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Spatial Organization of Repetition Rate Processing in Cat Anterior Auditory Field

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Abstract

Auditory cortex updates incoming information on a segment by segment basis for human speech and animal communication. Measuring repetition rate transfer functions (RRTFs) captures temporal responses to repetitive sounds. In this study, we used repetitive click trains to describe the spatial distribution of RRTF responses in cat anterior auditory field (AAF) and to discern potential variations in local temporal processing capacity. A majority of RRTF filters are band pass. Temporal parameters estimated from RRTFs and corrected for characteristic frequency or latency dependencies are non-homogeneously distributed across AAF. Unlike the shallow global gradient observed in spectral receptive field parameters, transitions from loci with high to low temporal parameters are steep. Quantitative spatial analysis suggests non-uniform, circumscribed local organization for temporal pattern processing superimposed on global organization for spectral processing in cat AAF.

Keywords

modulation transfer function; auditory cortex; core area; spatial correlation; modularity

1. Introduction

Processing human speech and animal vocalizations in auditory cortex requires continuous updating of incoming information on a segment by segment basis by cortical neurons (Wang et al., 2003). Measuring repetition rate transfer functions (RRTFs) captures response characterization to assess information for a temporal range that corresponds to commonly found periodicities of segment sequences and envelop modulation in communication sounds (Eggermont, 2001; Joris et al., 2004; Schreiner and Raggio, 1996). Response specificity to

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different ranges of stimulus repetition rates is shaped during the maturation process (Chang et al., 2005; Eggermont, 1996), and plays an important role in temporal perceptual learning (Bao et al., 2004; Beitel et al., 2003; Kilgard and Merzenich, 1998a).

Two commonly used measures to characterize RRTFs are vector strength (VS) and firing rate (FR). VS and FR estimate spike-timing precision to stimulus-locked responses and overall response magnitude in a particular time window, therefore, corresponding to major aspects of temporal and rate codes, respectively. However, VS measure excludes the response strength due to the normalization (see Methods), and FR measures do not incorporate temporal sensitivity. A third measure, the product of these two measures, i.e., phase-locked rate or synchronized rate (SR), has also been used to estimate temporal coding capacity (Eggermont, 1998; Joris et al., 2004). This measure appears to be useful to characterize RRTFs, in particular, by incorporating both timing and response strength measures. Our recent study of AAF shows that VS and FR carried non-redundant neural information regarding low repetitive sounds (1–30 Hz) by click trains (Imaizumi et al., 2010). Furthermore, the spatial organization of repetition rate information based on VS and FR showed different local clustering properties. Although temporal processing appears to be non-homogeneously distributed across auditory cortex, the spatial distribution of basic temporal processing parameters within cortical fields have not been studied with sufficient spatial resolution to reveal organizational principles (Bao et al., 2004; Kilgard and Merzenich, 1999; Schreiner and Urbas, 1986).

The core auditory cortex in mammals, in general, consists of a few functionally and anatomically distinct cortical areas (Kaas, 2011). In cats, primary auditory cortex (AI) and anterior auditory field (AAF) are the two main core processing stations (Imaizumi et al., 2004; Lee et al., 2004). These fields provide different neural information for behavioral tasks (Barnes and Lomber, 2003; Malhotra et al., 2004). AAF significantly contributes to temporal discrimination aspects, while AI contributes to both sound localization and temporal discrimination tasks. An emphasis in AAF on temporal coding is indicated by shorter onset latencies combined with higher temporal response precision and a wider range of envelope-following capacity (Kowalski et al., 1995; Linden et al., 2003; Rutkowski et al., 2003; Schreiner and Urbas, 1988). In this study, we ask how RRTF parameters are distributed across cat AAF. We investigated a wide repetition rate range (up to 250 Hz), however, the majority of relevant information was found for repetition rates <60Hz. Here, we describe the spatial distribution of RRTFs to discern potential variations in local temporal processing capacity in cat AAF. This may disclose distinctions in local circuits and information convergence as has been observed for spectral response properties in AI (Imaizumi and Schreiner, 2007; Read et al., 2001) and AAF (Imaizumi et al., 2004).

2. Methods

2.1. Surgery and animal preparation

Experiments were conducted on four cases (one right and three left hemispheres) of three adult female cats. All protocols were approved by the University of California, San Francisco Committee on Animal Research in accordance with federal guidelines for care and use of animals in research. Animals were sedated by intramuscular injections of a mixture of ketamine (22 mg/kg) and acepromazine (0.11 mg/kg). After venous cannulation, sodium pentobarbital (15–30 mg/kg) was administered and supplemented as needed throughout the surgical procedure. Following tracheotomy, a craniotomy was performed to expose the ectosylvian gyrus. The dura mater was partially removed, and the cortical surface was covered with viscous silicone oil. Before commencing the electrophysiological recordings, sodium pentobarbital anesthesia was replaced with a continuous intravenous infusion of a mixture of ketamine (2–10 mg/kg/h) and diazepam (0.05–0.2 mg/kg/h) in

lactated Ringers (1–3 ml/kg/h). To prevent edema and mucus secretion, dexamethasone (1.2 mg/kg, S.C.) and atropine sulfate (0.04 mg/kg, S.C.) were administered every 12 hours. Since recordings lasted for three to four days, an antibiotic (cephalosporin, 11 mg/kg, I.V.) was administered to prevent wound infection. Body temperature was monitored and maintained by a water heating pad at $37\pm 1^\circ\text{C}$. Electrocardiogram and respiration rate were monitored continuously during surgery and recording procedures.

2.2. Acoustic stimuli

Experiments were conducted in a double-walled, anechoic chamber (Industrial Acoustics, Bronx, NY). Stimuli were delivered by a STAX-54 headphone through a sealed tube into the acoustic meatus contralateral to the studied hemisphere. The system frequency transfer function was flat (± 6 dB) up to 14 kHz and rolled off 10dB/octave at higher frequencies.

Two different stimuli, pure tone bursts and click trains, were presented for measuring frequency response areas and RRTFs, respectively. Pure tone stimuli of 50ms duration (including 3-ms linear rise and fall time) were generated at intervals of 400–750 ms by a microprocessor (TMS32010, 16 bits resolution and 120 kHz digital-to-analog sampling rate). Frequency response areas were mapped by presenting 675 pseudo-randomized tone bursts at 45 different frequencies (3–5 octave range) and 15 sound levels (70 dB range in 5 dB steps). For RRTFs, click trains (monophasic, rectangular pulses of 200 μs duration; 500 ms train duration) were presented 15 times for repetition rates from 2 to at least 38 Hz (2 or 4 Hz steps) at sound level of 82–102 dB SPL (at peak level) depending on neural threshold (see below). For most sites that still showed phase-locked responses and/or elevated FRs at 38 Hz, higher repetition rates were presented (up to 250 Hz) until no clear evidence for stimulus-driven responsiveness was observed. For analysis, the 2 Hz stimulus was treated as 1 Hz because only one click was presented at an interval of 950 ms during the analysis window (550 ms) for spike counts (see below).

2.3. Recordings

Parylene- or epoxylite-coated tungsten microelectrodes (Micro Probes, Potomac, MD or Frederic Haer & Co., Bowdoinham, ME) with 0.5–4 M Ω impedance at 1 kHz were used for single- and multi-site recordings. Single or double microelectrodes were advanced perpendicular to the cortical surface with a hydraulic microdrive (David Kopf Instruments, Tujunga, CA). A video picture of the cortical surface was captured and digitized with a CCD digital camera (Cohu, San Diego, CA). Each recording site was marked on the digitized picture using Canvas software (Deneva, Miami, FL). The marked sites were used to reconstruct tessellation maps of the recording area (see below). Neuronal activity was obtained in main thalamocortical recipient layers (Huang and Winer, 2000). Action potentials were amplified and band-pass filtered (0.3–10 kHz; World Precision Instruments, Sarasota, FL, and Axon Instruments, Union City, CA), fed to an oscilloscope, and isolated from background noise with a time/amplitude window discriminator (BAK Electronic, Mount Airy, MD). For frequency response areas and RRTFs, spikes occurring in the first 50 ms or 550ms, respectively, after stimulus onset were recorded at 10 or 100 μs resolution for the analyses.

2.4. Data analysis

Data were analyzed using the MATLAB (Mathwork, Natick, MA) platform. StatView (SAS Institute, Cary, NC) was used for statistical analysis. Spectral receptive field parameters (RFPs) such as characteristic frequency (CF), minimum threshold, quality factors, and latency were obtained. Threshold was defined as minimum excitatory SPL, and estimated at 5 dB resolution. CF was defined as the frequency at which a single neuron or neuron cluster produced sound-evoked spikes at threshold sound level. Spectral bandwidths were

calculated as CF divided by excitatory bandwidth at 10 dB (Q10) or 40 dB (Q40) above threshold; the higher the Q-value, the more sharply tuned are the neurons. Latency was determined as the minimum value in the averaged latency-level function at CF and the two adjacent test-frequencies (CF $\pm$ 1/15 to 1/9 octaves). Results for spectral RFP distributions were presented elsewhere (Imaizumi et al., 2004).

For RRTFs, spike occurrence to the first click was discarded except for the 1 Hz stimulus. Spikes were counted from the second click onset to 550 ms after the first click onset (for 1 Hz stimulus, spikes occurring between the first click onset and 550 ms were used). VS and FR were used to measure temporal following activity (Eggermont, 1998; Joris et al., 2004). VS measures how well spikes are phase-locked to the clicks:

$$VS = \frac{\sqrt{(\sum \cos\theta)^2 + (\sum \sin\theta)^2}}{n}$$

$$\theta = 2\pi \frac{t}{T}$$

where n is the total number of spikes, t is time of spike occurrence, and T is the inter-click interval (Goldberg and Brown, 1969). Significance of synchronization was examined by a Rayleigh test ($p < 0.001$) (Mardia, 1972). SR was measured by multiplying VS and FR (Eggermont, 1998), and is equivalent to the un-normalized VS or the un-normalized first Fourier component of the PSTH spectrum (Joris et al., 2004). Fig. 1 illustrates two examples of the SR construction and the main measurements to characterize RRTFs. For illustration only, a polynomial cubic spline was used to connect data points. For analysis, however, a linear interpolation was employed to measure the RRTF parameters. Filled (or opened) circles represent data points with statistically significant (or non-significant) response synchrony to a given repetition rate (Fig. 1). Best repetition rate (BRR) was determined as the click repetition rate at which a neuron or neuron cluster produced the highest SR (e.g., 1 Hz in Fig. 1C and 18 Hz in Fig. 1F). Q50% values were calculated as BRR divided by bandwidth at 50% SRs (BW50% in Fig. 1C and F) (Liang et al., 2002). For Q-values of low-pass responses (e.g., Fig. 1C; ~9% of the total sites: 32/368), the lowest repetition rate of 1 Hz was used as low cutoff repetition rate. High cutoff repetition rate (HRR) was estimated from the 50% response. For 40 (out of 369) sites, 38 Hz (their highest tested repetition rate) was taken as HRR because the 50% reduction in SR was not reached. For these sites, the HRR may be an underestimate.

2.5. Classification of RRTF properties

RRTFs were classified into three temporal filter types, and were considered band-pass when the response peak was flanked by troughs in which the responses dropped <75% of the peak activity (Tian and Rauschecker, 1994). If one of the response troughs did not reach the criterion, RRTFs were considered either as low- or high-pass type.

2.6. Voronoi-Dirichlet tessellation map

To reconstruct the spatial distribution of RRTF parameters across the cortical surface, tessellation maps were calculated by Voronoi-Dirichlet tessellation (Kilgard and Merzenich, 1998b). The polygon surrounding each electrode penetration in the tessellation map characterizes the area assigned to the functional parameter at the recording site. Borders between neighboring polygons were determined from the midpoints of a straight line

between adjacent recording points. The value of each RFP or RRTF parameter in the cortical surface map is illustrated by color codes.

2.7. Spatial organization analysis

Two types of spatial organization analysis were performed complementarily. To investigate global spatial organization, spatial autocorrelation was used to estimate a measure of redundancy by determining Geary's C coefficient (Cliff and Ord, 1973). A Geary's C value is computed by autocorrelation of spectral RFPs or RRTF parameters between two adjacent recording sites:

$$C = \frac{(n-1) \sum_{ij} w_{ij} (x_i - x_j)^2}{2W \sum_{i=1}^n (x_i - \bar{x})^2}$$

where n is the number of recording sites, w_{ij} is a spatial weight at recording sites i and j , W is sum of all w_{ij} , x is the value of the variable, and $\bar{x}$ is mean of x . C values are based on value differences between pairs of observations for the whole map and quantify whether adjacent observations of the same phenomenon are correlated. They can vary between 0 and 2. A C value of 2 indicates perfect positive spatial correlation (high spatial uniformity and maximum neighbor similarity), while a C value of 0 corresponds to negative correlations (maximal dispersion and high value contrast between neighbors). A null hypothesis of random spatial distribution results in a C value of 1. In a Monte-Carlo analysis, the statistical significance of the experimental C values was derived from the C-value distribution of 10,000 randomized map versions.

To investigate local spatial organization, the value similarity between each polygon and its direct neighbors was examined. Statistical significance was obtained by Monte-Carlo analysis by which the value similarity was compared with 10,000 randomly redistributed neighboring polygon values. The statistical significance of the number of polygons with similar direct neighbors in each experimental map was determined in relation to those found in 1,000 randomized maps. This estimates the proportion of local parameter clusters.

3. Results

3.1. Filtering properties of repetition rate transfer functions

We examined RRTFs of 368 sites with a significant SR for, at least, one repetition rate as estimated by the Rayleigh test. These recording sites spanned CFs from 0.3 to 43 kHz (Table 1). We determined the AAF/AI border by the reversal of the CF gradient (Imaizumi et al., 2004; Imaizumi and Schreiner, 2007; Knight, 1977) for all cases but one (case 426L). A goal of this study is to reveal the spatial distribution of RRTF parameters. Fig. 2 illustrates two representative RRTFs that cover different ranges of repetition rates. Sites with lower and higher BRRs are illustrated in Fig. 2A–B, respectively. Fig. 3 illustrates the distribution of RRTF filter types. For SR (Fig. 3 center panel), a majority of sites (90%) had band-pass characteristic (e.g., Fig. 2), while low-pass filters comprised 9% of the sites (e.g., Fig. 1C) and high-pass sites were rare. Because SR is computed by multiplying VS and FR (Fig. 1), RRTF filter types for SR may share properties, to some extent, with those for VS or FR. VS and FR filter types are presented in the left and right panels in Fig. 3, respectively. For VS (Fig. 3 left panel), the filter type proportions were similar to SR. By contrast, FR filter types often differed from the SR filter types with a higher proportion of high-pass filters and fewer low-pass filters (Fig. 3 right panel). To further assess the computational influence of VS or

FR on SR, we examined whether BRRs determined for SR covary with those for VS (vsBRRs) or FR (frBRRs). Both were significantly correlated with those for SR (Fig. 4). However, vsBRRs were more highly correlated with BRRs ($r^2 = 0.27$) than frBRRs ($r^2 = 0.12$), which may reflect the higher filter type similarity between SR and VS (Fig. 3).

3.2. Distribution of repetition rate transfer function parameters

Three parameters represent our estimates of RRTFs. BRR and HRR reflect the preferred and upper limit of repetition rates, respectively, that neurons can follow in a time-locked fashion; Q50% values reflect the relative range of repetition rates (the higher the Q50% value, the more selective is the response to a particular range of repetition rates). Fig. 5A–B illustrates the linear correlations between BRRs and HRRs and Q50% for two cases (111L and 426L, identified by color; see Table 2 for statistical results). Both HRRs and Q50% values had strong linear correlation with BRRs: the higher the BRRs, the higher the HRRs and the narrower the temporal bandwidth (Fig. 5A–B). Although the slope of the regression analysis could differ significantly between different cases (see Fig. 5B), combining all four cases for the linear regression analysis showed a consistent result (Fig. 5C–D).

To examine spatial distribution pattern of RRTF parameters across the cortical surface in AAF, it can be helpful to remove the CF dependency of RRTF parameters (Cheung et al., 2001a; Imaizumi et al., 2004). Fig. 6A–C illustrates the average dependence of RRTF parameters on CF for one case (073L) with a statistically significant CF influence (see Table 3 for the statistical results). Second order non-parametric, local regression fits (a black line in Fig. 6A–C and color lines in Fig. 6D–F) indicate a general trend of RRTF parameters as a function of CF. For simplicity, Fig. 6D–F illustrates only local regression fits of RRTF parameters for CF without individual RRTF values. A wide range of RRTF parameters was encountered across the whole CF range (Fig. 6A–C). Although sites with CFs of ~10 to 30 kHz often showed the highest BRRs (Fig. 6A, D), overall no consistent CF dependency of BRR was evident. Because of the correlation of BRR values with HRR and Q50% (Fig. 5), a similar lack of CF dependency was seen for HRR (Fig. 6B, E). The highest HRRs obtained for AAF were, in general, ~60 to 70 Hz (Fig. 6B, Table 1). The bandwidths of RRTFs (Fig. 1), expressed as Q50%, also varied widely across the population. CF dependence of RRTF parameters was statistically significant only for one case (Fig. 6A–C; see Table 3). Therefore, RRTF parameters were largely independent from CF (Joris et al., 2004). It should be noted that, in cat AAF, some CF ranges are underrepresented (Imaizumi et al., 2004), e.g., in the 1–5 kHz range for case 073L (gray area in Fig. 6C). This may impede cross-case comparisons and population conclusions.

3.3. Spatial distribution of repetition rate transfer function parameters

Although RRTF parameters were largely independent of CF, their spatial distribution did not appear to be homogenous and revealed a tendency for spatial clustering. Tonotopic CF gradients (smoothed by a weighted least-squares linear regression model) on the cortical surface are illustrated in Figs. 7A, D and 8A, D for all four cases. The spatial distribution of responses to click trains showed a patchy local clustering of sites with similar RRTF parameter values (Figs. 7B, 7E and 8B, 8E). This clustering is also evident after removing the CF influence of the residual parameter values. Co-variations of RRTF parameters with CF were eliminated by a second order non-parametric, local regression (see Fig. 6). The spatial distribution of residuals (differences between model and observed values) of RRTF parameters was smoothed by a weighted least-squares linear regression model. This depiction of spatial organization emphasizes deviations from the CF-independent mean and indicates spatial coherence of RRTF values in form of small local clustering of neurons (Figs. 7C, 7F and 8C, 8F). Clustering of positive and negative value residuals along iso-frequency contours reflects a range of RRTF for each CF and non-random organization.

Cluster locations differed between cases. Transitions from loci with high to low residual values appeared to be steep, suggesting a local modular representation rather than shallow global gradients as observed for CF and latencies in cat AAF (Imaizumi et al., 2004, 2010).

Previous studies had suggested that first spike latencies to pure tone or other relevant stimuli are related to temporal following abilities (Eggermont, 1998; Liang et al., 2002; Lu and Wang, 2000; Schreiner and Raggio, 1996; Ter-Mikaelian et al., 2007). Fig. 9A and D illustrates the relationship between first spike latencies to pure tone (hereafter, latency) and BRRs. BRRs were significantly correlated with latencies for two of the four cases (Table 3): the shorter the latency, the higher the BRR (but see Eggermont, 1998). Other RRTF parameters were also correlated with latencies for some of the cases, although the correlations were weak (Table 3). To understand the spatial relationships between latencies and RRTF parameters, co-variations of RRTF parameters with latencies were eliminated by a second order non-parametric, local regression (Fig. 9A, D). For reference, the spatial distribution of latencies is illustrated in Fig. 9B and E. The shortest latencies (≤ 8 ms) occurred over a wide CF region (Figs. 7, 9)(see also Imaizumi et al., 2004). The spatial distribution of residuals BRRs, smoothed by a weighted least-squares linear regression model, revealed again local clustering of neurons with similar BRR residuals (Fig. 9C, F). The cluster locations for residuals based on latency (Fig. 9 C, F) and CF (Fig. 7 C, F) were very similar suggestive of latency and CF independent organizational principles. The spatial distributions of HRR and Q50% residuals after latency decorrelation also had similar trends to the CF-corrected distributions (results not shown). Overall, RRTF parameters were only weakly correlated with latency (Table 3).

To investigate whether RRTF parameters (BRR, HRR, and Q50%) are related to spectral RFPs (threshold, Q10, Q40, and latency) obtained for pure tone bursts, a factor analysis was conducted for the CF-corrected residuals across all four cases (Table 4). Based on eigenvalues > 1.0 , two independent factors emerged. Factor 1 reflects the (weak) negative covariation of latency with BRR and HRR. Factor 2 reflects a negative covariation between spectral filter selectivity (Q10 and Q40) and temporal filter selectivity (Q50%), i.e., sites with narrow spectral bandwidth tend to respond to wider range of repetition rates. Therefore, preferred temporal repetition rates (e.g., BRR) and sharpness of spectral tuning (e.g., Q40) are not related.

In a previous study, we have shown that VS- and FR-based mutual information about slow repetition rates show some local organization, while CF, minimum threshold at CF, and Q40 have a strong global organization (Imaizumi et al., 2010). We examined such a relationship for RRTFs. Global spatial autocorrelation, a measure of spatial redundancy, was estimated by calculating Geary's C coefficient (Cliff and Ord, 1973). A local similarity measure was also tested by Monte-Carlo analysis, which estimates the value similarity of each polygon with its adjacent polygons (see Methods). Spectral RFPs and latency revealed strong global (significant C values > 1.04) and local organization (significant numbers of sites with similar neighbors; see Fig. 10, open circles). RRTF parameters based on SR (BRR, HRR and Q50%) did not show significant global organization although local organization was evident for BRR and HRR (filled circles, Fig. 10). Proportions of clusters with significantly similar neighbors ranged from 11% for HRR to 19% for BRR (Fig. 10). Q50% did not reach a significant level for either global or local organization. frBRR showed small but significant global and local organization and vsBRR showed weak local clustering. Across all spectral and temporal parameters, strong correlation was found between global and local organization ($r^2=0.92$, $p<0.0001$, $y=1.37x-1.29$). However, these results indicate that local processing organization for BRR information that is captured by the SR is much weaker than for CF, threshold and Q40 but stronger than for latency, HRR and Q50%. Combined with related local clustering for repetition rate information carried by interstimulus intervals

(Imaizumi et al., 2010), this indicates the existence of functionally distinct, circumscribed local circuits for temporal processing superimposed on more global organizations of spectral information in cat AAF.

4. Discussion

For species-specific communication and speech perception, auditory cortex must decode continuously incoming information. Combined behavioral and lesion experiments have suggested that cat AAF contributes significantly to temporal information processing and perception (Barnes and Lomber, 2003). Measuring RRTFs captures a neuron's ability to maintain a temporally precise record and/or a rate-based code of event occurrences and properties. While VS and FR are most frequently considered for construction of RRTFs, in this study, we focused on SR, the product of VS and FR. SR has been postulated to provide a superior estimate of signal transmission capacity because temporal synchrony and spike number impinging on a neuron determine the efficacy of information transfer to postsynaptic stations (Eggermont, 1998, 2000; Joris et al., 2004).

4.1. Comparison of cat AAF with other model systems

The main range of temporal response parameters, including latency, observed in this study is in good agreement with previous studies in cat (Schreiner and Urbas, 1986, 1988), and potentially homologues regions in mouse (Linden et al., 2003), rat (Rutkowski et al., 2003) and ferret (Bizley et al., 2005). By contrast, in new and old world monkeys, core cortical fields (R and RT) directly anterior to AI may differ from this organization because they tend to show longer latencies (Bieser and Müller-Preuss, 1996; Kusmierek and Rauschecker, 2009) that are likely associated with lower phase-locked repetition rate following (Wang et al., 2008). There is a working hypothesis that monkey auditory cortical fields might be rotated because tonotopic gradient direction of AI in new and old world monkey differs from that in other species (Kaas, 2011). Based on the hypothesis, caudal medial area (CM) located caudomedial of AI in monkey might be a homologue of AAF in cat after $>90^\circ$ rotation. While neurons in monkey CM have shorter latency than in AI (Kajikawa et al., 2005), thalamocortical projection patterns to CM (de la Mothe et al., 2006) differ from those to AAF (Lee et al., 2004). Furthermore, CM may be more involved in sound localization task (Recanzone and Cohen, 2010), which contrasts the behavioral role of cat AAF (Lomber and Malhotra, 2008; Malhotra et al., 2004). How this difference between cat AAF and monkey R (or CM) may relate to the definition and expression of diverse functional streams, like in a 'what' and 'where' scheme (Lomber and Malhotra, 2008; Rauschecker and Tian, 2000; Recanzone and Cohen, 2010; Romanski et al., 1999) remains to be settled.

4.2. Comparison with other studies in AAF

The cortical encoding of periodic envelope or repetitive stimuli has been characterized with modulation transfer functions (MTFs) using amplitude modulated (AM) sounds or RRTFs using click trains, respectively. The majority of these studies focused on AI of anesthetized or awake animals (for review see Joris et al., 2004). By contrast, only a few studies have described RRTFs or MTFs in AAF.

In a first study, MTFs based on VS and FR using sinusoidal and rectangular AM sounds in lightly barbiturate-anesthetized cats were found to have BRR values that were a factor of 1.5–2 higher than those in the current study (Schreiner and Urbas, 1986). This difference may be accounted for by the fact that AM sounds tend to evoke higher BRRs than click trains in auditory cortex (Eggermont, 1998) combined with a comparatively low level of anesthesia in that study. A detailed study obtaining RRTFs using click trains and MTFs using AM tones and noise by single and multi-unit recordings in ketamine-anesthetized cats

(Eggermont, 1998, 2000) showed BRR and HRR values were ~50% lower than the values in the current study. Although the global methodologies were quite similar, several aspects may account for the observed differences. 1) The CF range explored in two studies was different (1.2–15.5 kHz versus 0.3–42.8 kHz in the current study). In some cases in the current study, higher BRR and HRR values were encountered at higher CF regions (Fig. 6), although no clear CF dependence was established. 2) Stimulus repetition rate ranges used in the two studies were different (1–32 Hz versus 1–38 Hz and for ~25% of sites at least up to 60 Hz in the current study). Because some sites in AAF are able to follow higher repetition rates (Imaizumi et al., 2010; Schreiner and Urbas, 1986), limiting the presented repetition rates potentially underestimates population RRTF values. 3) Eggermont (1998, 2000) utilized multi-unit recordings constructed from well-separated units, while our recordings were largely made from a small number of unresolved units. While the amplitude of accepted action potentials was several standard deviations above the noise, contamination from other sources than spiking of cortical neurons cannot be excluded. 4) Different stimulus presentation methods may have contributed (free field versus sealed earphones in the current study; see also Malone et al., 2007). Despite these potentially contributing factors, the relatively large differences in RRTF/MTF properties between different studies of cat AAF are not readily explained.

4.3. Comparison of AAF with AI

Two studies suggested that AAF neurons have higher following rates to AM frequencies than those in AI (Linden et al., 2003; Schreiner and Urbas, 1988), while another study suggested both fields have similar RRTF responses (Eggermont, 1998). Differences in following-ability of AAF versus AI is supported by shorter latencies in AAF than in AI (Bizley et al., 2005; Imaizumi et al., 2004; Linden et al., 2003; Rutkowski et al., 2003; Schreiner and Urbas, 1986, 1988). Neurons with the shorter latency have a smaller jitter of spike timing in repeated stimulus presentation (Heil, 1997; Phillips and Hall, 1990; Ter-Mikaelian et al., 2007). However, our current study could not unambiguously confirm such a relationship between following ability and latency in all studied cases (Table 3), while a factor analysis across all cases suggests a weak relationship (Table 4). In awake marmosets, the difference between AI and anterior core fields R and RT unfolds differently from cat (Wang et al., 2008). Marmoset AI had more synchronized neurons versus non-synchronized neurons to repetitive stimulus than the anterior fields (however, see Malone et al., 2007), implying that FR-dominated non-synchronized neurons in R (and RT) may respond to higher repetition rates than phase-locking neurons.

4.4. Effects of animal state on repetition rate transfer functions

Different anesthesia regimes affect RRTFs in a different way (Cheung et al., 2001b). Cat AI under isoflurane anesthesia evoked much slower RRTFs than under barbiturate anesthesia. Animal state also affects RRTFs. A pioneering study by Goldstein et al. (1959) described that AI neurons in awake cats produced higher RRTF values than those in anesthetized cats. This finding has been elaborated by a series of studies in awake, passively listening marmosets (and anesthetized cats) (Wang et al., 2008). In the awake marmoset AI, the proportion of FR dominant non-synchronized to VS dominant synchronized population is higher than in anesthetized cat AI. Thus, auditory cortex in awake state can follow higher repetition rates. However, a counter example has been found in a study of gerbil. AI neurons in an awake state showed lower spike-timing fidelity and followed lower AM rates than those in an anesthetized state (Ter-Mikaelian et al., 2007). It also has been shown that task-engagement and attention can modulate neural responses including temporal response aspects (Fritz et al., 2005; Hromádka and Zador, 2007). More detailed studies of effects of alertness and attention on RRTFs and MTFs are necessary.

4.5. Local modular organization of repetition rate processing in AAF

A main finding in this study is the presence of local spatial clusters or small modules containing similar values of BRRs or HRRs. The low spatial resolution and data pooling over several cases in a previous study was not sufficient to discern spatial inhomogeneities (Schreiner and Urbas, 1986). A patchy distribution of RRTF parameters has also been suggested for rat AI (Bao et al., 2004; Kilgard and Merzenich, 1999), although those observations were hampered by the relatively small size of rat AI. In species-specific calls or human speech sounds, repetitively modulated sounds are often carried by some tone or noise bursts. Therefore, the distribution of CF- (and latency-) neutral RRTF parameter residuals reflects a modular, inhomogeneous distribution of RRTF properties. The size of local clusters with similar temporal response properties was $<500\ \mu\text{m}$, unlike those observed for spectral clusters in AAF (Imaizumi et al., 2004). However, no clear and consistent global organization was observed and, unlike the spatial distribution of spectral RFP residuals in AAF (Imaizumi et al., 2004), transitions from regions with high to low RRTF parameters appeared to be steep, suggesting contrasting modes of processing distinguished by larger differences in BRR, HHR or Q50%. Modularity, defined as local homogeneity of certain RFPs, may be an expression of specific local network and connectivity properties and may reflect function-specific input/output streamlets (Schreiner and Winer, 2007).

Spatial organization of RRTFs or MTFs in cat or monkey AI has not been widely studied. One study explored MTF organization (using harmonic components carried by different fundamental frequencies) in cat AI by intrinsic optical imaging (Langner et al., 2009). Unlike the patchy local organization in AAF, the organization of preferred repetition/fundamental frequency rates was interpreted as continuous and arranged perpendicular to the tonotopic axis, at least for CFs up to 13 kHz. However, more detailed studies of the spatial arrangement of AM or click repetition rates are necessary.

It is of particular interest to know how local clustering of RRTF parameters is constructed. Our recordings were made from the main thalamocortical recipient layers. However, comparison of MTF properties among connected pairs of thalamic and cortical neurons indicated that the cortical modulation characteristics in AI were only weakly predictable from the thalamic inputs (Miller et al., 2001) and local influences, e.g., from inhibitory corticocortical inputs (De Ribaupierre et al., 1972; Wehr and Zador, 2005), seem to play a major role. Therefore, it is unlikely that thalamocortical projections alone determine local clustering behavior of RRTF parameters in AAF (Imaizumi et al., 2005; Lee et al., 2004). More likely, the functional clustering reveals patches of similar local and columnar networking supported by specific cortico-cortical convergences, similar to but not correlated with the organization of spectral RFPs in AAF (Imaizumi et al., 2004).

Overall, the nature of local clustering of temporal information may reveal the role of local circuit properties and computational principles as well as the fate of local computations in their relation to feed-forward, feedback, and lateral networks in core auditory cortex. In particular, a parameter-specific topographic framework of functional organization within different cortical fields is crucial for testing of hypotheses regarding specialized functional streams and substreams (Rauschecker and Tian, 2000; Recanzone and Cohen, 2010; Schreiner and Winer, 2007).

Research highlights

Repetition rate transfer functions capture temporal pattern responses in cat AAF.

The majority of synchronized rate transfer functions are bandpass.

The average best repetition rate is 15.5 ± 9.6 Hz, in line with other studies of auditory core areas.

Local clusters of similar response properties indicate a small-scale spatial organization for temporal processing.

Glossary

AAF	anterior auditory field
AI	primary auditory cortex
AM	amplitude modulated
BRR	best repetition rate
CF	characteristic frequency
CM	caudal medial area
FR	firing rate
frBRR	best repetition rate for firing rate
HRR	high cutoff repetition rate
MTF	modulation transfer function
Q10	spectral quality factor at 10 dB above threshold
Q40	spectral quality factor at 40 dB above threshold
Q50%	temporal quality factor at 50% response
R	rostral area
RFP	receptive field parameter
RRTF	repetition rate transfer function
RT	rostrotemporal area
SR	synchronized rate
VS	vector strength
vsBRR	best repetition rate for vector strength

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Fig. 1. Measurement method of temporal receptive fields by repetition rate transfer function (RRTF). A, D) Vector strength (VS) as a function of repetition rates. Data points were connected by a polynomial cubic spline fit for illustration. For analysis, a linear extrapolation was employed. Filled and opened circles represent significant and non-significant phase-locking based on a Rayleigh test ($p < 0.001$). B, E) Firing rate (FR) in spikes/15 stimulus repetitions as a function of repetition rates. A gray line and the thickness illustrate mean spontaneous FR and its S.D. C, F) Synchronized rate (SR; VS multiplied by FR) as a function of repetition rates. Site identification and characteristic frequency (CF) are shown. See Methods for explanation of detailed measurements. BRR: best repetition rate, HRR: high cutoff repetition rate, BW50%: temporal bandwidth at 50% of the response. (A–C) Low-pass site. BRR: 1 Hz, HRR: 10 Hz, Q50%: 0.11. (D–F) Band-pass site. BRR: 18 Hz, HRR: 33 Hz, Q50%: 0.70.

Fig. 2.

Representative RRTFs with low and high BRRs. A) Band-pass site with low BRR. BRR: 14 Hz, HRR: 29 Hz, Q50%: 0.56. B) Band-pass site with high BRR. BRR 46 Hz: HRR: 66 Hz, Q50%: 0.77. See Fig. 1's legend for further explanation.

Fig. 3. Histograms of RRTF filter types for VS, SR, and FR. Occurrence of different RRTF filter types is illustrated. LP: low-pass property, BP: band-pass property, HP: high-pass property.

Fig. 4. Correlation between BRRs for different measures. Linear regression analyses (black lines) were performed. A) BRRs for VS (vsBRR) as a function of BRRs for SR. B) BRRs for FR (frBRR) as a function of BRR. Data from all four cases were combined. Correlation values (r^2) and statistical probabilities were illustrated on the bottom right.

Fig. 5.
 A, B) Correlation between BRR and other RRTF parameters for two cases (case 111L and 426L). Linear regression analyses were performed between BRR and HRR or Q50% values.
 C, D) Data from all four cases were combined. See Table 2 for statistical results.

Fig. 6.

A–C) Distribution of RRTF parameters as a function of CFs for a significant case 073L. Black lines are fitted models by a second order non-parametric, local regression model (local weighting of a 0.5 vicinity span). D–F) A general trend of RRTF parameters as a function of CFs for three other cases. Colored lines are fitted models by a second order non-parametric, local regression model (local weighting of a 0.5 vicinity span). RRTF parameter values are omitted for simplicity. (A, D) BRRs as a function of CFs. (B, E) HRRs as a function of CFs. (C, F) Q50% as a function of CFs. See Table 3 for statistical results. Gray area in (C) show underrepresentation of CF ranges.

Fig. 7.

Spatial distribution of RRTF parameters and their residual values for two cases (case 073L and 111L). A, D) Tonotopic distributions were smoothed by a weighted least-squares linear regression. Black lines illustrate sulcus pattern. *sss*: suprasylvian sulcus, *aes*: anterior ectosylvian sulcus, D: dorsal, A: anterior, scale: 1 mm. B and E) RRTF parameters are reconstructed on the cortical surface by Voronoi-Dirichlet tessellation. C and F) Reconstruction of residual values of RRTF parameters was smoothed by a second-order, weighted least-squares linear regression. The residual values were calculated from the differences between fitted and observed values presented in Fig. 6.

Fig. 8. Spatial distribution of RRTF parameters and their residual values for two other cases (case 073R and 426L). A, D) Smoothed tonotopic distributions. B and E) RRTF parameter distributions. C and F) Distributions of residual values of RRTF parameters. See Fig. 7's legend for further explanation.

Fig. 9.

A, D) Correlation between BRRs and latencies for two cases (073L and 111L). Black thick lines are fitted models by a second-order non-parametric, local regression model (local weighting of a 0.5 vicinity span). See Table 4 for statistics. B, E) Latency gradients smoothed by a second-order, weighted least-squares linear regression. C, F) Smoothed residual values of BRR. The residual values were calculated from the differences between fitted and observed values presented in (A, D).

Fig. 10.

A linear relationship between global and local spatial organization in AAF. The mean proportion of polygons with high similarity to direct neighboring polygons (local spatial organization) is plotted as a function of the mean of spatial autocorrelation measure (global spatial organization) for the combined four cases. Error bars indicate standard error of the mean. Filled circles indicate RRTF parameters. Light gray area illustrates statistically non-significant regions for either measure. Dark gray area shows statistically non-significant regions for both measures. A linear regression analysis reveals a strong correlation ($r^2=0.92$, $p<0.0001$, $y=1.37x-1.29$).

Table 1

Value range (upper lines) and mean $\pm$ S.D. (lower lines) of RRTF parameters. For the total, only mean $\pm$ S.D. is shown.

Case	Site #	CF (kHz)	BRR (Hz)	HRR (Hz)	Q50%
111L	133	0.4–42.5	1–58	5.0–96.5	0.02–1.9
			17.6 $\pm$ 10.4	33.9 $\pm$ 15.1	0.6 $\pm$ 0.3
073L	76	0.6–38.8	1–42	4.8–62.0	0.10–2.1
			14.3 $\pm$ 9.7	34.1 $\pm$ 11.2	0.5 $\pm$ 0.3
073R	71	0.5–42.8	1–46	4.7–66.8	0.04–3.1
			14.8 $\pm$ 10.9	27.8 $\pm$ 14.5	0.7 $\pm$ 0.6
426L	88	0.3–35.0	1–34	3.1–39.3	0.05–7.5
			14.0 $\pm$ 5.8	25.5 $\pm$ 9.3	1.2 $\pm$ 1.5
Total	368	0.3–42.8	15.5 $\pm$ 9.6	30.8 $\pm$ 13.5	0.8 $\pm$ 0.9

CF: characteristic frequency, BRR: Best repetition rate, HRR: High cutoff repetition rate, Q50%: normalized temporal bandwidth at 50% response.

Table 2

Correlation values of r^2 and probabilities by ANOVA for a linear regression analysis performed between BRRs and HRRs or Q50% values.

Case	HRR	Q50%
111L	0.55 ($p<0.0001$)	0.22 ($p<0.0001$)
073L	0.29 ($p<0.0001$)	0.49 ($p<0.0001$)
073R	0.31 ($p<0.0001$)	0.23 ($p<0.0001$)
426L	0.15 ($p=0.0002$)	0.09 ($p=0.0051$)

Table 3

CF or latency dependence of RRTF parameters. Statistical significance was examined by ANOVA.

Case	CF dependency			Latency dependency		
	BRR	HRR	Q50%	BRR	HRR	Q50%
111L	N.S.	N.S.	N.S.	***	***	N.S.
073L	***	*	**	N.S.	***	N.S.
073R	N.S.	N.S.	N.S.	***	N.S.	*
426L	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.001$,

N.S.: not significant

Table 4

Factor analysis. Varimax orthogonal transformation was performed for CF-corrected residuals of receptive field parameters (RFPs) and RRTF parameters across all four hemispheres.

Parameter	Factor 1	Factor 2
Eigenvalue	1.86	1.30
Threshold	0.02	0.01
Q10	−0.12	0.73
Q40	0.06	0.78
Latency	−0.51	0.25
BRR	0.82	−0.01
HRR	0.83	0.06
Q50%	0.00	−0.53

Bold type represents the high correlation value between RFP and RRTF residuals based on eigenvalue of >1.