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Research paper

Neural coding strategies in auditory cortex

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Abstract

In contrast to the visual system, the auditory system has longer subcortical pathways and more spiking synapses between the peripheral receptors and the cortex. This unique organization reflects the needs of the auditory system to extract behaviorally relevant information from a complex acoustic environment using strategies different from those used by other sensory systems. The neural representations of acoustic information in auditory cortex can be characterized by three types: (1) isomorphic (faithful) representations of acoustic structures; (2) non-isomorphic transformations of acoustic features and (3) transformations from acoustical to perceptual dimensions. The challenge facing auditory neurophysiologists is to understand the nature of the latter two transformations. In this article, I will review recent studies from our laboratory regarding temporal discharge patterns in auditory cortex of awake marmosets and cortical representations of time-varying signals. Findings from these studies show that (1) firing patterns of neurons in auditory cortex are dependent on stimulus optimality and context and (2) the auditory cortex forms internal representations of sounds that are no longer faithful replicas of their acoustic structures.

Keywords: Auditory cortex; Marmoset; Temporal processing; Neural coding

1. Introduction

In this review, I will address two related issues in cortical coding of acoustic signals, temporal firing patterns of auditory cortex neurons and their relationship with time-varying structures of sounds, based on a series of recent studies carried out in awake marmosets in our laboratory. I will use findings from these studies to illustrate two types of neural representations of acoustic information in auditory cortex: the isomorphic (or faithful) representation of the acoustic structures and the non-isomorphic transformation of acoustic features. While the experimental evidence cited in this article is largely based on the studies in marmosets, the neural coding strategies discussed here are likely applicable to the auditory cortex of other primate and mammalian species.

For the auditory system, time is an essential variable of sensory inputs. This is fundamentally different from other sensory systems (e.g., visual and somatosensory systems) where sensory inputs can be static. In audition, one can hardly define a "static" sound. Acoustic signals are like flowing water in a stream; they are constantly changing as a function of time. The same time axis is also used by neural discharges throughout the auditory pathway. A major distinction between the audition and vision is the temporal precision of sensory receptors and resulting peripheral representations. For the auditory system, the temporal precision is in the order of less than 1 ms (or greater than 1000 Hz), whereas it is in the order of ~100 ms (or ~10 Hz) for the visual system. Traditionally, auditory researchers have focused on how the time axis of acoustic signals is preserved by neural firings, for example, by analyzing "phase-locking" to the carrier frequency or the envelope of sounds. At the level of the auditory nerve, the two time axes (of acoustic signals and neural firings) are well matched (to the limit of the phase-locking).

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It has become clear after many years of research that the two time axes begin to diverge from each other at successive processing stations. The question addressed in this review is how a time-varying signal is mapped onto a spike train of auditory cortex neurons that is a function of time itself. Understanding this problem helps up better understand neural coding strategies in auditory cortex.

The neural representation of time-varying signals in auditory cortex is of special interest to our understanding of mechanisms underlying speech processing. Time-varying signals are fundamental components of communication sounds such as human speech and animal vocalizations, as well as musical sounds (Rosen, 1992; Wang, 2000). Low-frequency modulations are important for speech perception and melody recognition, while higher-frequency modulations produce other types of sensations such as pitch and roughness (Houtgast and Steeneken, 1973; Rosen, 1992). Both humans and animals are capable of perceiving the information contained in temporally modulated sounds across a wide range of time scales from a few millisecond to tens and hundreds of milliseconds. Neural representations of time-varying signals begin at the auditory periphery where auditory-nerve fibers faithfully represent fine structures of complex sounds in their temporal discharge patterns (Johnson, 1980; Joris and Yin, 1992; Palmer, 1982; Wang and Sachs, 1993). At subsequent processing stations along the ascending auditory pathway, the upper limit of the temporal representation of repetitive signals gradually decreases (e.g., cochlear nucleus: Blackburn and Sachs, 1989; Frisina et al., 1990; Wang and Sachs, 1994; Rhode and Greenberg, 1994; inferior colliculus: Langner and Schreiner, 1988; Batra et al., 1989; Muller-Preuss et al., 1994; Krishna and Semple, 2000; Liu et al., 2006; medial geniculate body: Creutzfeldt et al., 1980; de Ribaupierre et al., 1980; Rouiller et al., 1981; Preuss and Muller-Preuss, 1990; Bartlett and Wang, 2007; auditory cortex: Schreiner and Urbas, 1988; de Ribaupierre et al., 1972; Eggermont, 1991, 1994; Gaese and Ostwald, 1995; Bieser and Muller-Preuss, 1996; Lu and Wang, 2000; Lu et al., 2001b; Wallace et al., 2002; Liang et al., 2002; Phan and Recanzone, 2007), due to biophysical properties of neurons and temporal integration of converging inputs from one station to the next. By the time neural signals encoding acoustic information reach auditory cortex, temporal firing patterns alone are inadequate to represent the entire range of time-varying sounds. The mechanism by which the auditory cortex solves the problem of representing time-varying signals serves as a good example to illustrate a fundamental principle of cortical processing: the transformation of stimulus features into internal representations that are no long faithful replicas of their physical structures.

2. The responsiveness of auditory cortex

It has been well documented that neurons in auditory cortex of barbiturate- or ketamine-anesthetized animals generally display transient responses to acoustic stimulation and typically respond to a brief stimulus with one or few spikes (Phillips, 1985; Calford and Semple, 1995; Heil, 1997; Schnupp et al., 2001; DeWeese et al., 2003). For short tone stimuli (duration less than 100–200 ms), the number of spikes evoked by each stimulus usually does not increase with increasing stimulus duration (Eggermont, 1997). Long duration tones failed to continuously evoke neural activity during stimulus (deCharms and Merzenich, 1996). These observations have long puzzled researchers across disciplines and raised serious questions about the role of auditory cortex in encoding ongoing acoustic signals. 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 primary auditory cortex (A1) are specialized to respond to brief stimulus events (Phillips, 1993) and that correlated firing between neurons, instead of firing rates of individual neurons, signal the presence of steady-state sounds (deCharms and Merzenich, 1996; Eggermont, 1997). On the other hand, there has been accumulating evidence that neurons recorded from auditory cortex of awake animals exhibit both onset and sustained discharges in response to continuous acoustic stimulation (Bieser and Müller-Preuss, 1996; Recanzone, 2000; Lu et al., 2001b; Chimoto et al., 2002; Malone et al., 2002; Mickey and Middlebrooks, 2003). Contrary to the long-held views on the transient nature of neural firing in auditory cortex, our recent studies showed that single neurons in auditory cortex of awake marmoset monkeys were capable of firing in a sustained manner for both short and long duration sounds, especially when the neurons were driven by their preferred (nearly optimal) stimuli. In contrast, responses became more transient (or phasic) when auditory cortex neurons responded to non-preferred stimuli (Wang et al., 2005).

2.1. Response to brief stimuli in the awake condition

Unlike single neurons in A1 of barbiturate- or ketamine-anesthetized animals that typically fire one or a few spikes per stimulus irrespective of stimulus duration, single neurons in A1 of awake marmosets discharge multiple spikes when stimulated by brief BF-tones. Fig. 1a shows the distribution of the number of spikes per stimulus presentation for 50-ms BF-tone stimulation recorded from A1 of awake marmosets (Wang et al., 2005). The majority of neurons discharged more than one spike per stimulus presentation (median = 2 spikes per trial). The distribution shown in Fig. 1a qualitatively differs from the similar measures obtained using brief tones in barbiturate- or ketamine-anesthetized animals (e.g. DeWeese et al., 2003). Furthermore, we found that the number of spikes per stimulus presentation generally increased with increasing stimulus duration (Fig. 1b: 100-ms BF-tones, median = 3 spikes per trial) in contrast to observations in barbiturate- or ketamine-anesthetized animals. The number of spikes evoked

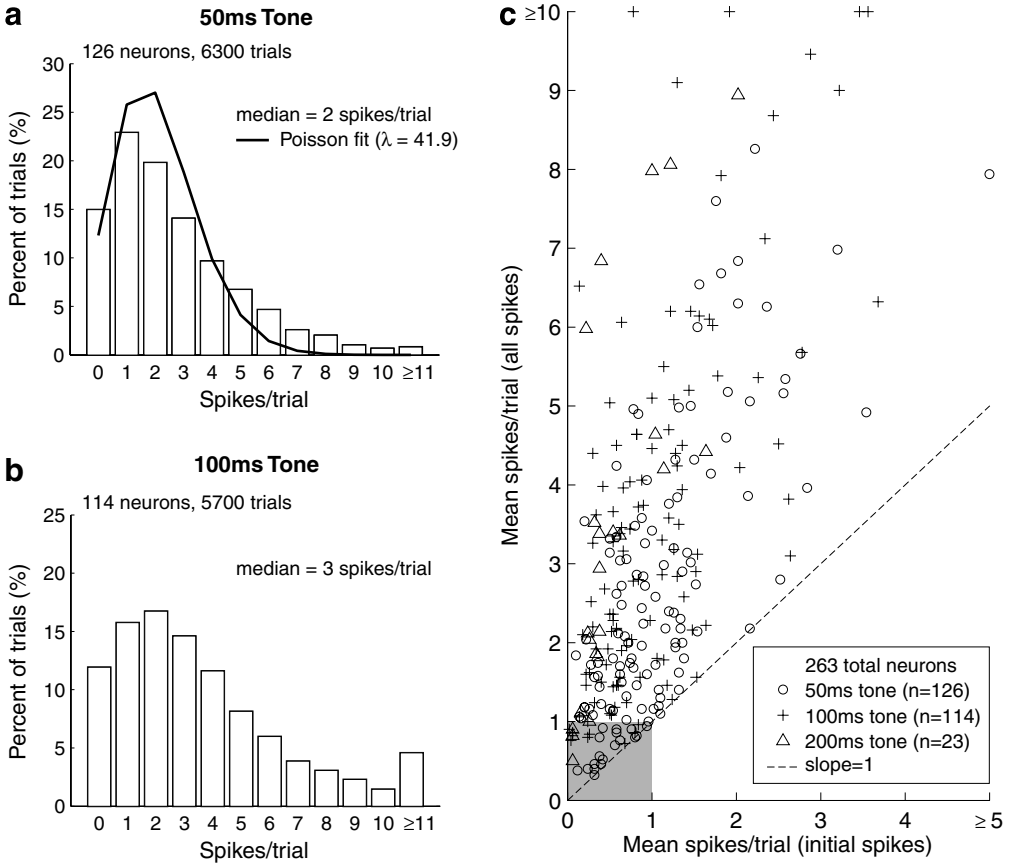

Fig. 1. Quantitative measures of single-unit responses to brief tones recorded from the primary auditory cortex (A1) of awake marmosets. The tones are set at each neuron's BF and preferred sound level (for non-monotonic neurons) or 30 dB above threshold (for monotonic neurons), delivered for 50 repetitions. (a) Histogram of spikes/trial count for 50 ms BF-tone responses calculated over the entire stimulus duration for 6300 stimulus presentations obtained from 126 neurons (median: 2 spikes/trial, equivalent to 40 spikes/s). The thick curve represents the minimum-mean-square fit by a Poisson distribution ($\lambda = 41.9$ spikes/s, $T = 0.05$ s, $r = 0.97$). (b) Same as A for 100 ms BF-tone responses (median: 3 spikes/trial, equivalent to 30 spikes/s). (c) Comparison between the counts of initial spikes ("onset response") and all spikes of tone-evoked discharges on a neuron-by-neuron basis. Mean spikes/trial count (per neuron) calculated over the entire stimulus duration ("all spikes") is plotted versus that calculated over the initial response period ("initial spikes", time window: [0, response latency + 10 ms]). The median value for initial spikes was 0.82 spikes per trial. The response latency is determined for each neuron using an accumulative spike count histogram. About 88% neurons (231/263) had more than one spike per stimulus. Adapted from Wang et al. (2005).

by each brief tone observed in A1 of awake marmosets is similar to that observed in A1 of awake macaque monkeys (see Table 2 of O'Connor et al., 2005). As shown by the analysis in Fig. 1c, neurons in A1 of awake marmosets continue to discharge after initial (onset) spikes. On Fig. 1c, if a neuron had only initial spikes, it should fall along the dashed line (slope of 1). If a neuron responded to each stimulus presentation with one or less than one spike on average, it should fall within the shaded square. Note that nearly all neurons were located above the dashed line, indicating that they had "sustained response" beyond "onset response". The median value for initial spikes (0.82 spikes/trial) was close to the ~1 spikes/trial value typically recorded in A1 of barbiturate- or ketamine-anesthetized animals, suggesting that the anesthesia had greater effects on sustained response than onset response. A recent study of tone-evoked responses in A1 of halothane-anesthetized cats showed greater extent of sustained discharges than the responses recorded from barbiturate- or ketamine-anesthetized animals (Moshitch et al., 2006), indicating less suppressive effects by halothane-anesthesia.

2.2. Response to long duration stimuli in the awake condition

It has long been thought that auditory cortex neurons are incapable of discharging continuously to long duration sounds (deCharms and Merzenich, 1996). This notion does not seem to hold in awake animals. In auditory cortex of awake marmosets, both simple and complex stimuli of long duration have been found to evoke sustained firings in particular neuronal populations (Wang et al., 2005). Although some neurons exhibited sustained firings in response to long duration pure tones (Fig. 2a) or broadband noises (Fig. 2b), the majority of cortical neurons did so when stimulated by their preferred stimuli that had greater temporal and spectral complexity than pure tones or broadband noises. For example, A1 neurons were usually more strongly driven by amplitude- or

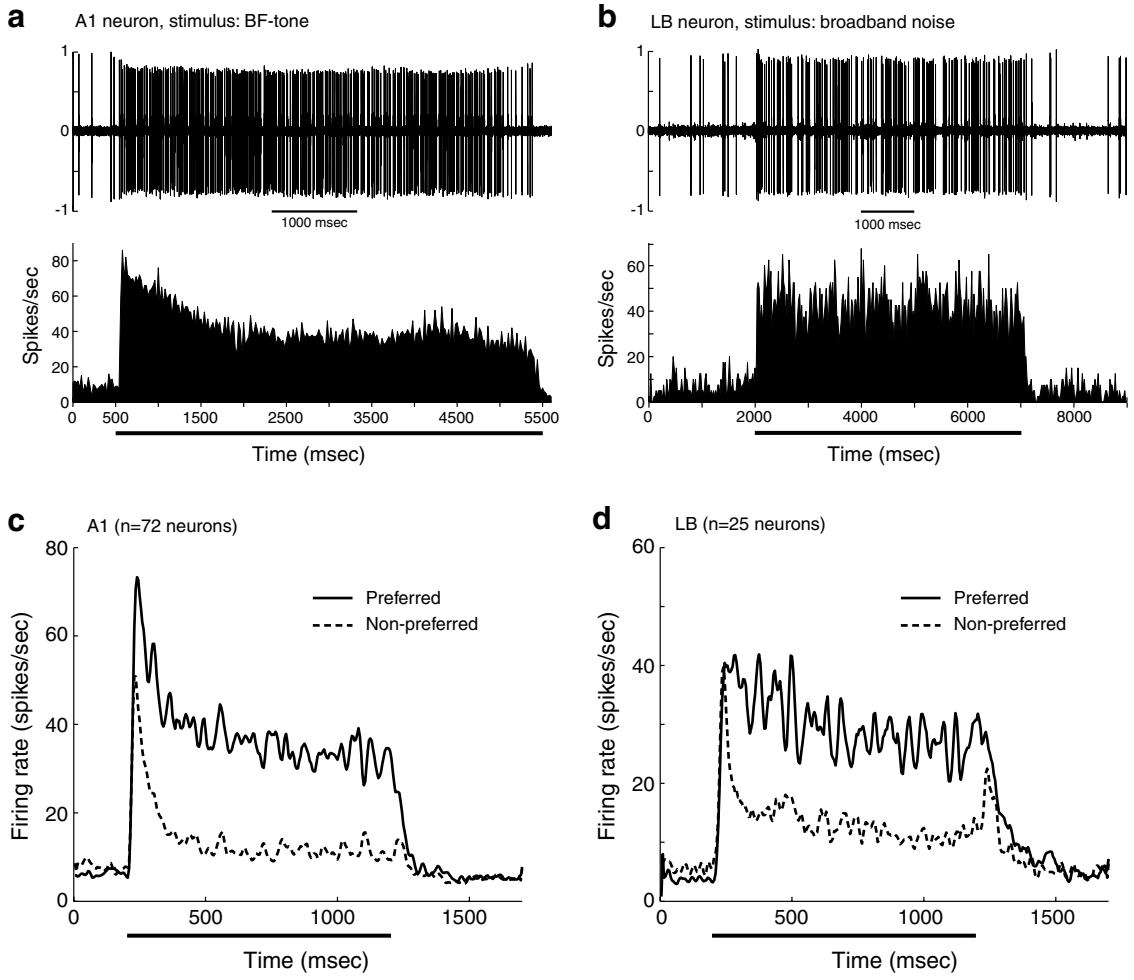

Fig. 2. (a and b) Single neuron examples of sustained firing evoked by long duration stimuli recorded from auditory cortex in awake marmosets. (a) A1 neuron. Stimulus: unmodulated pure tone at the neuron's BF (9.3 kHz), 80 dB SPL, rise/fall time 1-s, duration 5-s. Upper: Raw recording trace of the response to one presentation of the stimulus. Lower: PSTH computed from responses to 50 repetitions of the same stimulus (binwidth: 20 ms). (b) LB neuron. Stimulus: unmodulated broadband noise, 80 dB SPL, rise/fall time 5 ms, duration 5-s. Upper: raw recording trace of the response to one presentation of the stimulus. Lower: PSTH (20 repetitions, binwidth: 20 ms). Thick bar below *x*-axis: stimulus duration. (c and d) Temporal firing patterns evoked by preferred and non-preferred stimuli. The data are recorded from auditory cortex in awake marmosets. Mean PSTHs calculated from populations of A1 (c) and lateral belt (LB) (d) neurons in response to each neuron's preferred (solid) and non-preferred (dashed) stimuli, respectively. The preferred stimulus is a temporally modulated signal (an amplitude-modulated tone (sAM), or frequency-modulated tone (sFM), or amplitude-modulated noise (nAM)) and set at the best modulation frequency (BMF). The non-preferred stimulus is set at the modulation frequency corresponding to the minimum firing rate above BMF. A similar trend is observed at the non-preferred modulation frequency below BMF. PSTH binwidth: 5 ms (smoothed by a 5-point moving triangular window). Thick bar below *x*-axis: stimulus duration (1-s). Adapted from Wang et al. (2005).

frequency-modulated tones than by pure tones. Similarly, neurons in lateral belt areas typically responded more strongly to amplitude-modulated noises than to unmodulated noises (Liang et al., 2002). In both cortical areas, neural responses reached the maximum at "best modulation frequency" (BMF) and became weaker at modulation frequencies away from BMF (Wang et al., 2003). Accompanying this change in the response magnitude was a change in the temporal discharge pattern from strong sustained firing at BMF to weakly sustained firing or onset firing as the modulation frequency moved away from the BMF (Fig. 2c and d). In contrast to anesthetized animals (see recent review by Joris et al., 2004), many A1 neurons in awake marmosets responded to temporally modulated signals with sustained firings but without exhibiting stimulus-synchronized discharges. Statistically significant stimulus-synchronized discharges were not detected in 30–40% of A1 neurons when tested with sinusoidal amplitude-modulated (sAM) or sinusoidal frequency-modulated (sFM) stimuli (Liang et al., 2002). These observations show that auditory cortex neurons (in A1 and secondary cortical areas) are capable of generating true sustained firings in response to ongoing acoustic stimulation. The "sustained firing" referred to here differs from the situation where a neuron responds to a sequence of slowly repetitive sounds with a train of discrete spike clusters, each corresponding to one brief sound (e.g. Fig. 4 of deCharms et al., 1998).

2.3. The relationship between stimulus selectivity and cortical discharge patterns

Data shown in Fig. 2 demonstrate a general principle observed in awake marmoset auditory cortex, namely, when neurons are driven by their preferred stimuli, they respond not only with higher discharge rates, but also with sustained firing patterns throughout the stimulus duration. Our findings showed that whether a neuron responded to a stimulus with sustained firing depended crucially on the optimality of the stimulus (Wang et al., 2005). We found that neurons in auditory cortex of awake marmosets (especially those in upper cortical layers) were often highly selective to acoustic stimuli and, as such, the preferred stimulus (or stimuli) of a neuron only occupied a small region of the acoustic parameter space defined by spectral, temporal and intensity axes, as illustrated by Fig. 3a. 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 were preferentially driven by stimuli with intermediate spectral bandwidth and/or greater temporal complexity.

From a stimulus point of the view, our findings suggest that when auditory cortex is evoked by a sound, a particular population of neurons fire maximally throughout the duration of the sound, whereas responses of other less optimally driven neurons fade away quickly after stimulus onset, resulting in a selective representation of the sound across both neuronal population and time. From a neuron's point of the view, these findings suggest that the receptive field of a cortical neuron contains a restricted "sustained firing region" (corresponding to preferred stimuli) and a larger "onset firing region" (corresponding to non-preferred stimuli). In the auditory periphery, auditory nerve fibers typically respond to a wide range of acoustic signals with continuous firing as long as a stimulus' spectral energy falls within a neuron's receptive field. In other words, auditory nerve fibers have relatively low stimulus selectivity and their receptive field is largely made of a "sustained firing region". We suggest that at successive processing stations along the ascending auditory pathway, stimulus selectivity progressively increases and the proportion of the "sustained firing region" within the receptive field progressively decreases as illustrated by Fig. 3a. This explains why it is common for experimenters to encounter onset (phasic) responses in auditory cortex even in awake animals. The overall picture elucidated by these findings is that when a sound is heard, the auditory cortex first responds with transient (onset) discharges across a relatively large population of neurons. As the time passes, the activation becomes restricted to a smaller population of neurons that are preferentially driven by the sound. Because each neuron has its own preferred

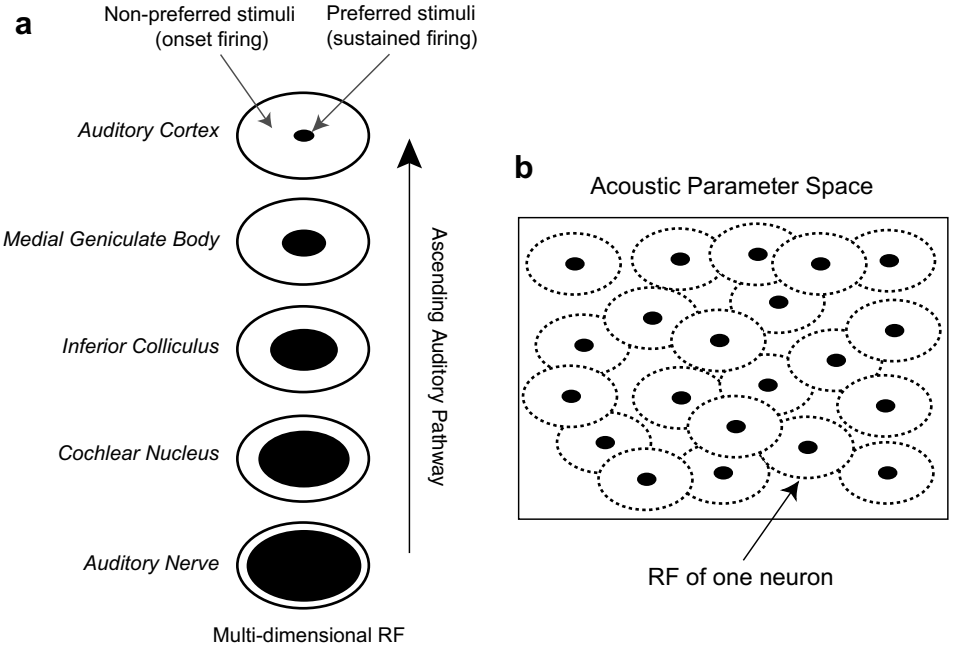

Fig. 3. The relationship between the stimulus selectivity and the responsiveness of auditory cortex neurons. (a) Illustration of progressively increasing stimulus selectivity and the relationship between sustained and onset firings along the ascending auditory pathway. The large ellipse represents the receptive field (RF) of a neuron in the acoustic parameter space which is multi-dimensional but illustrated here on a two-dimensional plane. The filled, smaller ellipse represents the "sustained firing region" (corresponding to preferred stimuli) of a neuron's RF. The open area within the large ellipse represents the "onset firing region" (corresponding to non-preferred stimuli) of a neuron's RF. A neuron exhibits sustained or onset firing depending on which region of its RF is stimulated. The neuron does not fire if stimuli fall outside of its RF. (b) Illustration showing that the auditory cortex could represent the entire acoustic parameter space by the sustained firing regions of individual neurons' RF.

stimulus that differs from preferred stimuli of other neurons, the neurons in auditory cortex collectively cover the entire acoustic parameter space with their sustained firing regions (Fig. 3b). Therefore, any particular sound can evoke sustained firing throughout its duration in a particular population of neurons in auditory cortex. This suggests that the cortical region(s) "lighted up" by acoustic stimulation in brain imaging studies correspond to neurons that are optimally driven by the acoustic stimulus.

3. Dual mechanisms for representing time-varying signals: functional mplications of synchronized and non-synchronized cortical responses

In the above section, we point out that a prominent feature of neural responses in awake auditory cortex is sustained firing. What functional roles can the sustained firing play? Our work in awake marmosets showed that the sustained firing in auditory cortex can serve to represent rapid time-varying signals (Lu et al., 2001b). It has long been noticed that neurons in the auditory cortex do not faithfully follow rapidly changing stimulus components (de Ribaupierre et al., 1972; Goldstein et al., 1959; Whitfield and Evans, 1965). A number of previous studies have shown that discharges of cortical neurons can only entrain to temporal modulations at a rate far less than 100 Hz (Bieser and Müller-Preuss, 1996; de Ribaupierre et al., 1972; Eggermont, 1991, 1994; Gaese and Ostwald, 1995; Lu and Wang, 2000; Schreiner and Urbas, 1988), compared with a limit of ~1 kHz for the auditory-nerve (Joris and Yin, 1992; Palmer, 1982). The lack of synchronized cortical responses to rapid, but perceivable temporal modulation has been puzzling. Because most of the previous studies in the past three decades prior to 2000 on this subject were conducted in anesthetized animals, with a few exceptions (Bieser and Muller-Preuss, 1996; Creutzfeldt et al., 1980; de Ribaupierre et al., 1972; Evans and Whitfield, 1964; Goldstein et al., 1959; Whitfield and Evans, 1965), it was speculated that the reported low temporal response rate in auditory cortex might be caused partially by anesthetics, which was shown to alter the temporal response properties of auditory cortex (Goldstein et al., 1959; Zurita et al., 1994).

We re-examined cortical representations of time-varying signals in A1 of awake marmosets (Lu et al., 2001b; Liang et al., 2002; Wang et al., 2003). Two types of cortical responses to periodic click trains were observed (Fig. 4). One type of cortical response (Fig. 4a) exhibited significant stimulus-synchronized responses to click trains at long inter-click intervals (>~25 ms) (Fig. 4c) but diminished at shorter ICIs. The second type of cortical response (Fig. 4b) did not exhibit stimulus-synchronized discharges, but instead showed monotonically changing discharge rate at short inter-click intervals (Fig. 4d). The observation that A1 neurons are responsive to rapid changes in inter-click intervals suggests that a discharge rate-based mechanism is responsible for encoding rapid time-varying signals. Neural responses to click trains observed in awake marmoset A1 (Fig. 4) differ from those observed in anesthetized cats (Fig. 5). The most crucial difference between the two conditions lies in "non-synchronized responses". Whereas a large proportion of neurons in A1 of awake marmosets exhibited prominent sustained firing throughout 1-s long click trains at short inter-click intervals (Fig. 4b), only a small proportion of neurons in A1 of anesthetized cats responded to click trains at short inter-click intervals and they did so by firing transiently after stimulus onset (Fig. 5b). We never observed any non-synchronized discharges in anesthetized cats that lasted throughout the duration of click trains at short inter-click intervals (Lu and Wang, 2000), nor did any previous studies in anesthetized animals.

We identified two populations of A1 neurons, referred to as synchronized and non-synchronized populations, which appeared to encode repetitive stimuli by spike timing and average discharge rate, respectively (Fig. 6). Neurons in the synchronized population showed stimulus-synchronized discharges at long inter-click intervals, but few responses at short inter-click intervals. This population of neurons can thus represent slowly occurring temporal events explicitly using a temporal code. The representation of inter-click interval by the synchronized population is therefore "isomorphic" because it is a faithful replica of a stimulus parameter. The non-synchronized population of neurons did not exhibit stimulus-synchronized discharges at either long or short inter-click intervals. This population of neurons can implicitly represent rapidly changing temporal intervals by their average discharge rates. The representation by the non-synchronized population is "non-isomorphic" because it has converted a stimulus parameter into an internal representation. The overlap between the encoding domains of these two populations of neurons allows the auditory cortex to represent a wide range of repetition rates (Fig. 6).

One may wonder why the auditory system makes such an effort to convert auditory-nerve spike trains with precise timing information on acoustic signals to seemingly sluggish non-synchronized cortical discharges. One reason is that this is necessary for the purpose of multi-sensory integration. For mammals, other sensory signals (e.g., visual, tactile) vary much more slowly with regard to time than do auditory signals, resulting in much slower peripheral representations of visual or tactile signals than that of auditory signals. However, at the level of cerebral cortex, neural signals representing all sensory information must operate with similar speeds with regard to time when they are integrated for multi-modal processing. The central nervous system seems to adapt a strategy to slow down the faster auditory signals coming from the periphery by converting them into non-synchronized responses in cortex in order to preserve useful auditory information.

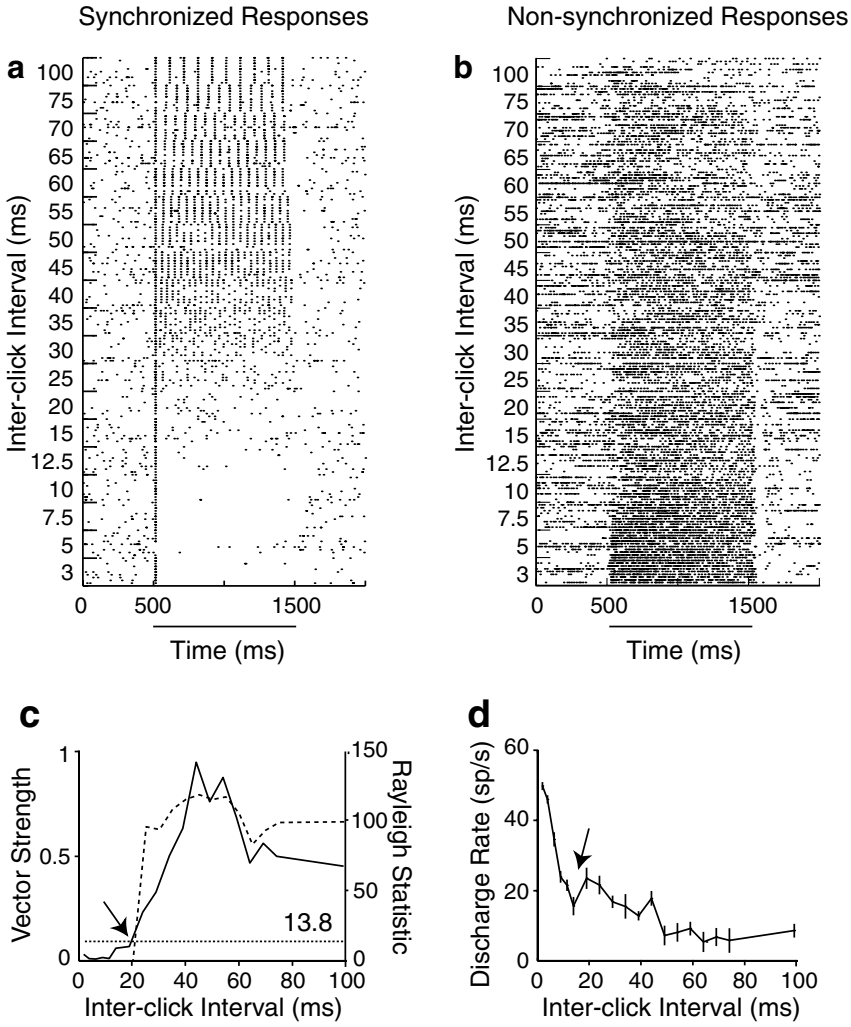

Fig. 4. Two distinct types of cortical responses to periodic click trains. (a,b) Examples of stimulus-synchronized and non-synchronized responses, respectively, to click trains recorded from primary auditory cortex (A1) of awake marmosets. The horizontal bar below *x*-axis indicates the stimulus duration (1000 ms). (c) Vector strengths (dashed line) and Rayleigh statistics (solid line) analyzed for the stimulus-synchronized responses shown in a. The dotted line (at the Rayleigh statistics of 13.8) indicates the threshold for statistically significant stimulus-synchronized activity ($p < 0.001$). A synchronization boundary is calculated and indicated by an arrow. (d) Driven discharge rate is plotted versus inter-click-interval for the non-synchronized responses shown in b. Vertical bars represent standard errors of the means (SEM). The arrow indicates calculated rate-response boundary. Adapted from Lu et al. (2001b).

4. Discrimination of acoustic transients: an example of firing rate coding

An often-raised concern on coding mechanisms based on firing rate is that firing rate is a relative measure, unlike discharge synchrony. In order to directly "read out" a stimulus parameter from firing rate (e.g., repetition rate), another representational dimension is needed, for example, a map or spatial distribution of neurons tuned to different repetition rates by their firing rates. On the other hand, the change in firing rate can encode the relative *change* in a stimulus parameter. Detecting changes in a sound or discriminating between two sounds is often more important than determining the real values of sound parameters when humans and animals are dealing with the acoustic environment. The rate coding should be adequate for such tasks. In this section, we use an example to illustrate a potential function of rate coding in discriminating acoustic transients.

The findings shown in Figs. 4–6 suggest that A1 neurons temporally integrate stimulus components within a time window of ~20–30 ms and treat components outside this window as discrete acoustic events (Wang et al., 2003). Humans and animals are known to discriminate changes in acoustic signals at time scales shorter than the temporal integration window of A1 neurons. Cortical neurons therefore must be able to signal such rapid changes. To demonstrate cortical neurons' sensitivity to rapid temporal changes within the putative temporal integration window, we studied A1 neurons in awake marmosets using a class of temporally modulated signals termed ramped and damped sinusoids. A damped sinusoid consists of a BF-tone carried amplitude-modulated by an exponential function, and has a fast onset followed by a slow offset. The rate

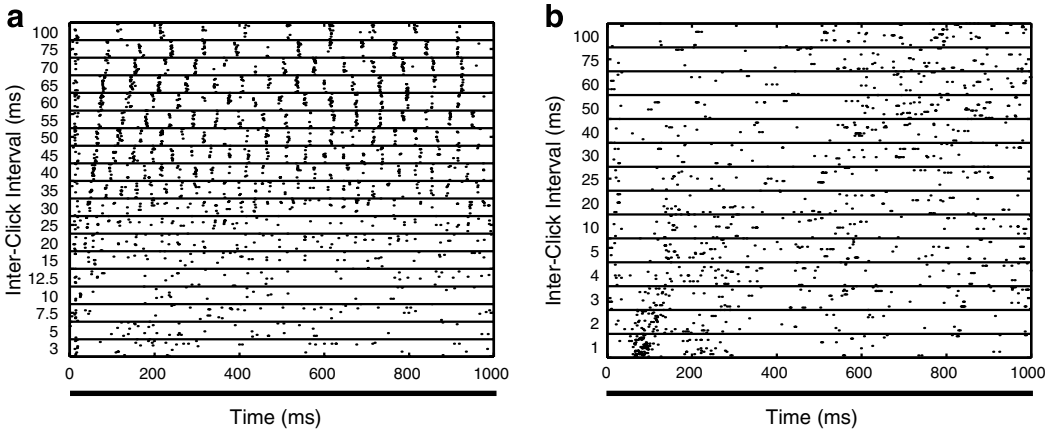

Fig. 5. Representative examples of temporal discharge patterns in response to periodic click trains recorded from A1 of barbiturate- or ketamine-anesthetized cats. (a) A unit with synchronization responses at long inter-click intervals. The stimulus-synchronized response stopped at 25–30 ms ICI. (b) A unit showing a rate-change response at short inter-click intervals, but no stimulus-synchronized response at long inter-click intervals. The horizontal bar below the *x*-axis indicates stimulus duration (1000 ms). Adapted from Lu and Wang (2000).

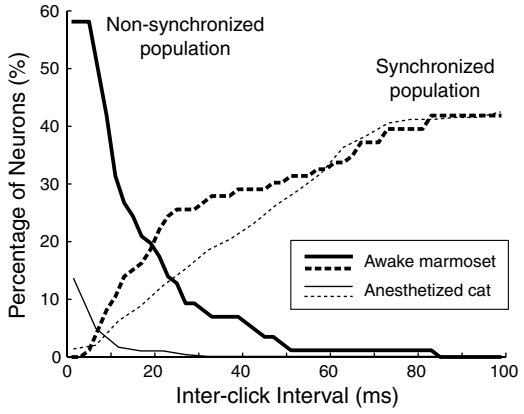

Fig. 6. Dual mechanisms for encoding slow and fast repetition rates by two populations of auditory cortex neurons. A combination of temporal and rate representations can encode a wide range of inter-click intervals (ICI). The dashed line shows the percentage of neurons with synchronization boundaries less than or equal to a given ICI. The solid line shows the percentage of neurons with rate-response boundaries greater than or equal to a given ICI. Thick curves are based on the data of two neuronal populations recorded from A1 of awake marmosets, one with stimulus-synchronized discharges ($N = 36$, dashed curve) and the other with non-synchronized discharges ($N = 50$, solid curve), respectively (Lu et al., 2001b). Thin curves show the data obtained from A1 of anesthetized cats using click train stimuli (Lu and Wang, 2000), analyzed in the same way as the data from awake marmosets.

of amplitude decay is determined by an exponential half-life parameter. A ramped sinusoid is a time-reversed damped sinusoid. Both types of sounds have identical long-term amplitude spectra. Patterson, (1994a,b) characterized psychophysical performance of human subjects in discriminating ramped versus damped sinusoids, therefore providing a basis for comparing cortical responses in differentiating these temporal asymmetric stimuli.

Most A1 neurons showed clear preference (in terms of firing rate or synchrony) for periodic sequence of ramped or damped sinusoids (Lu et al., 2001a). Some neurons responded nearly exclusively to one stimulus type (ramped or damped). The response asymmetry was observed in average discharge rate, but not necessarily in stimulus-synchronized discharges. In Fig. 7, we compare response asymmetry of populations of A1 neurons with the psychophysical performance in discriminating ramped versus damped sinusoids by humans (Lu et al., 2001a). The shape of the curve based on average discharge rate is qualitatively similar to psychophysical data with both tone carriers (Patterson, 1994a) and wide-band noise carriers (Akeroyd and Patterson, 1995). The psychophysical performance across the half-life appears to be related to the percentage of A1 neurons that showed significant response asymmetry in their average discharge rates. A population measure based on discharge synchrony, on the other hand, reveals that only a very small portion of A1 neurons (<5%) showed response asymmetry in their temporal discharge patterns for the stimulus period used (25 ms). These results show that discharge-rate based cortical representations can serve as the basis to discriminate rapid acoustic transients, in the absence of stimulus-synchronized responses. The close correlation between psychophysical and physiological data shown in Fig. 7 suggests that discharge rate-based cortical representations can play important functional roles.

5. Differences between awake and anesthetized auditory cortex as revealed by responses to time-varying signals

Goldstein et al. (1959) showed that click-following rates of cortical evoked potentials were higher in unanesthetized cats than in anesthetized ones. We have studied responses of A1 neurons to click train stimuli in both awake marmosets (Lu et al., 2001b) and anesthetized cats (Lu and Wang, 2000) in our laboratory. There were several important differences between response properties observed in these two preparations. First, in contrast to A1 neurons in anesthetized cats, which responded strongly to both wide-band (rectangular) and narrow-band clicks, the majority of A1 neurons in awake marmosets responded weakly or, more

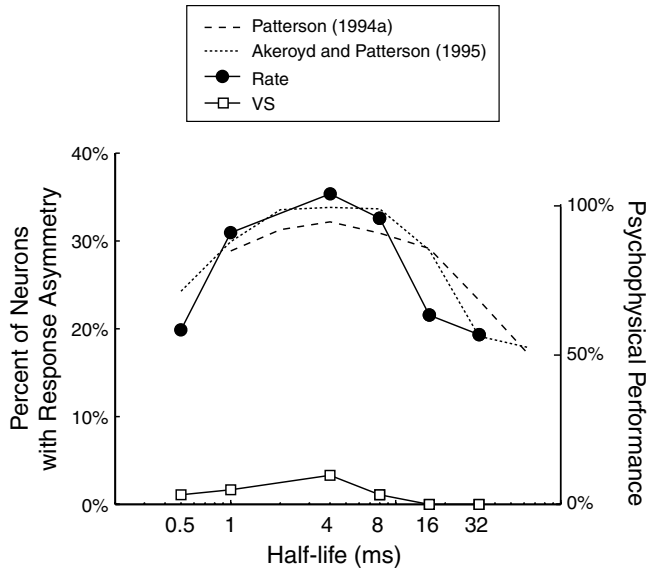

Fig. 7. Comparison between asymmetry preference of A1 neurons in awake marmosets and human psychophysical performance in discriminating ramped and damped sinusoids. The stimuli used in physiology experiments consist of ramped or damped sinusoid segments, with a period of 25 ms, repeated consecutively for 500 ms. For each neuron, the carrier frequency is set to a neuron's BF and the half-life is varied from 0.5 to 32 ms. The percentages of neurons (left ordinate) having significant asymmetry indices based on discharge rate are indicated as *Rate* (*solid line with filled circles*). The percentages of neurons with significant asymmetry indices in vector strength (VS) are indicated as *VS* (solid line with open squares). Human psychophysical performance curves (right ordinate), using ramped and damped sinusoids, are shown for tone carriers (dashed line), averaged over the different carrier frequencies (Patterson, 1994a), and noise carriers (dotted line) (Akeroyd and Patterson, 1995). The discharge rate-based asymmetry index was defined as $I_{\mathrm{Rate}} = (R_r - R_d)/(R_r + R_d)$, where R_r and R_d are the discharge rates (minus spontaneous discharge rate) to the ramped and damped sinusoids, respectively. The discharge rate is set to 0 for the asymmetry index calculation if it is less than 0 (i.e., when a neuron's firing is suppressed below its spontaneous level during stimulus presentation). A positive I_{Rate} indicates that a neuron responded more strongly to the ramped than damped sinusoids whereas a negative I_{Rate} indicates the opposite. The vector strength-based asymmetry index is defined as $I_{\mathrm{VS}} = (\mathrm{VS}_r - \mathrm{VS}_d)$, where VS_r and VS_d are the vector strengths calculated for the responses to the ramped and damped sinusoids, respectively. Insignificant I_{VS} values ($p > 0.05$) are set to zero. I_{VS} of 1 indicates that the responses are perfectly synchronized to the ramped sinusoids with no significant synchronization to the damped sinusoids, whereas I_{VS} of -1 indicates the opposite. Statistical significance of the asymmetry indices is assessed using a *Wilcoxon rank sum test*. Adapted from Lu et al. (2001a).

often, were unresponsive to wide-band clicks, but could be strongly driven by narrow-band clicks. Using narrow-band clicks with various bandwidths, we were able to determine that the lack of responses to rectangular clicks was due to activations of side-band inhibition by these wide-band stimuli (unpublished observation). It appeared that such side-band inhibitions were much stronger in A1 of awake animals than in anesthetized animals. Second, stimulus-following rates were higher in awake marmosets than in A1 of anesthetized cats (Fig. 6). This finding is consistent with the earlier finding shown by Goldstein et al. (1959). Third, and most importantly, the large number of neurons with non-synchronized and sustained discharges (throughout stimulus duration) at short ICIs observed in A1 of awake marmosets were not observed in A1 of anesthetized cats (Figs. 4–6). Although these comparisons are made in A1 of two mammalian species, we suspect that such response differences resulted largely from two different experimental conditions (awake versus anesthetized) rather than from species-specific differences. A1 of both species appear to share many similar anatomical and physiological properties (Schreiner et al., 2000; Aitkin et al., 1986, 1988; Wang et al., 1995). It is also possible that these response differences partially resulted from laminar differences. In our studies of awake marmosets, recordings were made mostly from neurons in upper cortical layers (II–III), whereas the recordings in anesthetized cats were made primarily in middle cortical layers (IV), as is typical of other studies in anesthetized animals. This issue needs be resolved by future studies.

In summary, our observations and those of others have shown that the upper limit of discharge synchrony is higher in awake animals than in anesthetized animals. More importantly, sustained and non-synchronized responses to long duration, repetitive stimuli are largely absent in barbiturate- or ketamine-anesthetized animals, which suggests that neurons in awake auditory cortex are capable of dynamically engaging in the acoustic environment. In a broader sense, these observations indicate that response properties observed in anesthetized auditory cortex could be observed in awake auditory cortex, albeit differing quantitatively. However, the opposite is not true. That is, certain phenomena observed in awake auditory cortex might not be observable in anesthetized auditory cortex. The non-synchronized response discussed above is such an example. Therefore, it is important, in fact crucial, to look for novel neural coding principles in designing experiments conducted in awake and behaving animals.

An outstanding question is whether neurons with non-synchronized responses observed in the awake condition would remain silent in the anesthetized condition or discharge in a different manner. Given the prominence of neurons with non-synchronized responses in awake marmoset auditory cortex (Lu et al., 2001b) and the scarcity of such responses in anesthetized animals, we suggest that anesthesia disrupts neural processing that leads to the non-synchronized cortical responses.

6. What is the role of spike timing in awake auditory cortex?

The issue of spike timing in auditory cortex has long been of interest to auditory researchers. It was shown that the precision of the first spike latency in A1 of anesthetized cats was comparable to (Phillips and Hall, 1990; Phillips, 1993) or even better than (Heil and Irvine, 1997) that of auditory never fibers. A recent study took it further by claiming "binary spiking" in A1 of anesthetized rats (DeWeese et al., 2003). Because these previous studies were conducted in anesthetized animals, they likely missed sus-

tained discharges that A1 neurons in awake animals typically exhibit. But, what are potential roles that the spike timing plays in awake auditory cortex? We explored this issue using responses to time-varying signals (Lu and Wang, 2004). Our results show that the issue of spike timing in auditory cortex must be considered in proper context, i.e., under what stimulus conditions and for which population of cortical neurons.

Fig. 8 examines how crucial spike timing is for the synchronized and non-synchronized populations of A1 neurons. We randomized spike timing of A1 responses to click trains. The entropies of the unaltered spike times were then compared to those from the randomized version. The randomness, and therefore the entropy, of a spike train would increase if temporal structures were originally present in the spike train. The example in Fig. 8a–d shows the effect of this manipulation on a synchronized neuron. The discharge rate remained the same (Fig. 8c) but any synchronized responses were eliminated (Fig. 8d). The result of the randomization of spike times on the population of synchronized neurons was that they no longer had stimulus-synchronized spike trains (Fig. 8e). The ratio of the entropy of the unaltered spike train over the entropy of the randomized spike train was used as a measure to indicate the amount of spike timing information contained in a stimulus-evoked spike train. The average entropy ratio, calculated from the two populations of neurons, respectively, is plotted against the click train ICI (Fig. 8f, lines with symbols). For comparison, the entropy ratio was also calculated for spontaneous discharges (Fig. 8f, dashed line). Note that the entropy ratios for spontaneous discharges had values less than 1, indicating that spontaneous firing was not distributed completely randomly. In the case of the synchronized population (Fig. 8f, solid line with open circles), as the ICI increased, the entropy ratio began to drop near 30 ms and became significantly different from the entropy ratio of spontaneous discharges at 50 ms. It continued to be significantly different for all larger values of ICI, having a value nearly 0.85 at 100 ms ICI. This difference in entropy ratios demonstrated that the random-

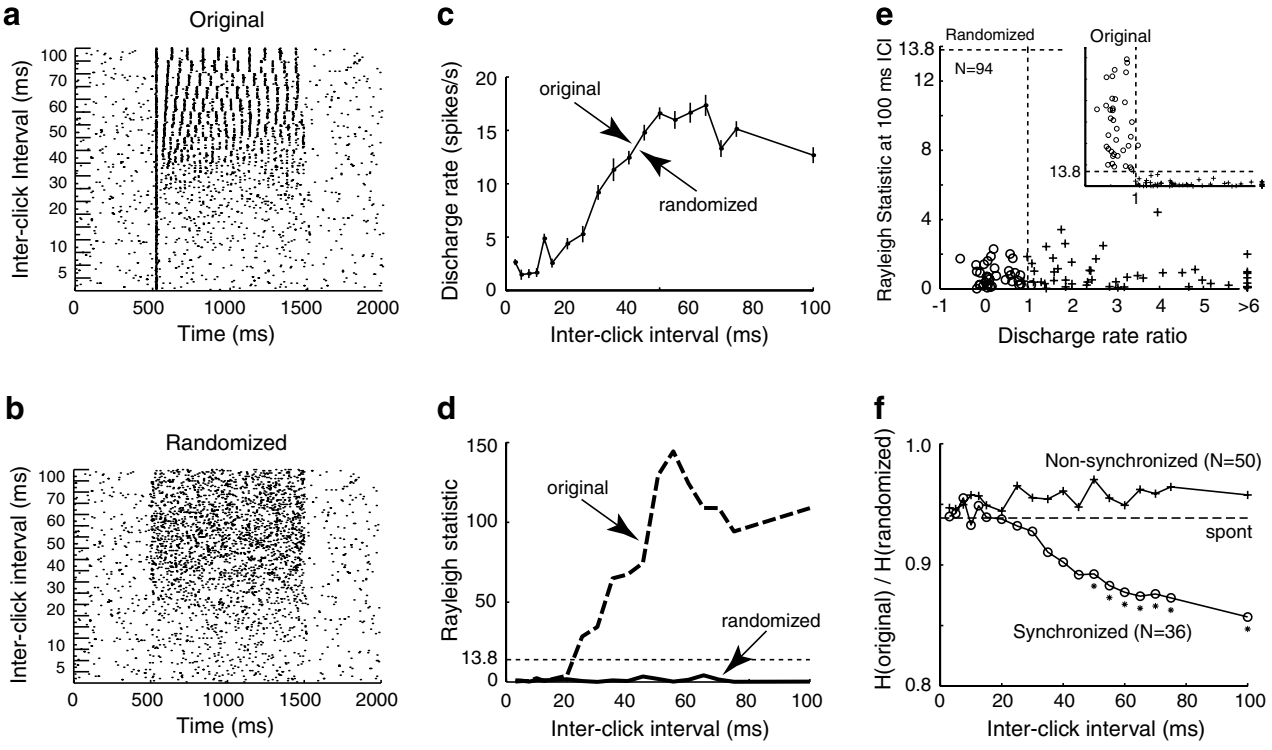

Fig. 8. Analysis of spike timing information in two populations of A1 neurons recorded from awake marmosets. Spike times over the duration of the stimulus are uniformly randomized, and the entropies of their ISI distributions are computed. (a) Dot raster of a cortical neuron's responses to click train stimuli. This neuron shows stimulus-synchronization to regular click trains in its responses. (b) Dot raster of A after spike time randomization. (c) Randomization of spike timing has no effect on discharge rate. Curves from randomized and original responses overlap exactly. (d) Randomization of spike timing reduces stimulus-synchronization measure, Rayleigh statistic, to non-significant values. (e) The effects of randomization on the two populations of neurons. Synchronized neurons are marked with open circles, and non-synchronized neurons are marked with '+'s. The abscissa is the discharge rate ratio, the ratio of the discharge rate for a 3 ms inter-click interval (ICI) click train to that at 100 ms inter-click interval. The ordinate is the Rayleigh statistic calculated at 100 ms ICI. Values above the dashed line at 13.8 indicate statistically significant stimulus-synchronization. The inset shows the results from the original responses (from Lu et al., 2001b). (f) Entropy ratio of original to randomized spike times as a function of inter-click interval for synchronized units (line with circles) and non-synchronized units (line with crosses), respectively. The curves represent the averaged entropy of the original divided by the average entropy of the randomized spike times. The horizontal dashed line indicates the entropy ratio computed from the spontaneous activity prior to the stimuli for synchronized and non-synchronized units. Points that are significantly different from the entropy ratio of spontaneous activity are indicated with '*'s ($p < 0.05$, *Wilcoxon rank sum*). Adapted from Lu and Wang (2004).

ness of the spike trains for the synchronized population was less than that of their randomized versions at ICIs longer than ~30 ms. The curve for the average entropy ratio of the non-synchronized population was fairly flat over the range of ICIs tested (Fig. 8f, solid line with crosses). In addition, none of the ratios were significantly different from that of the spontaneous discharges. The fact that the entropy ratio of the non-synchronized population was consistently higher than that of spontaneous discharges across ICIs indicated that stimulus driven discharges in these neurons were at least as random as those of spontaneous firing.

We quantified the precision of spike timing of the responses to click train stimuli for the synchronized population of neurons. In general, spike timing dispersion was smaller at stimulus onset than at successive stimulus events for an ongoing stimulus. Fig. 9 shows that the coefficient of variation (CV) of the response latency calculated from the onset responses of periodic click trains was significantly ($p < 0.001$, *Wilcoxon ranksum*) smaller than the CV calculated from all responses except for sparsely occurring clicks (crosses in Fig. 9, responses to 100 ms ICI click train). The results shown in Fig. 9 indicate that, for the synchronized population, spike time precision was better in the onset response than in the responses to successive stimulus events. Compared to the synchronized population, the non-synchronized population had greater dispersion in spike timing for both onset and sustained responses (Lu and Wang, 2004).

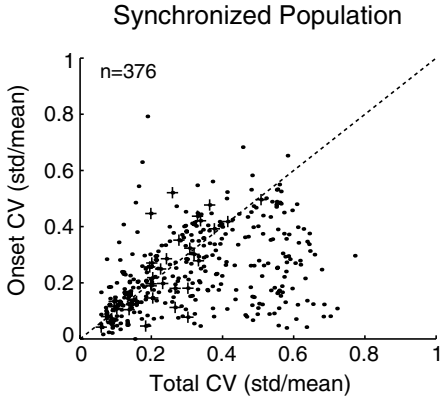

Fig. 9. Analyses of the precision of spike timing in the responses of the synchronized populations of neurons to click trains recorded from A1 of awake marmosets. The coefficient of variation (CV) of spike time latencies, relative to the click that evoked the response, is used to measure the precision of spike timing. $CV = \sigma/\mu$, where μ is the mean latency of the response to each click and σ is the standard deviation (SD) of the latency. Onset CV is calculated from the onset response for each click train (or the response to the first click). Total CV is calculated and averaged from the responses to all clicks in a click train. Each data point represents the response from a single stimulus ICI. '+'s indicate responses to the 100 ms ICI click train. Onset CV: median = 0.22, [25%,75%] = [0.13, 0.35]). Total CV: median = 0.30, [25%, 75%] = [0.15, 0.48]). Adapted from Lu and Wang (2004).

In summary, spike timing on the occurrence of acoustic events is more precise at the first event than at successive ones, and more precise with sparsely distributed events (longer time intervals between events) than with densely packed events. These results indicate that auditory cortex neurons mark sparse acoustic events (or onsets) with precise spike timing and transform rapidly occurring acoustic events into firing rate-based representations.

7. Functional implications of temporal-to-rate transformation in auditory cortex

The significant reduction in the upper limit of stimulus-synchronized discharges and the emergence of non-synchronized discharges in the auditory cortex, vs the auditory periphery, have important functional implications. First, it shows that considerable temporal-to-rate transformations have taken place by the time auditory signals reach the auditory cortex. The importance of "non-synchronized" neural responses is that they represent processed (or non-isomorphic) instead of preserved (or isomorphic) information. Second, it suggests that cortical processing of sound streams operates on a "segment-by-segment" basis rather than on a "moment-by-moment" basis as found in the auditory periphery. This is necessary for complex integration to take place at this level of the auditory system, since higher-level processing tasks require temporal integration over a time window preceding and following a particular time of interest. Third, the reduction in the temporal limit on stimulus-synchronized discharges in auditory cortex is a prerequisite for multi-sensory integration in the cerebral cortex. Auditory information is encoded at the periphery at a much higher temporal modulation rate than the rates at which visual or tactile information is encoded at the periphery, but discharge synchrony rates are similar across sensory cortical areas. The slow-down of temporal response rate along the ascending auditory pathway is necessary for rapid auditory information to be integrated in the cerebral cortex with information from other sensory modalities that is intrinsically slower.

An important implication of the study on repetition rate coding (Lu et al., 2001b) is that it demonstrates the two types of neural coding strategies: isomorphic and non-isomorphic representations. These coding strategies are also found in representing other stimulus features by A1 besides inter-click intervals. Another example of the non-isomorphic representation is the coding of the spectral envelope. Whereas the gross shape of the spectral envelope of a complex sound (e.g. a marmoset vocalization) is encoded by tonotopically organized neurons (an isomorphic representation) (Wang et al., 1995), finer features of the spectral envelope such as the spectral contrast are encoded by A1 neurons with discharge rate (a non-isomorphic representation) (Barbour and Wang, 2003a,b). In comparison, neural representations of a click train or a vowel's spectrum at the auditory periphery are entirely isomorphic (up to the phys-

ical limit of receptors). It is likely that non-isomorphic transformations take place progressively along the ascending auditory pathway leading to auditory cortex, making cortical representations further away from physical (acoustical) structures of sounds, but presumably closer to internal representations underlying auditory perception. The non-isomorphic transformation observed in auditory cortex is possibly an intermediate stage for the transformation from acoustical to perceptual dimension. The cortical representation of pitch is an example of acoustical-to-perceptual transformation (Bendor and Wang, 2005, 2006).

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