ms best-frequency-tones. Thus, unlike single neurons in A1 of anaesthetized animals, which typically fire one or fewer action potential per stimulus irrespective of stimulus duration[1–5], single neurons in A1 of awake marmosets discharge in a Poisson-like manner when stimulated by brief (50 ms) best-frequency-tones. To further analyse discharge patterns evoked by tone stimuli, we compared the count of initial action potentials (from stimulus onset time to 10 ms after response latency) with that of all action potentials (from stimulus onset time to offset time) of tone-evoked discharges on a neuron-by-neuron basis (Fig. 4c). If a neuron had only initial action potentials, it should fall along the dashed line (slope of 1). If a neuron responded to each stimulus presentation with an average of one or fewer action potentials, it should fall within the shaded square in Fig. 4c. Note that nearly all neurons were located above the dashed line, indicating that they had sustained discharges beyond the initial action potentials. The median value for initial action potentials was 0.82 per trial (close to the value of ~1 per trial typically recorded in A1 of anaesthetized animals). Of the 263 neurons tested, 231 neurons (88%) had more than one action potential per stimulus. These data clearly show that A1 neurons in the awake condition do not discharge in a binary mode in response to brief tones. The distribution shown in Fig. 4a differs qualitatively from the similar measure obtained in anaesthetized rats[5].

The functional role of sustained discharges has been extensively studied in visual cortex[21], but much less in auditory cortex. Our findings show that whether a neuron responds to a stimulus with sustained discharges depends crucially on the optimality of the stimulus. Specifically, we suggest that auditory cortex neurons fire in a sustained manner when they are driven by their preferred stimuli, but show either mostly onset discharges or no discharges at all when stimulated by non-preferred stimuli. We found that neurons in the auditory cortex of awake marmosets are often highly selective to acoustic stimuli, and as such, the preferred stimulus (or stimuli) of a neuron only occupies a small region of

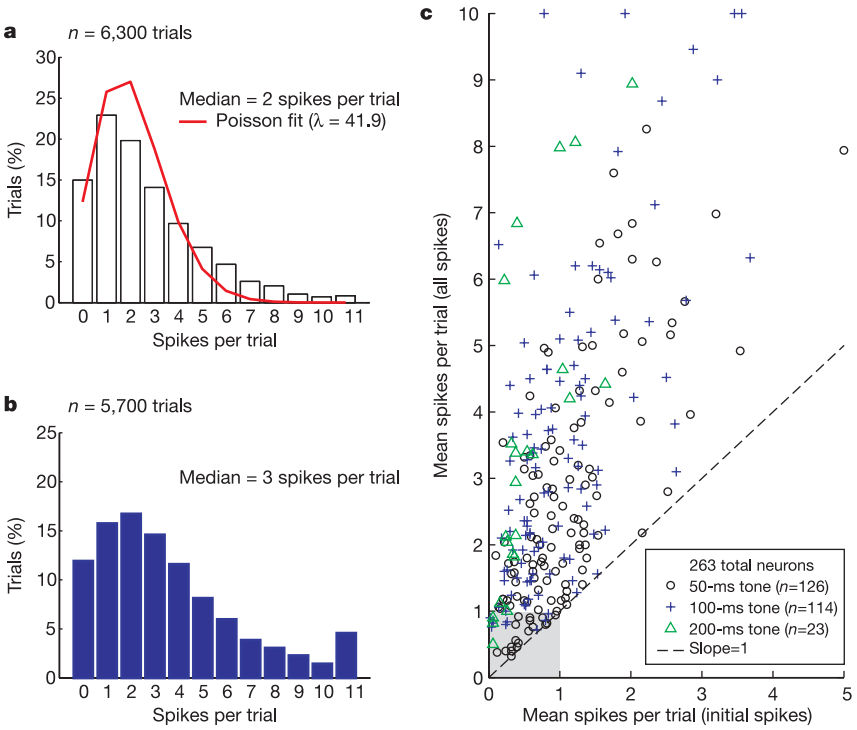

Figure 4 | Quantitative measures of single-neuron responses to brief tones. The tones were set at each neuron's best frequency and preferred sound level (for non-monotonic neurons) or 30 dB above threshold (for monotonic neurons), and delivered for 50 repetitions. **a**, Distribution of spikes per trial for 50-ms best-frequency-tone responses, calculated over the entire stimulus duration for 6,300 stimulus presentations obtained from 126 neurons (median 2 spikes per trial, equivalent to 40 spikes s^{-1}). The thick red curve represents the least-squares fit by a Poisson distribution ($\lambda = 41.9$ spikes s^{-1}, $T = 0.05$ s, $r = 0.97$). **b**, Same as **a** but for 100-ms best-frequency-tone responses obtained from 114 neurons (median 3 spikes per trial, equivalent to 30 spikes s^{-1}). **c**, Mean spikes per trial (per neuron), calculated over the entire stimulus duration ('all spikes') versus that calculated over the initial response period ('initial spikes', time window from 0 to response latency + 10 ms). The response latency was determined for each neuron using an accumulative spike count histogram.

the acoustic parameter space (defined by spectral, temporal and intensity axes). This explains why it is common for experimenters to encounter onset (phasic) responses in the auditory cortex even under unanaesthetized conditions.

The observations provided in this report have important implications for neural coding mechanisms in the auditory cortex. First, sustained discharges in the auditory cortex show greater stimulus specificity than onset discharges. Second, the lack of stimulus-synchronized firing patterns in the sustained responses indicates that such responses are transformed (instead of preserved) representations of time-varying acoustic signals. Third, the different temporal discharge patterns evoked by preferred and non-preferred stimuli suggest that auditory cortex neurons adapt to non-preferred stimuli more quickly than to preferred stimuli. These findings show that the auditory cortex is capable of dynamically responding to the acoustic environment with sustained firing from optimally driven neurons and onset firing from others. When a sound is heard, the auditory cortex first responds with transient (onset) discharges across a relatively large population of neurons. As time passes, the activation becomes restricted to a smaller population of neurons that are preferentially driven by the sound.

These observations have immediate implications for interpreting spatial and temporal activation patterns of the auditory cortex recorded by other techniques commonly applied to alert human subjects, for example, electroencephalography (EEG), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). The sustained discharges in the auditory cortex probably result from or are enhanced by intracortical processing, both within a cortical area (via recurrent or interlaminar connections) and from higher cortical areas (via efferent feedback connections). The underlying cellular and network mechanisms remain to be identified.

In contrast to sustained discharges, onset discharges in the auditory cortex might have different roles in representing the external acoustic environment. For example, widespread onset responses with short latency might allow the auditory cortex to detect quickly (albeit less discriminatively) the occurrence of sounds from prey, predators and the environment. The precision of the onset action potential timing is preserved throughout the ascending auditory pathway, from the auditory nerve[22] to the auditory cortex[12], and can thus provide precise timing information to mark the onset of a sound or transitions in an ongoing acoustic stream[15,23,24]. There could also be species-specific differences regarding the roles of onset and sustained discharges in cortical coding. For example, the presence of sustained discharges appears to be less prominent in bat auditory cortex even under unanaesthetized conditions[25]. The sonar signals of bats are extremely brief, and their communication sounds are much shorter[26] than species-specific vocalizations of marmosets[27] and other non-human primates. However, the extent of any sustained discharges would not be fully revealed if only brief stimuli were used in experiments.

METHODS

Animal preparation and recording procedures. Animal preparation and recording procedures have been detailed in previous publications from our laboratory[15,19]. Single-neuron activity was recorded from three awake marmosets trained to sit quietly during recording sessions, using tungsten microelectrodes (impedance 2–5 MΩ at 1-kHz), and continuously monitored by the experimenter while data recordings progressed. The signal-to-noise ratio of action potential waveforms was typically >10:1 in our recordings (often much greater). Judging by the depth of recording and response characteristics,

the majority of recorded single neurons were from layers II–III and, to a lesser extent, from layer IV. The location of the A1 was determined by its tonotopic organization[28,29] and its relationship to the lateral belt area. Acoustic stimuli were generated digitally (sampling rate 100 kHz) and delivered in free-field through a loudspeaker located ~1 m in front of the animal, in a double-walled, soundproof chamber with the interior covered by 3 inches of acoustic absorption foam. Stimuli included pure tones, band-pass or broadband noises, sinusoidal amplitude- or frequency-modulated tones (sAM or sFM), and sinusoidal amplitude-modulated band-pass or broadband noises (nAM).

Determination of a neuron's stimulus preference. Single neurons recorded from the auditory cortex of awake marmosets are highly selective for stimulus parameters (in time, frequency and intensity domains). A neuron may require not only a proper carrier frequency, sound level and spectral bandwidth, but also a proper temporal modulation frequency in order to be maximally driven. We use the term 'preferred stimulus' to refer to stimuli that were locally optimal (evoking maximum firing rate) along one or more stimulus dimensions. For example, the preferred stimulus for an A1 neuron could be an sAM tone with a carrier frequency of 8 kHz, modulation frequency of 32 Hz and 60 dB sound pressure level (SPL). Because of technical difficulties involving sampling over multiple stimulus dimensions, the true optimal stimulus of a cortical neuron could not be easily determined using current analytical methodologies. The preferred stimuli used in our experiments were optimized in carrier frequency, sound level, temporal modulation frequency and spectral bandwidth, and could be considered the 'best stimulus' in this context, probably approaching the optimal stimulus of a neuron.

Once a single neuron was isolated, its preferred stimulus was determined using the following procedure. (1) We first determined a neuron's preference for tone or noise. A1 neurons were typically easily driven by tones, whereas LB neurons were more responsive to noises than tones, consistent with earlier observations in macaque monkeys[20]. (2) For tone-preferring neurons, a best frequency was determined using pure tones delivered at various frequencies (20–40 steps per octave, depending upon the neuron's sharpness of tuning). For noise-preferring neurons, a centre frequency was determined using band-pass noises at various centre frequencies, with a preferred bandwidth that maximized evoked responses. Stimuli were delivered at 10 dB above a neuron's estimated threshold. The best frequency estimated by tones was generally similar to the centre frequency estimated by band-pass noises in neurons that did not show a clear preference for tone or noise. (3) The rate-level function of a neuron at its best frequency or centre frequency was then obtained (0–100 dB SPL in 5–10-dB steps) using the stimulus optimized in the above procedures. Similar to previous observations in awake macaque monkeys[30], a large proportion (~70%) of single neurons in A1 or LB in awake marmosets had non-monotonic rate-level functions for which a preferred sound level could be determined. For neurons with monotonic rate-level functions, the threshold sound level at best frequency or centre frequency was determined. (4) The preferred temporal modulation frequency was determined using sAM (or sFM, depending upon a neuron's preference) or nAM stimuli, for tone- or noise-preferring neurons, respectively, at various modulation frequencies (typically 4–512 Hz, in octave steps). The carrier frequency was set at a neuron's best frequency (or centre frequency). The sound level was set at the preferred level (for non-monotonic neurons) or 30 dB above threshold (for monotonic neurons). For sAM and nAM stimuli, the modulation depth was 75–100%. For sFM stimuli, the frequency modulation depth was set at a preferred value for the neuron. For nAM stimuli, a preferred bandwidth was chosen for the noise carrier. A majority of A1 and LB neurons showed preference for a particular modulation frequency. Some neurons did not respond to unmodulated tones or noises and could only be driven by sAM, sFM or nAM stimuli. For these neurons, their best frequency (or centre frequency) was determined by varying the carrier frequency of temporally modulated stimuli. When necessary, the above process was iterated to optimize all stimulus parameters.

Data analysis. For neurons tested with temporally modulated stimuli (Figs 2 and 3), a total of 158 single neurons recorded from three marmosets showed band-pass tuning by mean firing rate to modulation frequencies above 10 Hz. Sustained responses at BMF to at least one of the test stimuli were observed in 113 neurons (71.52%). A sustained response was defined as having a minimum firing rate of 5 spikes s^{-1} during both the first and second halves of the stimulus (1-s stimulus duration). Out of 113 neurons, 72 neurons were recorded from A1, 25 from LB and 16 from the rostral and medial areas surrounding A1. The median spontaneous firing rates were 2.98 spikes s^{-1} (A1 neurons), 3.83 spikes s^{-1} (LB neurons) and 3.1 spikes s^{-1} (all neurons). The distribution of spontaneous firing rates of all 113 neurons can be fitted by an exponential function $y = 20.53\exp(-0.27x)$, $(r = 0.92)$.

A total of 263 single neurons were studied with short duration best-frequency-tones in A1 of three animals (Fig. 4). Responses of all neurons were significantly above spontaneous firing ($P < 0.01$, Wilcoxon rank sum test). The median spontaneous firing rate of this population of neurons was 1.8 spikes s^{-1} (25–75% percentile range, 0.7–4.68 spikes s^{-1}). The distribution of spontaneous firing rates of all 263 neurons can be fitted by the exponential function $y = 57.66\exp(-0.28x)$, $(r = 0.97)$.

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