Neuronal activation times to simple, complex, and natural sounds in cat primary and nonprimary auditory cortex

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Carrasco A, Lomber SG. Neuronal activation times to simple, complex, and natural sounds in cat primary and nonprimary auditory cortex. J Neurophysiol 106: 1166–1178, 2011. First published June 8, 2011; doi:10.1152/jn.00940.2010.—Interactions between living organisms and the environment are commonly regulated by accurate and timely processing of sensory signals. Hence, behavioral response engagement by an organism is typically constrained by the arrival time of sensory information to the brain. While psychophysical response latencies to acoustic information have been investigated, little is known about how variations in neuronal response time relate to sensory signal characteristics. Consequently, the primary objective of the present investigation was to determine the pattern of neuronal activation induced by simple (pure tones), complex (noise bursts and frequency modulated sweeps), and natural (conspecific vocalizations) acoustic signals of different durations in cat auditory cortex. Our analysis revealed three major cortical response characteristics. First, latency measures systematically increase in an antero-dorsal to postero-ventral direction among regions of auditory cortex. Second, complex acoustic stimuli reliably provoke faster neuronal response engagement than simple stimuli. Third, variations in neuronal response time induced by changes in stimulus duration are dependent on acoustic spectral features. Collectively, these results demonstrate that cortical circuitry; latency measures; extracellular recording; conspecific vocalizations; frequency modulated sweeps; stream of activation in auditory cortex.

ACCURATE AND RAPID SEMANTIC interpretation of acoustic signals emitted by predators, mates, and food sources enhances the chances of survival and reproduction (Darwin 1859). Thus it is reasonable to assume that species that rely on auditory information as cues for communication possess a well-developed and efficient auditory processing system. In this study, we provide evidence for the presence of a directional pattern of neuronal activation among regions of auditory cortex in one such species, the carnivorous mammal Felis catus.

The auditory pathway of the domestic cat presents an excellent model for the investigation of cortical activation time. Pertinent to the present study are the observations of response latency characteristics of medial geniculate body (MGB) neurons (Calford 1983; Calford and Webster 1981; Lennartz and Weinberger 1992). These reports demonstrated that activation of neurons within the ventral nucleus of the MGB precedes the response engagement of neurons in the dorsal nucleus of the MGB during tonal stimulation. The reported difference in response latency of MGB neurons, in addition to the previously characterized thalamocortical connections in the cat (Huang and Winer 2000; Kishan et al. 2008; Lee and Winer 2008a; Winer et al. 2005), suggests that comparable differences in neuronal activation time should be present in regions of auditory cortex. Evidence for this proposition has been supported by investigations not only in cat (Carrasco and Lomber 2009a, 2009b; Eggermont 1999a, 1999b; Harrington et al. 2008; He and Hashikawa 1998; Imaizumi et al. 2004; Loftus and Sutter 2001; Rouiller et al. 1991; Schreiner and Urban 1988; Stecker et al. 2003, 2005) but also in other animals including guinea pig (Horikawa et al. 2001), rat (Polley et al. 2007; Reimer et al. 2011), ferret (Bizley et al. 2005), monkey (Kajikawa et al. 2005; Kikuchi et al. 2010; Recanzone et al. 2000), and human (Inui et al. 2006). While these studies have demonstrated that the arrival of acoustic information to auditory cortex varies among cerebral locations, they do not, however, provide information with regard to activation time variations provoked by spectral and temporal features of acoustic signals. Hence, the present investigation examined changes in response time induced by frequency modulated (FM) sweeps and conspecific vocalizations across various fields of auditory cortex.

Based on the aforementioned reports, we investigated the response latency of auditory cortical neurons during the presentation of artificially generated acoustic signals. In addition, natural and time-reversed cat vocalizations were used to investigate the effects of ecologically relevant information to cortical response time. In total, three hypotheses were established before data collection. First, neuronal response activity across auditory cortical fields displays an orderly pattern of activation. Second, acoustic signals with distinct spectral characteristics, but comparable duration time, have similar cortical response latencies. Third, ecologically relevant acoustic stimuli result in a distinct pattern of neuronal response characteristics compared with nonecologically relevant, but spectrally comparable, acoustic signals. Our results demonstrate that while substantial differences in response latency are present across fields of cat auditory cortex, response complexity is highly dependent on spectral and temporal acoustic features. Furthermore, our analysis revealed a systematic antero-dorsal to postero-ventral neuronal activation engagement among auditory cortical regions. Collectively, these findings demonstrate that while neuronal activation in auditory cortex is dependent on conduction times determined by neuroanatomic architecture, spectral and temporal acoustic characteristics play an important role in determining neuronal response latency.

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MATERIALS AND METHODS

Overview

Neuronal activity in response to simple, complex, and conspecific acoustic signals was measured in the right auditory cortex of nine adult (>6 mo) cats housed in an “enriched colony” where social interactions and toys were available 24 h a day. Human interactions and television programming were also provided during the workday. All procedures were approved by the University of Western Ontario Animal Use Subcommittee of the University Council on Animal Care and were implemented in accordance with the US National Research Council’s Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (2003) and the Canadian Council on Animal Care’s Guide to the Care and Use of Experimental Animals (Olfert et al. 1993).

Surgical Preparation

Animal preparation and recording procedures were performed as detailed in previous publications (Carrasco and Lomber 2009a). In brief, surgery was composed of two stages. First, cats were sedated with a cocktail of ketamine (4 mg/kg im) and Domitor (0.05 mg/kg im). An indwelling catheter was then placed in the cephalic vein. A 0.5 mg/kg intravenous injection of dexamethasone was administered, and animal recovery was monitored. Second, on the morning after presurgical procedures, the animal was premedicated with atropine (0.02 mg/kg sc) and acepromazine (0.02 mg/kg sc). A state of anesthesia was induced (pentobarbital sodium 25 mg/kg iv) and maintained with supplemental doses of pentobarbital sodium (Cheung et al. 2001). Anesthesia levels were monitored by electrocardiogram and blood oxygen concentration levels. A rectal probe was used to record body temperature, and a water-filled heating pad (Gaymar) maintained the core temperature of the animal at 37°C. The mucosa of the pharynx was anesthetized with a topical anesthetic (Cetacaine) to inhibit the gag reflex, and the trachea was intubated with a cuffed endotracheal tube to maintain adequate ventilation. Respiration was unassisted. A craniotomy was performed over the auditory cortex of the right hemisphere, and the dura was resected. Desiccation was prevented by applying a layer of silicone oil to the pial surface. A head-holder was attached to the frontal bone of the skull with dental acrylic and secured to a stereotaxic frame via a carrier (Kopf). Ear bars and palato-orbital restraints were removed to permit unobstructed access of acoustic signals. The exposed cortical region was digitally photographed to maintain a record of the location of each electrode penetration. Hydrating fluids, 2.5% dextrose/half-strength lactated Ringer solution (4 ml/kg -1 h-1 iv), were delivered via an infusion pump. Incidence of edema and respiratory secretions was reduced by administration of dexamethasone (1.0 mg/kg iv) and atropine (0.03 mg/kg sc) on a 12-h schedule.

Recording Procedures

Multiunit and single-unit neuronal activity was measured with Parylene-coated tungsten microelectrodes with impedances of 1–2 MΩ (FHC). Recordings were conducted at a depth of ~1,200 μm measured orthogonally from the cortical surface (layer IV). All recordings were limited to the crest of the gyri in an effort to reduce the likelihood of inconsistent laminae responses. Signals were band-pass filtered (500 Hz to 5,000 Hz), amplified (>10,000), and digitized at 25,000 Hz. Recording sessions varied in duration from 36 to 92 consecutive hours.

Stimulus Generation and Presentation

Recordings took place on an electrically shielded vibration-free table (Technical Manufacturing) enclosed within a double-walled sound chamber. Two sound transducers, TS-A1072R (Pioneer) and ECl (Tucker-Davis Technologies), were utilized. Transducers were placed immediately adjacent to each other during calibration and stimulus delivery. All signals were digitally generated with a 24-bit D/A converter at 156 kHz (Tucker-Davis Technologies) and delivered in the free field 15 cm away from the left ear, measured at the center of the head. Except for pure tone stimulation, all signals were presented at 65 dB sound pressure level (SPL). The present investigation reports unpublished neuronal response properties to pure tones, noise bursts, FM sweeps, and conspecific vocalizations from seven animals. Neuronal responses to pure tones were added and analyzed in conjunction with a set of recordings collected from two animals from previous studies conducted in the laboratory under comparable conditions.

Pure tones. Receptive fields were constructed by presenting 2,064 pure tones (5-ms rise and fall times, cosine squared gated, 25 ms in duration; Fig. 1A) in a pseudorandom order. The stimulus set consisted of 16 intensities ranging from 0 to 75 dB SPL in 5-dB steps and 129 frequencies in 1/16th-octave steps ranging from 250 Hz to 64,000 Hz. Each frequency-intensity combination was presented once at a rate of 2.5 Hz.

Frequency modulated sweeps. Logarithmic upward FM sweeps, 25, 50, 100, 250, and 500 ms in duration (5-ms rise and fall times, cosine squared gated), were presented 250 times each in a pseudorandom order at a rate of one repetition every 2 s (Fig. 1B). Each noise burst was composed of frequencies ranging from 1 to 32 kHz.

Conspecific vocalization. A cat vocalization 0.87 s in duration was presented. The vocalization was acquired from the laboratory of Jos Eggermont and has been used and described in a previous study (Gourewich and Eggermont 2007). The original acoustic signal was resampled to match the 156-kHz sampling rate of the other signals in the stimulus set. Subsequently, the signal was time-reversed. The resulting forward and backward meows were presented 100 times at a rate of 1 repetition every 3 s (Fig. 1D). The rise and fall times of the forward meow were ~0.2 and ~0.5 s, respectively.

Data Analysis

Neuronal activity was quantified and classified based on response latency and acoustic tuning characteristics. A custom-made computer program written in Matlab (MathWorks) was used to generate 1-ms binned peristimulus time histograms (PSTHs). Variability of response time was determined by constructing individual and group PSTHs. Response latencies were examined by measuring onset times, defined as the first bin in the PSTH exceeding 4 standard deviations above spontaneous activity levels, and peak times, defined as the first bin in the PSTH with the highest spike rate. Onset and peak mean response times were determined by averaging the corresponding measures of all recording sites within a cortical field. Note that mean values do not necessarily have to correspond to the time of peak activity in group PSTHs, as individual records may contain unusual responses such as increased activity at the offset of acoustic signals. In the case of pure tones, neuronal responses to signals of different intensities and frequencies were combined into a single PSTH. The characteristic frequency (CF) of receptive fields was defined as the tone frequency that evoked a reliable response at the lowest intensity level. Tuning characteristics were determined by an experienced observer blind to the stimulus conditions, and CF cortical representations were generated with Voronoi tessellation maps (Fig. 2) (Kilgard and Merzenich 1998). Variations in neuronal activity across time were evaluated with cumulative probability density functions. Auditory cortical field borders were delineated based on tonotopy (Carrasco and Lomber 2009a, 2009b).
In situations where single-unit activity was recorded in response to various acoustic signals, statistical significance was measured with a Wilcoxon signed-rank test. In contrast, statistical comparisons between the responses of separate neuronal clusters were conducted with a two-tailed unpaired Student t-test. The Wilcoxon signed-rank test was not adequate for neuronal cluster comparisons because multiunit recordings do not guarantee that neuronal activity was recorded from the same group of cells.

Fig. 1. Time and frequency domain illustrations of acoustic stimuli. A: representative illustration of an 8-kHz pure tone. The complete tonal stimulation set was composed of 16 intensities and 129 frequencies. B: white noise burst signal. The complete set of noise burst signals was composed of 25-, 50-, 100-, and 250-ms-long noise bursts. Note that short noise bursts and pure tones shared the same duration and rise-fall rates (A and B). C: first 10 ms of an upward frequency modulated (FM) sweep. Variations in duration were equivalent to the set of noise burst signals. D: spectrogram and time function of cat vocalization presented during recording procedures. Note that neuronal responses to time-reversed vocalization of this signal were also investigated.

Fig. 2. Schematic illustration of tuning organization in cat auditory cortex. A: location of specific fields of auditory cortex in cat cerebrum. Red square encompasses the fields presented in B. B: representative distribution of characteristic frequencies within cortical loci investigated. Borders (white lines) were defined based on tonotopic organization. Polygons correspond to estimation of cortical region with response properties similar to recorded site. A1, primary auditory cortex; A2, second auditory cortex; AAF, anterior auditory field; dPE, dorsal posterior ectosylvian area; DZ, dorsal zone of auditory cortex; FAES, auditory field of anterior ectosylvian sulcus; IN, insular region; iPE, intermediate posterior ectosylvian area; PAF, posterior auditory field; T, temporal region; VAF, ventral auditory field; vPAF, ventral posterior auditory field; vPE, ventral posterior ectosylvian area. The sulci are indicated by italics: aes, anterior ectosylvian sulcus; ss, suprasylvian sulcus; pes, posterior ectosylvian sulcus. D, dorsal; A, anterior; P, posterior; V, ventral.
RESULTS

The main objective of the present investigation was to quantify neuronal response latencies in primary and nonprimary fields of cat auditory cortex. Simple, complex, and conspecific acoustic stimuli were used to induce neuronal responses in primary auditory cortex (A1), second auditory field (A2), anterior auditory field (AAF), and the posterior auditory field (PAF). The results are presented in four sections. First, a description of electrophysiological response markers used during cortical field characterization is provided. Second,
changes in peak response latency measures provoked by variations in spectral composition of acoustic signals are compared. Third, onset and peak neuronal response latencies are analyzed as a function of stimulus duration. Last, changes in neuronal activation time induced by acoustic signals varying in spectral structure and recorded from the same set of single units are discussed.

Border Demarcation

Essential to the interpretation of functional results in the present study was the identification of border locations among auditory cortical regions. Demarcation of field boundaries was established based on CF distribution maps (Fig. 2). Specifically, reversals in frequency representation, lack of tonotopy, and anatomic location were used as interfield border determinants (Imaizumi et al. 2004; Knight 1977; Merzenich et al. 1973; Reale and Imig 1980). A reversal in frequency representation between A1 and AAF was generally observed near the dorsal tip of the anterior ectosylvian sulcus (aes). In contrast, frequency organization between A1 and PAF inverted near the posterior ectosylvian sulcus (pes) (Fig. 2). The border between A2 and A1 was determined by degradation of tonotopy ventral to A1 (Fig. 2). Dorsal zone of auditory cortex (DZ) borders were differentiated by proximity to the suprasylvian sulcus and lack of activation to simple acoustic stimuli near the dorsal posterior ectosylvian field (dPE) (Fig. 2). Finally, dPE was identified by a lack of response to pure tones (Fig. 2).

Response Latency to Acoustic Signals of Various Spectral Organizations

**Pure tones.** Response latencies of auditory cortical neurons were measured during pure tone exposure. In total, 2,064 tones of various frequencies and intensities were presented at each recording location (Fig. 1A). Onset response measures exhibited a progressive increase in time of engagement across an antero-dorsal to postero-ventral axis (onset latency means ± SE: AAF 10.66 ± 0.21 ms; A1 10.90 ± 0.22 ms; A2 13.67 ± 0.47 ms; PAF 15.13 ± 1.43 ms). Representative examples of neuronal activity variations across cortical fields are presented in Fig. 3. In addition, peak response analysis revealed similar differences in response latency among regions of auditory cortex. Generally, AAF neurons displayed early response latencies that preceded the sequential activation of A1, A2, and PAF neuronal engagement (peak latency means ± SE: AAF 16.11 ± 0.16 ms; A1 18.45 ± 0.23 ms; A2 24.51 ± 0.50 ms; PAF 38.26 ± 1.8 ms; Figs. 4 and 5A). Collectively, exposure to pure tones revealed a systematic increase in neuronal activation across an antero-dorsal to postero-ventral axis of auditory cortex.

**Noise bursts.** In addition to the simple structure of pure tones, the neuronal activity of A1, A2, AAF, and PAF neurons was measured in response to complex acoustic signals. Specifically, white noise bursts were used to determine neuronal response latencies (Fig. 1B). This analysis revealed constant onset response times across fields (onset latency means ± SE: AAF 8.68 ± 0.26 ms; A1 7.08 ± 0.14 ms; A2 7.31 ± 0.26 ms; PAF 7.89 ± 0.52 ms). However, peak cortical activation followed a progressive antero-dorsal to postero-ventral activation flow. Specifically, AAF neurons displayed response measures that preceded A1 peak latency times, while PAF and A2
neurons exhibited substantially longer activation times (peak latency means ± SE: AAF 12.29 ± 0.27 ms; A1 14.65 ± 0.60 ms; A2 20.0 ± 1.67 ms; PAF 18.76 ± 1.6 ms; Fig. 5B; note that latency values of individual units do not necessarily correspond with groups PSTH peaks; see Data Analysis in MATERIALS AND METHODS for explanation). This result demonstrates that cortical field location can be a crucial determinant of peak neuronal engagement time during complex acoustic signal exposure (Eggermont 1999b).

**Frequency modulated sweeps.** Environmental acoustic stimuli are generally composed of rapid variations in spectral characteristics. While the analysis of neuronal responses to pure tones and noise bursts is a valuable approach to the investigation of neuronal activation principles, such artificial

Fig. 5. Group multiunit peristimulus time histograms (PSTHs) in auditory cortex to short acoustic signals of various frequency compositions. A: PSTHs of response activity induced by 25-ms-long pure tones varying in frequency (250–64,000 Hz) and intensities (0–65 dB SPL). B: PSTHs of response activity induced by 25-ms-long white noise bursts at 65 dB SPL. C: PSTHs of response activity induced by 25-ms-long upward FM sweeps at 65 dB SPL. Note the consistent differences in response activity between cortical fields AAF → PAF regardless of acoustic signal stimulation. Colored regions represent ± SE. Nos. in parentheses indicate no. of recording sites per cortical field.

Fig. 6. Neuronal activation time evoked by forward and time-reversed conspecific vocalization. A: PSTHs of multiunit neuronal response activity induced by conspecific acoustic signal presentation in primary and nonprimary auditory cortical fields. B: PSTHs of multiunit neuronal response activity induced by time-reversed acoustic signal in auditory cortex. Note the long and delayed PAF response activity in both conditions. Colored regions represent ± SE. Nos. in parentheses indicate no. of recording sites per cortical field.
acoustic stimuli lack many of the properties found in naturally occurring sounds. There are, however, acoustic signals that can be generated in the laboratory to mimic aspects of sounds occurring in nature. One such stimulus is FM sweeps (Fig. 1C).

Hence, we recorded the activity of A1, A2, AAF, and PAF neurons during the presentation of upward FM sweep signals. Comparable to responses induced by pure tones and noise bursts, response activity times were identified among primary acoustic signals were presented at 65 dB SPL and lasted 25 ms. Note that in primary and nonprimary regions of auditory cortex, complex signals (noise burst) induced earlier response latencies than simple acoustic signals (tones).

Fig. 7. Effects of acoustic signal duration on neuronal activation time. A: PSTHs of multiunit response activity induced by 25-, 50-, 100-, 250-, and 500-ms-long white noise bursts in auditory cortex. Note that early peak activation of AAF neurons is followed by A1, A2, and PAF neuronal responses in all conditions. Furthermore, note that neuronal response latencies do not substantially vary as a function of stimulus duration. B: PSTHs of multiunit neuronal response activity induced by upward FM sweeps (1–32 kHz) of various durations. Note that while FM signals provoked complex neuronal responses, AAF activation preceded A1, A2, and PAF neuronal engagement. Lines under PSTHs correspond to stimulus duration. Colored regions represent ±SE. Nos. in parentheses indicate no. of recordings sites per cortical field.

Fig. 8. Cumulative neuronal activity response during exposure to simple and complex acoustic signals: cumulative probability density functions of single-unit activity induced by noise bursts and pure tones. Note that in primary and nonprimary regions of auditory cortex, complex signals (noise burst) induced earlier response latencies than simple acoustic signals (tones).
and nonprimary regions of auditory cortex (onset latency means ± SE: AAF 12.70 ± 0.26 ms, A1 17.72 ± 0.47 ms, A2 16.39 ± 0.70 ms, PAF 19.0 ± 0.91 ms; peak latency means ± SE: AAF 16.22 ± 0.31 ms, A1 23.84 ± 1.66 ms, A2 25.88 ± 5.0 ms, PAF 24.79 ± 1.39 ms; Fig. 5C; note that individual unit values do not necessarily coincide with group PSTH peaks; see Data Analysis in MATERIALS AND METHODS for explanation). This result demonstrates that the antero-dorsal to postero-ventral activation pathway observed during pure tone and noise burst stimulation is also present during acoustic signals that mimic natural sounds.

**Conspecific vocalizations.** In addition to artificially generated acoustic stimuli, we investigated the response of A1, A2, AAF, and PAF neurons during exposure to naturally occurring and time-reversed cat vocalizations (Fig. 1D). Ecologically relevant stimuli allowed the analysis of neuronal responses to a sound with (forward) and without (time reversed) species-specific relevance but analogous spectral frequency components. Similar to the responses observed during FM presentations, forward and time-reversed meows resulted in complex response patterns (Fig. 6). However, as observed with the other acoustic signals used in this investigation, AAF exhibited the earliest onset and peak responses (onset latency means ± SE: forward: AAF 14.22 ± 0.35 ms, A1 116.51 ± 16.97 ms, A2 41.58 ± 13.58 ms, PAF 54.67 ± 25.07 ms; backward: AAF 15.13 ± 0.31 ms, A1 72.50 ± 13.33 ms, A2 52.38 ± 8.17 ms, PAF 30.67 ± 3.56 ms; peak latency means ± SE: forward: AAF 59.97 ± 18.99 ms, A1 308.15 ± 38.10 ms, A2 234.56 ± 72.93 ms, PAF 306.35 ± 118.39 ms; backward: AAF 85.60 ± 16.0 ms, A1 499.36 ± 46.14 ms, A2 312.76 ± 63.97 ms, PAF 145.23 ± 44.1 ms). Note that while the strongest neuronal activity observed occurred at presentation onset, various subsequent peaks, presumably related to spectral components of the signal, were exhibited (Fig. 1D). Consistent with results of tones and FM sweeps in this investigation, this analysis demonstrates that, regardless of signal complexity and semantic

Fig. 9. Representative single-unit activity recorded in response to simple, complex, and conspecific acoustic signals in primary and nonprimary auditory cortex. Raster plots illustrate the neuronal activity from 4 distinct cortical fields in a single animal. Panels are arranged in cortical fields (rows) and acoustic signal characteristics (columns). Neuronal activity generated in response to noise bursts, upward FM sweeps, forward and time-reversed (backward) conspecific vocalizations, and pure tones are presented. Panels in the left 2 columns are subdivided by lines indicating signal duration changes. Compare the simple response characteristics induced by noise bursts, pure tone, and short FM sweeps to the intricate response characteristics of conspecific vocalizations and long FM sweeps.
Response Latencies to Acoustic Signals of Different Durations

Specific aspects of acoustic signals are recognized not by frequency structure but by changes in temporal information. In an effort to identify one of the features that carries temporal information in an acoustic signal, the impact of signal duration on neuronal response time was measured during noise bursts and upward FM sweeps of various durations (50, 100, 250, or 500 ms). In all conditions, response patterns comparable to those observed during exposure to short (25 ms) acoustic signals were revealed. In particular, despite changes in signal duration or spectral structure, AAF activation occurred prior to PAF neuronal engagement (Fig. 7). However, neuronal response patterns across conditions varied considerably. Specifically, noise burst exposure induced early peak activity irrespective of acoustic signal duration (Fig. 7A). In contrast, neuronal responses to FM sweeps were highly influenced by signal duration and generated sustained and intricate patterns of activation (Fig. 7B).

Spectral Composition Influences Response Time

Visual inspection of Fig. 5 reveals that noise bursts and pure tones induce distinct neuronal response latencies. However, conclusions about this observation could not be established because neuronal activity was not measured under comparable conditions. Specifically, while pure tones were presented at multiple intensities, noise bursts were generated at a constant intensity of 65 dB SPL. In addition, measures were not conducted in the same group of cells. Consequently, to test this observation neuronal activity of single units was collected during exposure to pure tones and noise bursts of comparable intensities (65 dB SPL). Group PSTHs were calculated for the same groups of neurons during noise and pure tone presenta-

Fig. 10. Distribution of peak response latencies in primary and nonprimary auditory cortex evoked by simple, complex, and conspecific acoustic signals. Panels are arranged based on cortical field (rows) and acoustic signal properties (columns). Note the increases in peak response time as a function of FM sweep stimulus duration, lack of response time variation with changes in noise burst duration, and pattern of activation (AAF → PAF) in response to pure tone stimulation. Vertical lines in box plots demarcate lower quartile, median, and upper quartile values. The extent of the data is presented by whiskers emanating from the left and right ends of the box plot. Outliers are illustrated by + signs. No. of recordings sites per cortical field is described in Figs. 5–7.
bursts: AAF 12.52 ms; pure tones: AAF 14.88 ms; and FM sweeps: AAF 11.25 ms.) Such differences in response times that pure tones and FM sweeps.

The present investigation demonstrates three functional principles of cortical response properties. First, activation of auditory cortical fields occurs in a systematic antero-dorsal to postero-ventral direction. Second, spectrally complex acoustic signals can induce faster cortical responses than signals with narrow bands (pure tones). Third, variations in response latency provoked by changes in acoustic stimulus duration are dependent on acoustic spectral features.

Systematic Activation of Auditory Cortex

The present study revealed an orderly progression of neuronal engagement in auditory cortex. This pattern of activation is consistent with previous studies in rats (Polley et al. 2007; Reimer et al. 2011), ferrets (Bizley et al. 2005), cats (Carrasco and Lomber 2009a, 2009b, 2010; Imaizumi et al. 2004; Loftus and Sutter 2001; Stecker et al. 2003), and humans (Inui et al. 2006). While the consistency of these findings across various animal models suggests that directional patterns of cortical activation might be a common trait across species, limited understanding of the functional influence of neuroanatomic connections on cortical response time impedes the ability to conclude the presence of information flow pathways across auditory cortex. Nonetheless, neuroanatomic tracing studies in the cat have established that thalamocortical and corticocortical connections are the principal source of input to auditory cortex (Lee and Winer 2008a, 2008b, 2008c; Morel and Imig 1987). Thus it is plausible that the effects observed in the present investigation were regulated by a combination of thalamic and cortical response characteristics. Evidence of possible thalamic influence on cortical response time has been provided from electrophysiological studies demonstrating differences in response time across various divisions of MGB (Calford 1983; Calford and Webster 1981; Lennartz and Weinberger 1992). Conversely, reversible deactivation studies have revealed functional properties of corticocortical connections by showing that neuronal silencing of anterior auditory cortical fields decreases the response properties of neurons in adjacent posterior cortical fields (Carrasco and Lomber 2009a, 2009b, 2010). In the present investigation pure tones and noise bursts triggered similar activation of sensory receptors at comparable times, but the subsequent engagement of cortical neurons differed significantly (Figs. 8–10). Consequently, the variation in response time impedes the ability to determine the presence of information flow pathways across auditory cortex. Nonetheless, neuroanatomic tracing studies in the cat have established that thalamocortical and corticocortical connections are the principal source of input to auditory cortex (Lee and Winer 2008a, 2008b, 2008c; Morel and Imig 1987). Thus it is plausible that the effects observed in the present investigation were regulated by a combination of thalamic and cortical response characteristics. Evidence of possible thalamic influence on cortical response time has been provided from electrophysiological studies demonstrating differences in response time across various divisions of MGB (Calford 1983; Calford and Webster 1981; Lennartz and Weinberger 1992). Conversely, reversible deactivation studies have revealed functional properties of corticocortical connections by showing that neuronal silencing of anterior auditory cortical fields decreases the response properties of neurons in adjacent posterior cortical fields (Carrasco and Lomber 2009a, 2009b, 2010).

Stimulus Duration and Response Time

In an effort to gain further insight into the relationship between acoustic features and cortical neuronal activity, we investigated the effects of acoustic signal duration on neuronal response latency. Our analysis revealed that while signal length is relatively unimportant during noise burst presentation, it is a dominant feature of cortical activation time during FM sweep exposure. Specifically, noise bursts induced a single early peak of activity despite considerable changes in signal duration (Fig. 7A). In contrast, FM sweeps were highly sensitive to variations in signal length (Fig. 7B). Comparable results have been reported in the marmoset (Wang et al. 2005a), where preferred acoustic signals provoke sustained neuronal responses and nonpreferred stimulus signals result in transient neuronal activity irrespective of signal duration. Therefore, stimulus duration does not seem to play a major role in cortical responses unless the spectral characteristics of the signal vary across time.

Neuronal Architectonics and Acoustic Properties

The observed differences in activation time induced by changes in acoustic signal properties are intriguing. Namely, how can neuronal signals that commence approximately at the same time in the cochlea, and putatively travel similar pathways, result in distinct activation times of cortical neurons? In the present investigation pure tones and noise bursts triggered the activation of sensory receptors at comparable times, but the subsequent engagement of cortical neurons differed significantly (Figs. 8–10). Consequently, the variation in response time cannot be explained by differences in receptor activation
times and must be related to other aspects of acoustic features. Signal bandwidth and presentation protocol are good candidates for the observed discrepancies in response time. Particularly important to this argument is stimulus structure. Specifically, pure tones were randomly presented one at a time, FM sweeps moved sequentially across the frequency spectrum, and white noise burst signals contained a wide range of simultaneously presented frequencies. A plausible mechanism for the observed phenomena is a differential magnitude of activation caused by the richness of spectral components that mimics the effects of stronger acoustic intensity, whereby louder stimuli result in faster neuronal responses. While each stimulus set activated the same group of receptors, they differed in the amount of concurrent neuronal engagement evoked during each presentation. Specifically, pure tones activated neurons within a specific frequency range, while noise bursts provoked activation across a wide spectrum of frequencies. Thus it is conceivable that the time of neuronal engagement measured in auditory cortex is related to the magnitude of receptor activation induced by acoustic stimulation. In addition, intricate and not well-understood properties of the ascending pathway are likely contributors to the response latencies observed in the present investigation.

Response Latency Characteristics

Electrophysiological, psychophysical, and neuroanatomic investigations have provided evidence for the existence of various cerebral cortical regions that preferentially respond to sound (Imig and Morel 1984, 1985; Imig et al. 1977; Lomber and Malhotra 2008; Winer et al. 1977). While neuroanatomic investigations have relied on various neuronal markers for cortical field identification, electrophysiological investigations have generally been limited to neuronal selectivity of acoustic spectral properties. In particular, frequency selectivity has been the prevailing property measured during field border identification (Imaizumi et al. 2004; Knight 1977; Merzenich et al. 1975; Reale and Imig 1980). The results of the present investigation provide further evidence of a relationship between neuronal response time and field location (Bendor and Wang...
Comparison to the Visual System

Numerous studies of the visual system have measured the time of cortical activation in response to sensory stimulation (Azzopardi et al. 2003; Bullier and Nowak 1995; Maunsell and Gibson 1992; Raiguel et al. 1989; Schmolesky et al. 1998; Wang et al. 2005b). In effect, models of visual information flow have been constructed on the premise of differential response times (Raiguel et al. 1989). In an effort to develop a model of acoustic information processing in auditory cortex, a comparison of cortical activation characteristics between the two systems should prove helpful. A crucial question for this comparison is, How similar is the activation pattern of visual and auditory cortical fields? Differences in response latencies among cortical regions in each system demonstrate a fundamental similarity (Bullier and Nowak 1995; Eggermont 2000; Inui and Kakigi 2006; Schmolesky et al. 1998). In visual cortex, fields that are involved in the analysis of low-level sensory information display early neuronal activation, while regions involved in specialized or higher-order analysis of sensory signals have longer response latencies (Bullier and Nowak 1995). Collectively, these characteristics have resulted in the development of a model of information processing that involves both parallel and serial components (Bullier and Nowak 1995). Based on the present investigation, and the well-established system of visual processing, anterior auditory cortical fields are good candidates for the early analysis of low-level stages of acoustic processing, while posterior fields are good candidates for the latter analysis of high-level acoustic scenes. However, this hypothetical conclusion will only be validated with further investigations into the functional response properties of primary and nonprimary fields of auditory cortex.

Other Considerations

A difficult problem in the analysis of neuronal activation time is the need to define a point of activity as a representative measure of response engagement. While a single instance in time can provide accurate information about neuronal response changes, it lacks the ability to offer a comprehensive description of the overall dynamics of neuronal response properties. Therefore, to avoid potential biases in our results, instants in time (onset and peak activity) as well as cumulative probability density functions are reported. The necessity for both techniques is evident in the analysis of neuronal responses with substantial variability in peak response.

A second consideration is neuronal receptive field characteristics. Specifically, cortical activity driven by tonal stimulation is influenced by receptive field properties such as threshold and bandwidth. While this analytical concern is valid, it is unlikely that these neuronal response features incited incorrect interpretations of the data. Evidence for this assertion is apparent in the comparable neuronal activation induced by simple, complex, and natural acoustic signals across auditory cortex. Specifically, the frequency bandwidth of noise bursts and FM sweeps used ensured a substantial or complete coverage of all receptive field structures recorded. Nevertheless, similar cortical activation sequences were revealed as those obtained during tonal stimulation. As demonstrated in Fig. 13, tuning characteristics may not be the sole contributor of variations in response latency properties.

Finally, it is also important to note that anesthesia in the present study may have induced neuronal response patterns not present during awake states. However, comparable results of studies conducted in various states of alertness in other species indicate that the findings of the present investigation may not substantially vary as a function of anesthetic levels (Bizley et al. 2005; Inui et al. 2006; Recanzone et al. 2000).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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