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REVIEW

NEURAL CODING OF TEMPORAL INFORMATION IN AUDITORY THALAMUS AND CORTEX

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Abstract—How the brain processes temporal information embedded in sounds is a core question in auditory research. This article synthesizes recent studies from our laboratory regarding neural representations of time-varying signals in auditory cortex and thalamus in awake marmoset monkeys. Findings from these studies show that 1) the primary auditory cortex (A1) uses a temporal representation to encode slowly varying acoustic signals and a firing rate–based representation to encode rapidly changing acoustic signals, 2) the dual temporal-rate representations in A1 represent a progressive transformation from the auditory thalamus, 3) firing rate–based representations in the form of a monotonic rate-code are also found to encode slow temporal repetitions in the range of acoustic flutter in A1 and more prevalently in the cortical fields rostral to A1 in the core region of marmoset auditory cortex, suggesting further temporal-to-rate transformations in higher cortical areas. These findings indicate that the auditory cortex forms internal representations of temporal characteristics of sounds that are no longer faithful replicas of their acoustic structures. We suggest that such transformations are necessary for the auditory cortex to perform a wide range of functions including sound segmentation, object processing and multi-sensory integration. © 2008 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: auditory cortex, medial geniculate body, marmoset, temporal processing, neural coding.

Contents

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 melodies and rhythms (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. For the auditory system, time is an essential variable of sensory inputs (Rosen, 1992). This is fundamentally different from other sensory systems (e.g. visual and somatosensory systems) where sensory inputs can be static.

An acoustic signal's temporal information is directly represented by the temporal patterns of neural activity throughout the initial stages of the auditory pathway. At the auditory periphery, auditory-nerve fibers faithfully represent fine structures of complex sounds in their temporal discharge patterns (Johnson, 1980; Palmer, 1982; Joris and Yin, 1992; Wang and Sachs, 1993). At subsequent processing stations along the ascending auditory pathway, the upper limit of this stimulus synchronized temporal representation gradually decreases (e.g. cochlear nucleus (CN): Blackburn and Sachs, 1989; Frisina et al., 1990; Wang and Sachs, 1994; Rhode and Greenberg, 1994; inferior colliculus (IC): Langner and Schreiner, 1988; Batra et al., 1989; Müller-Preuss et al., 1994; Krishna and Semple, 2000; Liu et al., 2006; medial geniculate body (MGB): Creutzfeldt et al., 1980; de Ribaupierre et al., 1980; Rouiller et al., 1981; Preuss and Müller-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 Müller-Preuss, 1996; Lu and Wang, 2000; Wallace et al., 2002; Liang et al., 2002; Phan and Recanzone, 2007; Malone et al., 2007), due to biophysical properties of neurons and temporal integration of converging inputs from one station to the next (Wang and Sachs, 1995; Young and Sachs, 2008). 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 that are perceived by humans and animals.

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 (Joris et al., 2004; Joris and Smith, 2008). At the level of the auditory nerve, the temporal pattern of an acoustic signal and that of corresponding neural firings are well matched (to the limit of the phase-locking). It has become clear after many years of research that the precision of this temporally-based neural representation gradually decreases at successive processing stations. The question addressed here 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 us better understand neural coding strategies in auditory cortex. The mechanism by which the auditory cortex solves the problem of representing time-varying signals serves as a good model to understand a fundamental principle of cortical processing: the transformation of stimulus features into internal representations that are no longer faithful replicas of their physical structures.

TEMPORAL AND FIRING RATE–BASED REPRESENTATIONS OF TIME-VARYING SIGNALS IN AUDITORY CORTEX: SYNCHRONIZED AND NON-SYNCHRONIZED CORTICAL RESPONSES

It has long been noticed that neurons in the auditory cortex do not faithfully follow rapidly changing stimulus components (Goldstein et al., 1959; Whitfield and Evans, 1965; de Ribaupierre et al., 1972). 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 (Palmer, 1982; Joris and Yin, 1992). The upper limit of synchronized auditory cortical responses appeared to be similar when measured by amplitude-modulated sounds (Schreiner and Urbas, 1988) or acoustic pulse trains (Lu and Wang, 2000) in neurons tuned to high best frequencies or by pure tones in neurons tuned to low best frequencies (Wallace et al., 2002).

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 Müller-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; Lu and Wang, 2004). We observed that when a sequence of sounds was presented as stimuli (Fig. 1A), the responses of some neurons in the primary auditory cortex (A1) were time-locked to individual sound events (Fig. 1B), whereas other neurons did not (Fig. 1C). The latter groups of neurons appeared to respond to sound events that were separated by short time intervals. On the basis of such hints, we investigated the responses of A1 neurons to time-varying sounds using periodic acoustic pulse trains whose inter-click intervals (ICIs) were systematically varied (Lu et al., 2001b). Two types of cortical responses to periodic click trains were observed (Fig. 2A, B). One type of cortical response exhibited significant stimulus-synchronized responses to click trains at long ICIs (>~25 ms) but diminished at shorter ICIs (Fig. 2A). The second type of cortical response did not exhibit stimulus-synchronized discharges, but instead showed monotonically changing discharge rate at short ICIs (Fig. 2B).

Neurons in both the synchronized and non-synchronized populations were found to be selective to the temporal asymmetry of an acoustic signal's envelope within a short time window (Lu et al., 2001a,b). When the repetition period of the ramped and damped sinusoids (see the inset above Fig. 2C, D) was systematically varied, a neuron could show stimulus-synchronized discharge patterns at long repetition periods and, at the same time, an overall selectivity to temporal asymmetry (Fig. 2C). As shown by the example of a synchronized neuron in Fig. 2C, discharge rates to damped sinusoids were consistently higher than those to the ramped sinusoids for almost all repetition periods tested. Stimulus-synchronized neurons with selectivity to ramped stimuli were also encountered (Lu et al., 2001b). The observation in Fig. 2C indicates that the explicit temporal representation of inter-stimulus interval at coarser time scales can occur concurrently with a firing rate-representation of fine temporal features by single neurons. The selectivity of temporal asymmetry at different repetition periods was observed in non-synchronized neurons as well. In the example of a non-synchronized neuron illustrated in Fig. 2D, as the repetition period was increased from 3 ms to 20 ms, discharge rates decreased in a similar manner to responses to click-train stimuli while overall responses to the ramped sinusoids were stronger than to the damped sinusoids. These observations suggest that within the non-synchronized population, firing rate-representations of two different temporal features can occur concurrently in the same neuron. These results indicate that a neuron's preference to rapid temporal changes within a short time window was largely independent of its response property as defined by sequential stimuli.
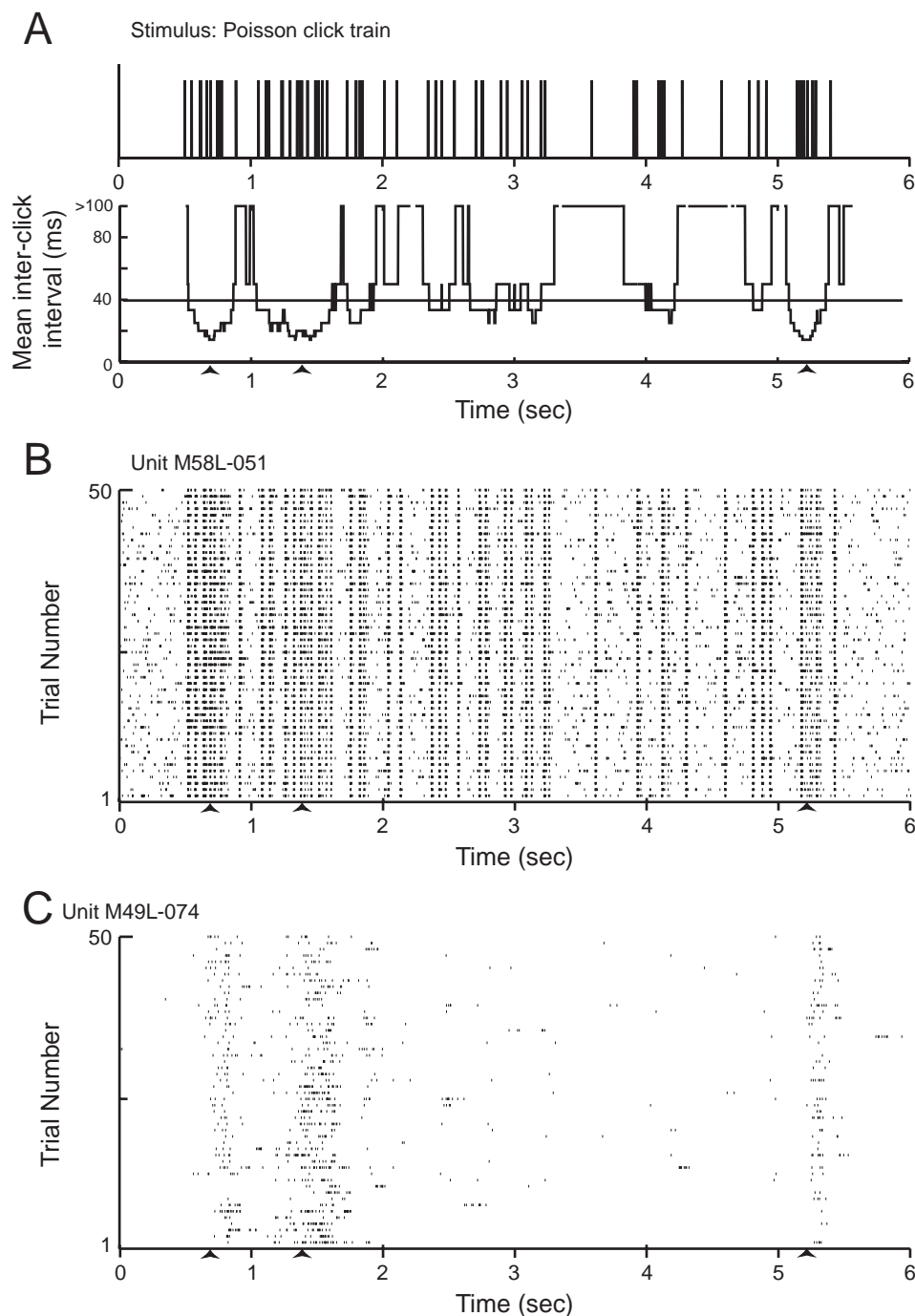
Fig. 1. Examples of two distinct types of cortical responses to aperiodic click trains. (A) *Upper*: illustration of the stimulus, a Poisson-distributed click train (duration: 5 s, stimulus onset/offset times: [0.5, 5.5] s). *Lower*: mean ICI of the click train (averaged over a moving time window of 200 ms). For clarity, mean ICIs longer than 100 ms are truncated in the plot. The three arrows on the *x* axis point to the times where the click train has the three shortest mean ICIs (also marked on the *x* axis of B and C). (B) Dot raster of the response of an example A1 (A1) neuron to 50 repetitions of the click train stimulus shown in A. This neuron exhibits time-locked firings to many individual clicks. (C) Dot raster of the response of another example A1 neuron (same format as in B). This neuron only fires at selective times when ICIs are sufficiently short. Data are from Lu et al. (2001b).

The observations that A1 neurons are responsive to both rapid changes within a short time window and the inter-stimulus intervals suggest that discharge rate–based mechanisms are responsible for encoding rapid time-varying signals. The two populations of A1 neu-

rons, referred to as *synchronized* and *non-synchronized* populations, appeared to encode repetitive stimuli by spike timing and average discharge rate, respectively (Fig. 3). Neurons in the synchronized population showed stimulus-synchronized discharges at long inter-stimulus
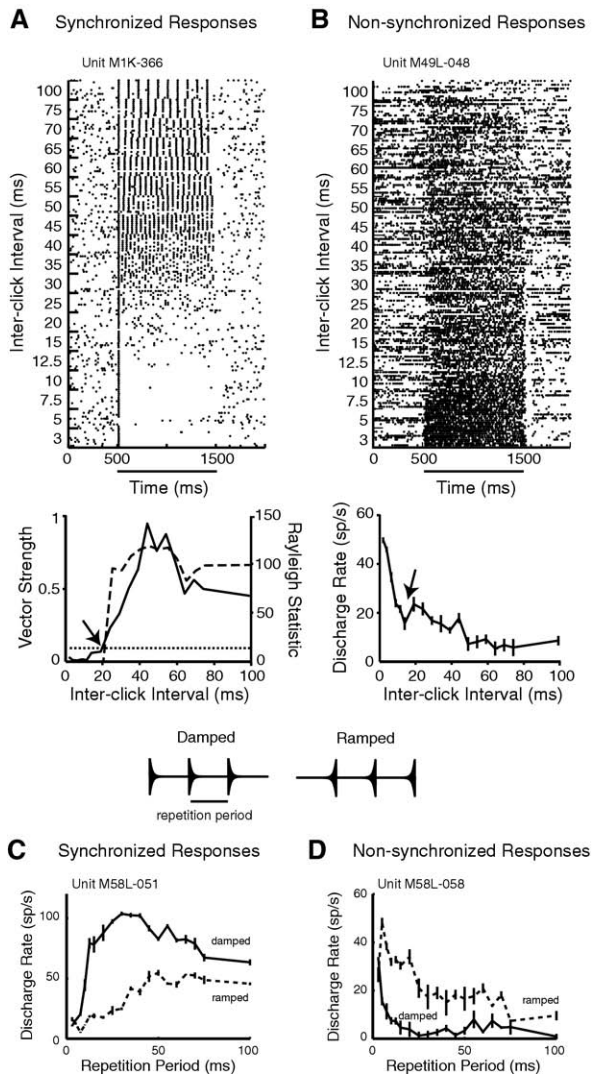
A Synchronized Responses

Unit M1K-366

B Non-synchronized Responses

Unit M49L-048

Damped

Ramped

repetition period

C Synchronized Responses

Unit M58L-051

D Non-synchronized Responses

Unit M58L-058

Fig. 2. Two distinct types of cortical responses to periodic click trains. (A) An example of stimulus-synchronized responses to click trains recorded from A1 of awake marmosets. *Top*: Dot raster. The horizontal bar below *x* axis indicates the stimulus duration (1000 ms). *Bottom*: Vector strengths (dashed line) and Rayleigh statistics (solid line) analyzed for the stimulus-synchronized responses shown in the top plot. 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. (B) An example of non-synchronized responses to click trains recorded from A1 of awake marmosets. *Top*: Dot raster. *Bottom*: Driven discharge rate is plotted versus ICI for the non-synchronized responses shown in the top plot. Vertical bars represent standard errors of the means (S.E.M.). The arrow indicates calculated rate-response boundary. (C) Response of a synchronized neuron to a sequence of ramped or damped sinusoids with different repetition periods (3–100 ms) and a fixed half-life (Lu et al., 2001a). This neuron responded more strongly to damped sinusoids across different repetition periods. Average discharge rates for ramped (*dashed line*) and ramped (*solid line*) stimuli are plotted as functions of stimulus repetition period. Vertical bars represent standard errors of the means (S.E.M.). (D) Example of a non-synchronized neuron that responded more strongly to ramped sinusoids across different repetition periods. The format is the same as in C. Adapted from Lu et al. (2001b). The inset above C and D shows examples of ramped and damped sinusoids.
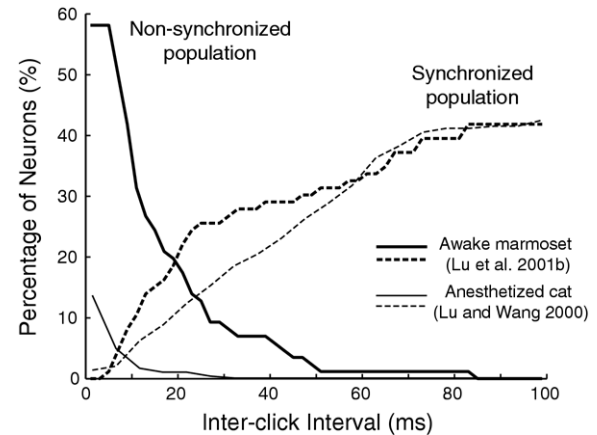

Fig. 3. Dual mechanisms for encoding slow and fast repetition rates by two populations of auditory cortex neurons. A combination of temporal and rate representations can encode a wide range of ICIs. The dashed line shows the percentage of neurons with synchronization boundaries less than or equal to 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.

intervals, but few responses at short ICIs. This population of neurons can thus represent slowly occurring temporal events *explicitly* using a temporal code. The representation of ICI 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 ICIs. 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. 3).

Neural responses to click trains observed in awake marmoset A1 (Lu et al., 2001b) differ fundamentally from those observed in anesthetized animals (Joris et al., 2004). The most crucial difference between the two conditions lies in "non-synchronized responses." For example, whereas a large proportion of neurons in A1 of awake marmosets exhibited prominent sustained firing throughout 1-s long click trains at short ICIs (Fig. 2B), only a small proportion of neurons in A1 of anesthetized cats responded to click trains at short ICIs and they did so by firing transiently after stimulus onset (Lu and Wang, 2000). We never observed any non-synchronized discharges in anesthetized cats that lasted throughout the duration of click trains at short ICIs (Lu and Wang, 2000), nor did any previous studies in anesthetized animals.
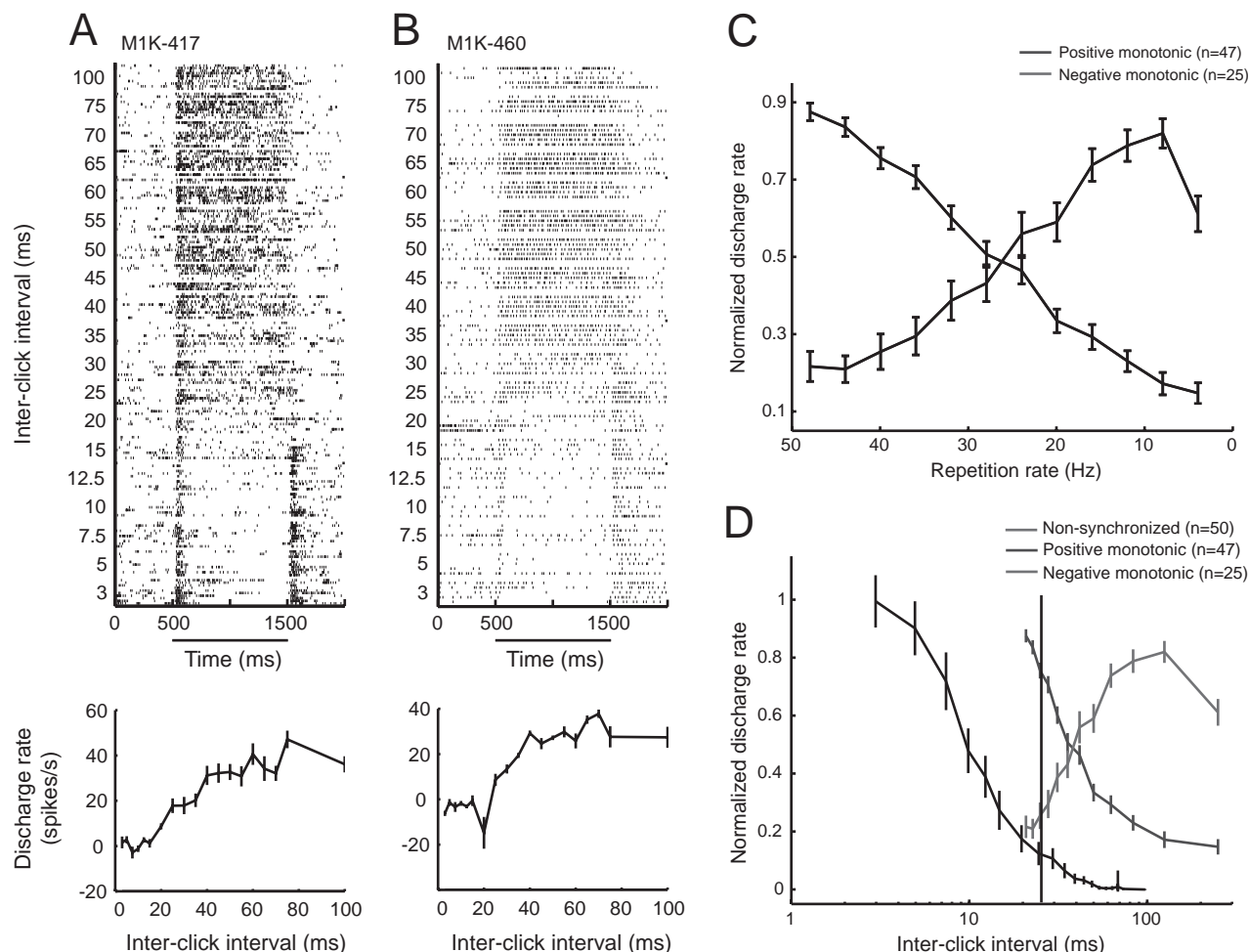
Fig. 4. Positive and negative monotonic tuning in firing rate of auditory cortex neurons. (A, B) Two examples of negative monotonic neurons that exhibit unsynchronized responses to periodic click trains within the perceptual range of acoustic flutter recorded from the awake marmoset auditory cortex. *Top*: Dot raster. *Bottom*: Driven discharge rate is plotted versus ICI. Vertical bars represent standard errors of the means (S.E.M.). Data are from Lu (2002). (C) Normalized discharge rates for positive (solid curve) and negative (dashed curve) monotonic neurons plotted versus repetition rate. This figure only includes data from unsynchronized neurons, a subset of data included in Fig. 2b of Bendor and Wang (2007). Error bars represent standard error of the mean (S.E.M.). (D) Comparison between non-synchronized (dotted curve), positive monotonic (solid curve) and negative monotonic (dashed curve) neurons. Normalized discharge rates are plotted as a function of ICI. The vertical dashed line marks the perceptual boundary between flutter and pitch at 40 Hz (25 ms). The upper limit of flutter is ~45 Hz and the lower limit of pitch is ~30 Hz. Data of non-synchronized neurons are from Lu et al. (2001b). Data of positive and negative monotonic neurons are the same as in C.

FIRING-RATE BASED REPRESENTATIONS OF TIME-VARYING SIGNALS IN AUDITORY CORTEX: POSITIVE AND NEGATIVE MONOTONIC RATE TUNING

Findings shown in Figs. 2 and 3 demonstrated that A1 neurons could encode rapid time-varying signals using firing-rate-based mechanisms. In our earlier experiments in awake marmoset auditory cortex, we also observed a small sample of neurons that responded to click trains in a manner opposite to the "non-synchronized neurons" illustrated in Fig. 2 (Lu, 2002). These neurons responded to the click trains with an increasing firing rate when the ICI became longer but surprisingly showed no stimulus-synchronized firing at these long ICIs (Fig. 4A, B). Comparing the unit in Fig. 4A with the synchronized unit shown in Fig. 2A, one notices that both responded to increasing ICI,

but the former showed no stimulus-synchronized firing whereas the latter did. In a recent study (Bendor and Wang, 2007), we systematically investigated this type of neural responses in marmoset auditory cortex and found that such responses exist in a substantial number of neurons in both A1 and more prevalently in auditory fields rostral to A1. We use the term "unsynchronized responses" to refer to the responses to acoustic pulse trains lacking stimulus-synchronized firings, whether in the domain of short or long inter-stimulus intervals.

The study by Bendor and Wang (2007) showed that auditory cortex neurons could respond with "unsynchronized responses" to decreasing or increasing ICI (or equivalently to increasing or decreasing repetition rate) with monotonically increasing firing rate. We referred to these two types of unsynchronized neurons as being "positive

monotonic" and "negative monotonic," respectively (Bendor and Wang, 2007). Fig. 4C and 4D shows the population-averaged firing rate as a function of repetition rate or ICI for these two neuronal populations, respectively. Positive monotonic unsynchronized neurons showed a similar trend as the "non-synchronized" neurons reported in Lu et al. (2001b), i.e. increasing firing rate with decreasing ICI (or increasing repetition rate), except that they encoded a different range of ICIs (Fig. 4D) that corresponded to the perceptual range of acoustic flutter (Miller and Taylor, 1948). Non-synchronized neurons instead utilized a rate code to represent repetition rates above the range of acoustic flutter and within the range of pitch (Krumbholz et al., 2000). Negative monotonic unsynchronized neurons showed the opposite trend as the "non-synchronized" neurons. The positive and negative monotonic rate tuning can also be seen if both synchronized and unsynchronized neurons were included (see Fig. 2b of Bendor and Wang, 2007). These observations suggest that firing rate–based coding mechanisms play a much bigger role in representing time-varying sounds than previously thought even within the ICI range that stimulus synchronization can occur in cortical neurons.

Our findings in marmosets suggest that the auditory and somatosensory cortex (Salinas et al., 2000; Luna et al., 2005) may encode time-varying signals using similar strategies. The boundary between perceiving discretely occurring events (flutter) and a fusion of individual events into a continuous stream (vibration/pitch) happens at roughly the same repetition rate (40 Hz) in the two sensory systems. In both A1 and S1, one neural population encodes flutter stimuli with a stimulus synchronized rate code, while a second neural population encodes pitch/vibration with a non-synchronized monotonic rate code. Matching the perceptual boundary between flutter and vibration/pitch, the neural coding boundary between these two neural populations is also at a repetition rate of 40 Hz. Therefore the similarities between these two sensory systems suggest that the neural coding strategy (temporal or rate representation) and neural coding boundaries have a direct consequence on the percept (flutter versus vibration/pitch) and perceptual boundaries irrespective of the sensory modality.

COMPARISON OF TEMPORAL CODING PROPERTIES IN A1 AND THE ROSTRAL CORE FIELDS

In the core region of primate auditory cortex, two auditory fields (R and RT) rostral to A1 have been identified (Morel and Kaas 1992; Kaas and Hackett 2000). We observed that synchronized neurons were more commonly found in A1, whereas a higher percentage of unsynchronized neurons was found in the rostral fields (Bendor and Wang, 2007). Fig. 5A shows spatial distributions of synchronized and unsynchronized neurons in A1 and rostral fields recorded from awake marmoset monkeys (Bendor and Wang, 2007). The spatial distributions were significantly different between synchronized and unsynchronized neu-
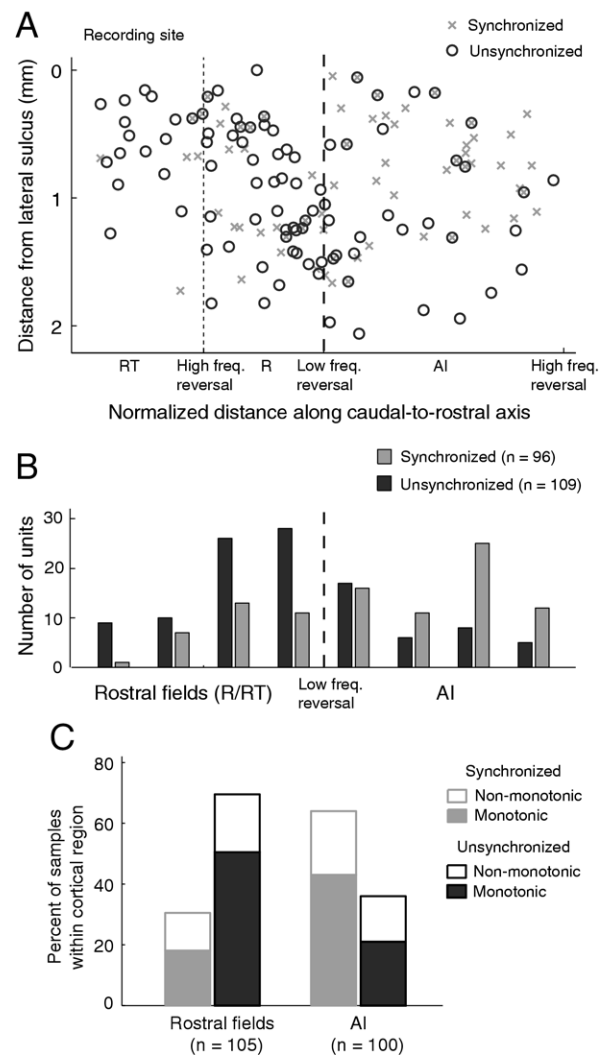

Fig. 5. Distributions of synchronized and unsynchronized neurons in A1 and the rostral fields (R, RT) of marmosets. (A) Spatial distributions of synchronized (cross) and unsynchronized (circle) neurons in A1 and rostral fields based on data four hemispheres (three left, one right). Normalized recording site positions are shown. The distributions are obtained by first creating a normalized map of recording sites across all animals based on the cochleotopic gradient, and then comparing recording site locations along the caudal-to-rostral and medial-to-lateral axis, respectively. (B) A histogram showing the spatial distribution of synchronized (gray bars) and unsynchronized (black bars) neurons across A1 and the rostral fields. (C) Comparison of the proportion of monotonic (filled bar) and non-monotonic (unfilled bar) responses to repetition rate for synchronized (gray bars) and unsynchronized (black bars) neurons in A1 and the rostral fields. Adapted from Bendor and Wang, (2007).

rons along the caudal-to-rostral axis, parallel to the lateral sulcus (Fig. 5B) but not along the medial-to-lateral axis perpendicular to the lateral sulcus (Bendor and Wang, 2007). Furthermore, there was no significant difference in the distribution of synchronized and unsynchronized neurons within A1 along the caudal-to-rostral axis (Fig. 5B). Roughly two-thirds of the synchronized neurons were located in A1, while two-thirds of the unsynchronized neurons were located in the rostral fields (Fig. 5C). Data in Fig.

5C further show that the change from a synchronized to an unsynchronized response between A1 and the rostral fields occurred mainly in the monotonic population. These findings show that the degree of synchronization in neural firings drops in the rostral fields and a monotonic rate code is used in place of the temporal representation. Neurons encoding flutter with unsynchronized positive and negative monotonic responses have also been observed in secondary somatosensory cortex (Salinas et al., 2000; Luna et al., 2005), suggesting that the auditory and somatosensory system also have similar neural coding strategies for flutter in non-primary cortical areas.

Similar proportions of neurons with positive and negative monotonic responses were observed in the rostral fields, whereas the majority of A1 neurons (~70%) were positive monotonic (Bendor and Wang, 2007). Synchronized neurons in both A1 and the rostral fields had stimulus-synchronized discharges over the entire range of acoustic flutter. Unsynchronized neurons in both A1 and the rostral fields did not synchronize within the range of flutter but had significant mean population vector strengths at repetition rates below the lower limit of flutter. These findings demonstrate that the temporal-to-rate transformation continues within the core region of the auditory cortex. More specifically, these and other findings from marmoset auditory cortex show that a second temporal-to-rate transformation takes place in auditory cortex over the perceptual range of acoustic flutter (Bendor and Wang, 2007), while the first temporal-to-rate transformation in "non-synchronized neurons" is over the range of pitch (Lu et al., 2001b). Thus, flutter's discrete (non-fused) percept may be due to the fact that there is significant stimulus synchronization occurring in A1 over its perceptual range, whereas at higher repetition rates, fusion occurs (in the range of pitch) as a reliable temporal representation of repetition rate is no longer available. The differential roles of non-synchronized neurons and pitch-selective neurons (Bendor and Wang, 2005) in the representation of pitch are still an open question.

COMPARISON OF TEMPORAL AND RATE REPRESENTATIONS AT A1 AND MGB

Our work in the auditory cortex of awake marmoset demonstrated a shift of neural coding from temporal to firing rate–based representations. To what extent is the cortical representation different from its preceding stage, the auditory thalamus? To address this question, we studied MGB responses to the same type of temporally modulated stimuli (click train) in awake marmosets (Bartlett and Wang, 2007). We found that MGB neurons had much lower synchronization boundaries than A1 neurons, i.e. MGB neurons were able to synchronize to much faster repetition rates than A1 neurons (Fig. 6A). The median synchronization boundary for MGB neurons was 5.2 ms (Bartlett and Wang, 2007), compared with the median synchronization boundary of 21.3 ms for A1 neurons (Lu et al., 2001b). On the other hand, the boundaries of non-synchronized responses in MGB neurons were also shifted to shorter ICIs compared with cortical neurons. The median non-synchronized rate-boundary of MGB neurons
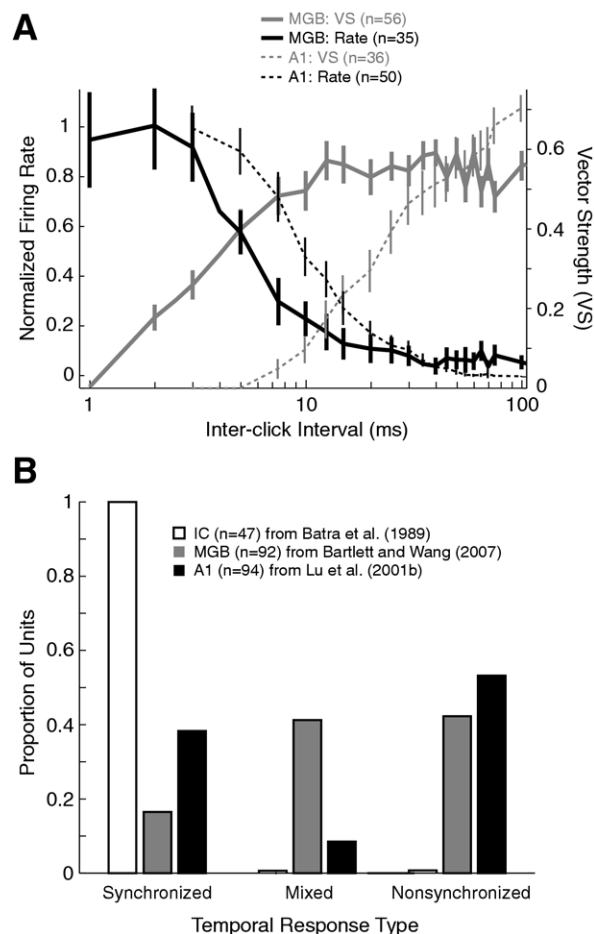
Fig. 6. Comparison of temporal response properties between auditory cortex and subcortical regions. (A) Comparison between A1 and MGB. Stimulus-synchronized firings are quantified by the vector strength (VS) (A1: *thin gray dashed curve*. MGB: *thick gray solid curve*, including both synchronized and mixed neurons). Non-synchronized firings are quantified by the normalized firing rate (A1: *thin black dashed curve*. MGB: *thick black solid curve*). Error bars represent standard error of the mean (S.E.M.). MGB data are from Bartlett and Wang (2007). A1 data are from Lu et al. (2001b). (B) MGB transitions the transformation from a synchronized representation in IC to synchronized and non-synchronized representations in auditory cortex. The proportion of units in each auditory region (IC: *open bars*, MGB: *gray bars*, A1: *black bars*) is plotted for each temporal response type (synchronized, mixed and on-synchronized). IC data are from Batra et al. (1989). MGB data are from Bartlett and Wang (2007). A1 data are from Lu et al. (2001b). The total number of units from each region is shown in parentheses. Adapted from Bartlett and Wang (2007).

was 5.7 ms (Bartlett and Wang, 2007), compared with the median non-synchronized rate-boundary of 12.9 ms in A1 neurons (Lu et al., 2001b).

The synchronized and non-synchronized populations of neurons in the MGB and A1 represented complementary ICI ranges by stimulus-synchronized temporal representation and non-synchronized firing-rate representation. As shown in Fig. 6A, the MGB firing rate of non-synchronized neurons was near maximal at short ICIs (≤3 ms) and decreased rapidly at longer ICIs (3–10 ms). Over this same ICI range, the MGB population vector strength increased rapidly. The MGB temporal and rate representations are clearly segre-

gated at ~10 ms ICI (Fig. 6A, solid curves), whereas the A1 temporal and rate representations are not clearly segregated until ~30 ms ICI (Fig. 6A, dashed curves).

Our data from MGB and A1 of awake marmosets show that there is a greater degree of temporal-to-rate transformation in A1 than in MGB. The data also showed that there were clearly non-synchronized responses in MGB, although we only observed positive monotonic tuning for repetition rate. There has been little evidence of non-synchronized responses in IC from the literature. In Fig. 6B, we compare the data recorded from single-units in unanesthetized animals from IC (Batra et al., 1989, rabbits), MGB (Bartlett and Wang, 2007, marmosets) and A1 (Lu et al., 2001b, marmosets). The main difference between IC, MGB and A1 representations of repetition rate appears to be in the creation of separate synchronized and non-synchronized responses at MGB and A1. The MGB acts as a transition stage in this transformation with the emergence of non-synchronized responses. An interesting and puzzling observation is the relatively large proportion of "mixed responses" in MGB, in which both synchronized and non-synchronized responses were present in the same neuron at long and short ICIs, respectively (Bartlett and Wang, 2007). In contrast, only a small proportion of neurons were found to have the mixed responses in A1 (Fig. 6B). It is yet unclear whether the non-synchronized and mixed responses observed in MGB are the result of a cortico-thalamic feedback loop or are generated within MGB, given that they do not appear to exist in IC according to previous studies in unanesthetized animals (e.g. Batra et al. 1989). These important issues require further studies in awake animals in which cortico-thalamic feedback circuits are experimentally manipulated.

DIFFERENCES BETWEEN AWAKE AND ANESTHETIZED AUDITORY CORTEX AS REVEALED BY RESPONSES TO TIME-VARYING SIGNALS

A striking difference between awake and anesthetized auditory cortex is prevalent sustained firing in response to time-varying sound (Wang et al., 2005). 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 auditory cortex neurons to click train stimuli in both awake marmosets (Lu et al., 2001b; Bendor and Wang, 2007) 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 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 (Lu, 2002). 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. 3). This finding is consistent with the earlier finding shown by Goldstein et al. (1959). Third, and most importantly, the large number of unsynchronized neurons at both short and long ICIs observed in the auditory cortex of awake marmosets (Lu et al., 2001b; Bendor and Wang, 2007) was not observed in anesthetized cats (Lu and Wang, 2000). Although these comparisons are made between 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. Another outstanding question is whether neurons with unsynchronized responses observed in the awake condition would remain silent in the anesthetized condition or discharge in a different manner. Given the prevalence of neurons with non-synchronized responses in awake marmoset auditory cortex and the scarcity of such responses in anesthetized animals, we suggest that anesthesia disrupts neural processing that leads to the unsynchronized cortical responses. A recent study compared neural responses in A1 between anesthetized and unanesthetized conditions and showed that anesthesia had profound effects on the trial-to-trial variability and reliability of discharge and thus significantly altered temporal firing patterns of A1 neurons (Ter-Mikaelian et al., 2007).

FUNCTIONAL IMPLICATIONS OF TEMPORAL-TO-RATE TRANSFORMATION IN AUDITORY CORTEX

The prevalence of rate-coding neurons in auditory cortex has important functional implications. It shows that considerable temporal-to-rate transformations have taken place by the time auditory signals reach the auditory cortex. The importance of the "unsynchronized" neural responses is that they represent processed instead of preserved temporal information. 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 (Wang et al., 2003). 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. 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 primary sensory cortical

areas. The slowdown of temporal response rate along the ascending auditory pathway and accompanying temporal-to-rate transformation is necessary for rapid auditory information to be integrated in the cerebral cortex with information from other sensory modalities processed at slower rates. It is also possible that the neural circuits for memory operate using firing-rate codes (Romo et al., 1999; Sakai and Miyashita, 1991), and therefore all information, including temporal information, must be ultimately represented using firing rate.

The prevalence of unsynchronized neural firing in auditory cortex of awake animals also poses technical challenges for quantitatively characterizing such responses. Methods that rely on precise stimulus-locked discharges such as commonly used spike-triggered averaging techniques are inadequate to characterize neurons with unsynchronized responses. Alterative methods that take into consideration of such cortical firing patterns need be utilized (Yu and Young, 2000; Barbour and Wang, 2003a,b) and further developed.

Whereas we have emphasized the importance of firing-rate-based codes in this article, a number of studies have suggested roles for spiking timing in information coding in auditory cortex under various physiological and behavioral conditions. For example, Walker et al. (2008) showed that neurometrics based on the temporal discharge patterns of populations of ferret A1 neurons closely matched the psychometric performance curve of human listeners in detecting local time reversals in a marmoset twitter call, but only if the spiking patterns were resolved at temporal resolutions of 20 ms or better. Spike timing in auditory cortex (mostly in the form of first or onset spike latency) has also been suggested to play a role in discriminating animal vocalizations (Schnupp et al., 2006), in tracking fine temporal structure of complex sounds (Elhilali et al., 2004), in conveying location-related information (Furukawa and Middlebrooks, 2002) and in encoding acoustic parameters (Heil, 2004). It should be pointed out that most of previous studies on spike timing were conducted in anesthetized animals. A recent study by Ter-Mikaelian et al. (2007) showed that anesthesia can in fact significantly increase the temporal precision of A1 neurons to both tones and amplitude-modulated stimuli, suggesting that the role of spike timing must be considered in the absence of anesthesia.

In our own analyses of spike timing based on recordings from awake marmoset auditory cortex, we showed that the spike timing on the occurrence of acoustic events was 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 (Lu and Wang, 2004). When it comes to the question of how auditory thalamus and cortex neurons encode time-varying signals, it is not simply an issue of whether spike timing is important, but *when* it is important, i.e. under what stimulus conditions and in which population of neurons.

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