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ORIGINAL ARTICLE

Age-Related Changes in Temporal Processing of Rapidly-Presented Sound Sequences in the Macaque Auditory Cortex

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Abstract

The mammalian auditory cortex is necessary to resolve temporal features in rapidly-changing sound streams. This capability is crucial for speech comprehension in humans and declines with normal aging. Nonhuman primate studies have revealed detrimental effects of normal aging on the auditory nervous system, and yet the underlying influence on temporal processing remains less well-defined. Therefore, we recorded from the core and lateral belt areas of auditory cortex when awake young and old monkeys listened to tone-pip and noise-burst sound sequences. Elevated spontaneous and stimulus-driven activity were the hallmark characteristics in old monkeys. These old neurons showed isomorphic-like discharge patterns to stimulus envelopes, though their phase-locking was less precise. Functional preference in temporal coding between the core and belt existed in the young monkeys but was mostly absent in the old monkeys, in which old belt neurons showed core-like response profiles. Finally, the analysis of population activity patterns indicated that the aged auditory cortex demonstrated a homogenous, distributed coding strategy, compared to the selective, sparse coding strategy observed in the young monkeys. Degraded temporal fidelity and highly-responsive, broadly-tuned cortical responses could underlie how aged humans have difficulties to resolve and track dynamic sounds leading to speech processing deficits.

Key words: hearing loss, normal aging, presbycusis, rhesus monkey, sparse

Introduction

In age-related hearing loss (ARHL, or presbycusis), a majority of elderly humans find it difficult to understand speech, particularly in noisy and hearing-challenging environments (Gates and Mills 2005; Humes et al. 2012).The neural capacity to resolve rapid temporal events such as gaps, the duration, and the rate of acoustic features is necessary for perceptions of speech and conspecific vocalizations in humans and animals (Heffner and Heffner 1986; Nagarajan et al. 1999; Rauschecker and Scott 2009; Peelle and Wingfield 2016). In elderly humans with normal or impaired hearing thresholds, speech comprehension performance is correlated with temporal processing deficits, for example elevated gap-detection thresholds and a reduced ability to process temporal cues of consonants (Snell et al. 2002; Mazelová et al. 2003; Gordon-Salant et al. 2006). Animal models of ARHL have provided several lines of neural evidence that temporal processing deficits are present throughout the auditory neuroaxis of aged animals. For example, weakened and delayed auditory brainstem responses (ABRs) and elevated neuronal activity have been shown in the cochlear nucleus, the inferior colliculus, and the auditory cortex, implying that peripheral hearing loss cannot merely explain these results (Backoff and Caspary 1994; Walton et al. 1998; Schatteman et al. 2008; Walton 2010; Parthasarathy and Bartlett

2012; Parthasarathy et al. 2014). These processing deficits in aged animals have been suggested to be a consequence of an imbalance between excitatory and inhibitory mechanisms during aging, and these effects are prevalent along the ascending auditory pathway, as well as the auditory cortex (Caspary et al. 2008; Hughes et al. 2010; Syka 2010; Alvarado et al. 2014).

The macaque monkey has recently become a useful nonhuman primate model of ARHL given the homologous anatomy and neurophysiology of the auditory nervous system from the cochlea to at least the belt areas of the auditory cortex. Although ARHL studies in the macaque are currently limited compared with rodent models, the findings and implications on aging and perception are consistent with those shown in both humans and rodents. Cochlear histopathologies (Engle et al. 2013), ABRs (Ng et al. 2015), and histochemical profiles within the brainstem (Gray et al. 2014a, 2014b), midbrain (Engle et al. 2014), and thalamus (Gray et al. 2013) all show differences between young and geriatric animals that are consistent with rodent and human data. Further, response properties of auditory cortical neurons in both the core area and the caudal lateral belt area in geriatric animals have been shown to have elevated spontaneous and sound-evoked activity with rapid onset response latency and broader spatial tuning (Juarez-Salinas et al. 2010; Engle and Recanzone 2013). Temporal processing of amplitude-modulated (AM) noise is similarly degraded during aging. Geriatric monkeys showed an overall loss of AM-rate tuning (2–128 Hz) in the core, decreased numbers of temporal coding neurons, and a reduced ability to phase-lock to the envelopes of AM noise (Overton and Recanzone 2016). These findings reveal that age-related changes along the auditory neuroaxis compromise the capacity of the auditory cortex to process multiple features of a sound, providing a compelling model to study neural mechanisms of hearing loss commonly present in elderly humans at the cortical level.

The ability to distinguish discrete acoustic features embedded in a rapid, continuous auditory stream is fundamental to auditory perception, and particularly for speech comprehension in humans. At low temporal frequencies, core neurons of young macaque monkeys synchronize their responses to the stimulus envelope of tone-pip sequences, and are capable of distinguishing middle-tone components within a stimulus sequence (Phan and Recanzone 2007). To systemically evaluate age-related differences in temporal processing in this study, we used 4 tone-pip and noise-burst sequences with equal periods of stimulus durations and intervals. Sound sequences from slow to fast temporal rates (6–48 ms durations) provided an opportunity to track the dynamics of firing rate and phase-locking within and across stimulus types, cortical regions, as well as age groups. These stimuli span the perception of periodicity (6–18 ms durations; 167–55 Hz), thought to be important for voicing and prosody, and the perception of the envelope (24–48 ms durations; 42–21 Hz), thought to be important for tempo and consonant discrimination (Rosen 1992). We predicted that auditory neurons in the old monkeys would have elevated spontaneous and stimulus-evoked responses, and reduced temporal precision in firing relative to the stimulus envelopes, compared with those in the young monkeys. We also tested the hypothesis that neural representation of sound sequences would be altered at the population level of activity in the aged auditory cortex.

Materials and Methods

Subjects

Five adult male rhesus macaques (*Macaca mullata*) were used in the current experiment. Over the course of the study, 3 young monkeys were 5.1–6.2 years (monkey F), 6.3–7.5 years (monkey G), and 9.5–11.5 years (monkey L), while 2 old monkeys were 24.1–25.8 years (monkey A) and 24.4–26.2 years (monkey B). Macaques age at approximately 3 times the rate of humans (Ng et al. 2015). A portion of neural data from these monkeys has been reported in the context of different studies (Woods et al. 2006; Juarez-Salinas et al. 2010; Engle and Recanzone 2013; Overton and Recanzone 2016). The present data regarding temporal coding of rapidly presented sequences has not been reported elsewhere. All animal subjects were raised at the California National Primate Research Center at the University of California at U.C. Davis, and had no history of exposure to ototoxic drugs, excessive loud noise, or ear infections. They did not show auditory impairments with normal detection audiograms between 0.5 and 16 kHz and broadband noise stimuli (Juarez-Salinas et al. 2010; Ng et al. 2015). All experimental procedures adhered to the National Institute of Health's guidelines and were approved by the U.C. Davis Institutional Animal Care and Use Committee.

Stimuli and Apparatus

The recording procedures were the same as those described in our previous studies (Juarez-Salinas et al. 2010; Engle and Recanzone 2013; Overton and Recanzone 2016) and so are only briefly summarized here. A head-post and a recording chamber was surgically implanted to allow for a vertical approach to the superior temporal gyrus. Every recording session started with lowering a tungsten electrode (2–4 MΩ; FHC, Maine) with a hydraulic microdrive (Narishige, Japan) into the left hemisphere. Search stimuli to locate auditory-responsive neurons included clicks, tones, band-passed, and broadband noises, all presented through a speaker contralateral to the recording chamber or at a frontal location (±30° in azimuth, 0° in elevation). All speakers were 1 m from the center of the interaural axis. Neural activity was displayed on an oscilloscope and audio monitored. Neurons with driven activity were isolated with a time-amplitude window discriminator (BAK Electronics), and their characteristic frequencies and stimulus threshold levels were audio-visually determined by the experimenter. This was done by adjusting the frequency and decreasing the stimulus intensity to find the frequency that could reliably evoke a response in the isolated neuron at the lowest stimulus intensity. Spike activity was recorded by a computer at a temporal resolution of 1 ms. Neurons were later identified to either the core (A1, R and RT) or the belt (CL and ML) based on the location in the recording grid, frequency tuning, other response properties, and the frequency progression along the rostrocaudal axis of the superior temporal plane (Juarez-Salinas et al. 2010). Recordings from areas R, RT, and ML were also used to define the borders of areas A1 and CL.

Stimuli were created similarly to the method described in Phan and Recanzone (2007). Sequences of 4 tone pips and 4 noise bursts were generated at eight stimulus durations. For a given sequence the acoustic stimulus duration, either the tone-pip or noise-burst was the same as the interstimulus interval and were presented at durations of 6, 12, 18, 24, 30, 36, 42, and 48 ms (2-ms linear rise/fall). Each stimulus was presented at 60 or 65 decibel sound pressure level (dB SPL, A-weighted) with a ±2-dB variation between-stimulus sequences to young and old monkeys, respectively. The increased intensity level for the aged monkeys was designed to create a comparable sensation level as the younger monkeys. Further, this 5-dB difference did not have an effect on results reported on our previous study (Overton and Recanzone 2016). These stimuli were presented

well above the detection thresholds of 0.5–16 kHz (~55 dB, Juarez-Salinas et al. 2010) and ABR thresholds (30 dB for click stimuli; Ng et al. 2015) of the 2 old monkeys. Therefore, the stimuli were presented at a level matching to hearing ranges of the old monkeys. Tone-pip stimuli were always centered at the characteristic frequency of a given neuron, defined as described above. Noise-burst stimuli were broadband Gaussian noise. Tone pips and noise bursts at each duration were presented in randomly interleaved fashion, along with other stimuli not reported here, for 12 trials per session.

Recording experiments were conducted in a sound booth (Industrial Acoustics Company) lined with echo-attenuating foam while the monkey sat in an acoustically-transparent primate chair. Two young monkeys (F and L) listened to stimulus sequences while performing a simple go/no-go sound localization task. This task required the monkey to depress a lever to start the trial, then 3 to 7 stimuli were presented from 1 location. The stimulus then was presented at a different location, followed by an audible click of the solenoid that provided a small amount of fluid reinforcement. If the monkey then released the lever a larger amount of fluid reinforcement was provided. The third young monkey G and the 2 old monkeys (A and B) sat quietly and heard the same sounds, but were not required to press a lever. They received the same large juice reward at about the same intervals. We have extensively tested the possibility that task engagement could influence response properties of isolated neurons between the "active" young monkeys (F and L) and the "alert" young monkey G in our previous studies and have found no significant differences or trends (Woods et al. 2006; Juarez-Salinas et al. 2010; Engle and Recanzone 2013). The current study compared response profiles of cortical neurons between monkeys F and L (lever response to location changes) and monkey G (no lever response), and no observable difference was present in terms of onset response latency, characteristic frequency, spike discharge, and vector strength (VS) between these animals, consistent with our previous reports regarding auditory coding in these cortical areas between these 2 behavioral conditions (Woods et al. 2006; Juarez-Salinas et al. 2010; Engle and Recanzone 2013). Further, and consistent with those findings, we have found no evidence that the behavioral state influenced any aspect of the neuronal response to sequence stimuli, which are the only responses analyzed in this study.

Data Analysis

Peri-stimulus time histograms (PSTHs) were constructed in 1-ms time bins to visualize activity patterns associated with the sound envelopes of tone-pip and noise-burst sequences at different stimulus durations. Response latencies to tone-pip and noise-burst stimuli were estimated for each isolated unit defined as the median latency to the first-spike at least 10 ms or longer after the stimulus onset, pooled from all stimulus duration conditions. This allowed us to consider the latency difference of core and belt neurons with respect to tone and noise stimuli, and provided a reliable estimate for neurons with relatively high spontaneous activity, particularly in the geriatric case. Spontaneous activity of a neuron was estimated from spike counts during the initial 5-ms interval from the trial onset, across all stimulus presentations of tone and noise sequences (960 ms total). This time period was selected as it was before any driven activity of the cortical neuron was possible due to the travel delay of the sound from the speaker to the tympanic membrane and the synaptic delay through the auditory neuroaxis. The firing rate of a neuron was based on the stimulus sequence duration and median latency, parallel to our previous study (Phan and Recanzone 2007). This was calculated using a duration that consisted of the sound duration for the 4 stimulus presentations and the 3 intervals (e.g., 6-ms tone pips: 6 ms $*$ (4 tones + 3 intervals) = 42 ms) and then we added the median first-spike response latency of that neuron. For each neuron, spike data was normalized to its spontaneous activity in 1-ms steps, and averaged within the stimulus sequence duration. The resultant value was then defined as the average firing rate of a neuron at the specific stimulus duration. As spontaneous activity of auditory cortical neurons was always large in magnitudes at old monkeys (Juarez-Salinas et al. 2010; Overton and Recanzone 2016), data normalization was required to assess the extent of activity change due to the auditory stimulus. This procedure offered an objective, accurate measure of stimulus-driven spike discharge, as opposed to raw spike values. It also allowed us to pool neural data across stimulus conditions and cortical regions for advanced statistical comparisons. A signal-to-noise ratio (SNR) for tone pips (or noise bursts) was computed for each unit, such that the maximum firing rate associated with a stimulus duration was divided by the spontaneous activity of that neuron. If the spontaneous activity of a neuron was less than one spike per second, the value of one was used to compute the ratio.

Temporal Coding Analysis of Auditory Response

To measure how well a neuron synchronized or showed phase-locking responses to temporal features of sound sequences, VS was calculated using 1-ms time bins. A pip/noise duration and the interpip/noise interval was considered as one feature cycle (e.g., 12 ms for a 6-ms tone pip or noise burst). Each spike was assigned a vector with a length of 1 and phase assigned as the time of occurrence relative to the feature period. The calculation was defined as follows (adapted from Yin et al. 2011; Niwa et al. 2013):

$$VS = \frac{\sqrt{\left(\sum_{i=1}^{n} \sin\theta_i\right)^2 + \left(\sum_{i=1}^{n} \cos\theta_i\right)^2}}{n}$$

$$\theta_i = 2\pi \frac{(t_i \; modulo \; p)}{p}$$

The variable n is the total number of spikes; θ_i is the phase of each spike in radians and calculated with the MATLAB command "modulo", and t_i is the time occurrence of a spike from the stimulus onset, and p is the feature period. Values of VS range from 0 (no synchrony) to 1 (perfect synchrony). The Rayleigh test of uniformity, $2n\,(VS)^2$, was used to determine the statistical significance of the phase-locking response (Lu and Wang 2000; Mardia and Jupp 2000). The Rayleigh test is an approximation of a chi-square test constrained with 2 degrees of freedom, appropriate for circular distributions. For a given stimulus duration, the calculated value >13.8 indicate that the synchronization of neuronal activity reflected a sample of an oriented distribution that is not attributed to chance ($P < 0.01$; Bunnen and Rhode 1978; Phan and Recanzone 2007). Neurons with a VS > 0.1 and the Rayleigh statistics >13.8 to at least 1 stimulus duration for tone pips or noise bursts were considered to be synchronized units. We further evaluated how readily a synchronized neuron followed sound envelopes, and quantified this as the "temporal sensitivity index", defined as 1–(n/16), where n was the number of sound stimuli to which it significantly synchronized to. The more sound stimuli a neuron

synchronized to, the closer this index is to zero. Thus, the metric gives an indication of how readily (less selectively) a neuron synchronized to sounds with different temporal durations.

In addition to VS, this study also employed cross-correlation analysis to estimate the degree of similarity between the 2 time-varying signals, the presented sound sequence and the trial-average spike train of a neuron. A sliding dot product of the 2 signals shifted along a time window of the signal duration was calculated, with the resultant value at the maximum when the 2 signals match (i.e., peaks and/or troughs between them align). We assumed that if a neuron responded to and temporally followed a tone pip or noise burst, it would display isomorphic-like activity pattern resembling the sound envelope. The sound signal was represented as a vector of values of 1 and 0 to signify the "on" and "off" periods of tone pips/noise bursts at a given stimulus duration. The spike data and the sound signal were the same length in 1-ms time bins, and divided into 4 cycles. Each cycle represented one "on" and one "off" period of tone pips or noise bursts (i.e., 2 $*$ stimulus duration). A cross-correlation coefficient between the 2 signals at each cycle was computed in MATLAB with the command "xcorr" and the normalization option "coeff". The resultant output was a vector of correlation coefficients as a function of time, which was (2 $*$ cycle period) – 1 ms long. For each cycle, the peak correlation and its corresponding time where the 2 signals yielded the highest correlation coefficient were noted. The time bin associated with the peak correlation was then divided by the length of a cycle to estimate the time lag between the 2 signals. The root-mean-square (RMS) value was computed from the vector of correlation coefficients to estimate the overall degree of similarity (i.e., average correlation) between the 2 signals at each cycle. Statistical tests were conducted in SPSS (19.0) and MATLAB (R2015b). Kolmogorov–Smirnov (K–S) tests and Wilcoxon rank-sum tests were used to determine if neural measures were significantly different between ages or cortical regions. Chi-square tests were used to examine if there was a significant difference in the number of evoked units between comparison groups, relative to chance. The critical probability level was set at 0.05, and was adjusted by the number of pairwise comparisons conducted accordingly (Bonferroni correction).

Analyses of Stimulus Representations in Auditory Coding

To assess whether the activity pattern of the auditory cortex differed between the young and old monkeys in representing tone pips and noise bursts, we further characterized stimulus-evoked activity based on response profiles of neurons to the 48 ms tone pips and noise bursts. Compared to fast temporal rates (e.g., 6 or 12 ms), the lowest temporal rate (i.e., 48 ms) in our study provided the optimal condition for neurons to respond and synchronize effectively throughout the stimulus duration, and thus served as a comparable condition across age groups and cortical regions. Neurons that were active primarily during sound onset periods (the first temporal cycle), showed "onset-only" responses to sounds. "Onset-plus" neurons responded to the sound onset and any of the remaining temporal cycles of a sound sequence (the second, third, or fourth temporal cycle). Continuous spike activity across all 4 temporal cycles was considered a "sustained" response characteristic of a neuron.

We conducted a multivariate pattern analysis, representational similarity analysis (RSA), to estimate auditory coding differences between the young and old monkeys, adapted from the RSA toolbox developed by Kriegeskorte et al. (Nili et al. 2014). This method assumes patterns of neural activation in a given area are informative of what it represented, and thus activation patterns of the given area will be correlated between stimuli sharing similar perceptual and/or cognitive properties (Kriegeskorte et al. 2008). We conducted RSA to evaluate the extent that the auditory cortex encoded stimulus attributes, for example stimulus-type and temporal information. For each neuron of a ROI (i.e., region of interest, for example old core), normalized trial-average firing rates across all stimulus conditions were arranged as column vectors of 64 conditions (i.e., 2 stimulus types $*$ 8 stimulus durations $*$ 4 cycles). Within each ROI, Pearson's correlations coefficients (r) were calculated between any 2 stimulus conditions, and yielded a set of correlation distance ($1 - r$) across the 64 stimulus conditions. The multivariate response data were then illustrated in a representational dissimilarity matrix (RDM) to show differences of evoked neural representations between stimulus conditions. When the correlations between 2 evoked neural patterns were strong (e.g., 12 ms tone pips vs. 18 ms tone pips), it indicated that the given brain region responded more similarly between the 2 stimulus sequences (correlation distances close to 0). In contrast, when the correlations between 2 stimuli were weak (e.g., 12 ms tone pips vs. 30 ms noise bursts), the neural representations between the 2 stimuli were more dissimilar (correlation distances close to 1). In addition, dendrograms were constructed with unweighted mean distance (MATLAB functions "linkage" and "dendrogram") across 64 stimulus conditions for each ROI. The agglomerative hierarchical cluster trees were used to visualize representational distances among 64 stimulus conditions. Stimulus conditions linked within a cluster suggested these features were encoded more similarly than those from other clusters. A cophenetic correlation coefficient (MATLAB function "cophen") was calculated to estimate how faithfully a dendrogram represented pattern dissimilarities among observations of the 64 stimulus conditions. A value of 1 indicated a perfect description of the observed pattern dissimilarities by a dendrogram.

For statistical testing, we determined the probability of obtaining an observed RDM of a given ROI by random sampling. For each ROI, the 64 stimulus-condition labels were randomly shuffled for each neuron, and a permuted RDM was computed. A correlation coefficient was then estimated between the permuted RDM and the observed RDM. A perfect correlation of 1 would occur when the observed RDM is compared to itself, and thus this measure examined how close a permuted RDM is to the observed RDM. A distribution of sampling correlation coefficients was created by repeating the procedure 10 000 times. The comparison for a given ROI was considered significant if the probability of the observed RDM was <0.05 (i.e., 97.5% confidence interval of the sampling distribution, 2-tailed). The same approach was used to test if an observed dendrogram per ROI (i.e., cophenetic correlation coefficient) was different from a sampling distribution. Nonparametric permutation statistics (t-tests; 10 000 samplings without replacement) were used to examine the effects of age and cortical region on pattern dissimilarities within and between-stimulus sequence types.

Results

The present study reports the results from recordings of a total of 588 units from the 5 monkeys, summarized in Table 1. Twenty-three units of monkey B were classified as R/RT neurons, and their response properties were similar to those of A1 neurons in the same monkey. There were no subtle differences in neural responses within a cortical region (A1 or lateral belt) of

Table 1. Distribution of auditory neurons recorded in the auditory core and lateral belt of the 5 monkeys. $N = 588$

Group	Monkey	Core		Belt		Total
		A1	R/RT	CL	ML	
Old	A	46	—	38	—	84
	B	98	23	36	1	158
Young	F	47	—	43	—	90
	G	97	—	—	—	97
	L	77	—	82	—	159

each age group. Therefore, the group of core neurons combined A1 and R/RT units, while the group of belt neurons was mainly caudal lateral belt neurons and one medial lateral belt neuron. Over half of the core neurons had CFs below 6 kHz in the old monkeys (57%) and the young monkeys (67%), while the majority of belt neurons had characteristic frequencies above 6 kHz in the old monkeys (59%) and the young monkeys (51%) (Supplementary Fig. 1). We also assessed if the CF of a neuron would vary with response onset latency, firing rate, VS, or other neural measures, and there was no significant correlation between CF and any of the neural measures ($P > 0.1$). Figure 1 illustrates examples of 4 neurons responsive to tone pips and noise bursts. Three common differences between the young and old subjects can be observed in the raster plots. (1) Neurons of the old subjects fired vigorously to sound stimuli, relative to those of the young ones. (2) Within the tone/noise intervals the old neurons often maintained strong spike activity, compared to the young neurons. (3) The young belt and core neurons exhibited response differences to tone pips and noise bursts, while the old neurons fired vigorously to both stimulus types.

Age-Related Decrease in Response Onset Latencies

Cortical auditory neurons of aged monkeys generally have short response latencies to sound stimuli (Engle and Recanzone 2013). For tone-pip stimuli, neurons of the old subjects showed shorter median first-spike latencies than those of the young subjects in both core (22.07 ± 0.59 vs. 24.07 ± 0.53; K–S test = 0.173, $P < 0.005$) and belt (19.03 ± 0.71 vs. 28.62 ± 0.75; K–S test = 0.611, $P < 0.0001$). It was also true for noise-burst stimuli in both cortical regions (Core: 22.82 ± 0.63 vs. 25.99 ± 0.63, K–S test = 0.236, $P < 0.0001$; Belt: 18.84 ± 0.77 vs. 27.96 ± 0.54, K–S test = 0.731, $P < 0.0001$). The majority of response latencies in old core and belt neurons had very short latencies (Fig. 2, black lines) in all conditions relative to the young ones, and the difference between the old and young was most prominent for the belt neurons. In the young monkeys, core neurons had shorter response latencies than belt neurons for both tone pips (K–S test = 0.338, $P < 0.0001$) and noise bursts (K–S test = 0.317, $P < 0.0001$). In contrast, the old belt neurons had shorter response latencies than old core neurons for noise bursts (K–S test = 0.276, $P < 0.001$) and there was also a similar trend toward significance for tone pips (K–S test = 0.205, $P > 0.05$ with Bonferroni correction). Within each age group, no significant difference in response latencies were present between tone and noise stimulus types (p-values ranged from 0.053 to 0.144). Our results not only revealed rapid onset responses of auditory neurons in the old monkeys, but also demonstrated a reversal of the response latency differences seen between the core and belt in young animals. Belt neurons responded to sounds with a longer latency than core neurons in the young monkeys, and the opposite was true in the old monkeys.

Increased Excitability of Spike Discharge Present in Aged Monkeys

Cortical neurons consistently display high spontaneous and stimulus-driven activity in the primary and secondary visual and auditory cortical regions of aged rats, cats, and monkeys (Schmolesky et al. 2000; Leventhal et al. 2003; Hua et al. 2006; Yu et al. 2006; Hughes et al. 2010; Juarez-Salinas et al. 2010; Engle and Recanzone 2013). Increased excitability in responses were also observed in our old animals. Collapsing between tone pips and noise bursts, old core and belt neurons had higher spontaneous activity than the young neurons (Core: 34.22 ± 2.02 vs. 14.35 ± 0.73, Wilcoxon rank-sum test, $P < 0.0001$; Belt: 41.17 ± 2.94 vs. 13.06 ± 0.69, Wilcoxon rank-sum test, $P < 0.0001$; old vs. young, respectively). To clarify the degree of stimulus-driven activity of core and belt neurons that varied with age, we separated the neuron population into synchronized and non-synchronized types. Our criteria followed those of Lu et al. (2001) where a synchronized neuron had to have a VS > 0.1 and the Rayleigh statistics >13.8 for at least one stimulus sequence (see Supplementary Table S1 for details). Figure 3 shows high stimulus-driven activity in old neurons across stimulus durations relative to the young neurons. For synchronized units, old core neurons had higher driven activity than young core neurons at most stimulus durations (Fig. 3*B*,*D*). It was also true for the belt neurons to noise stimuli (Fig. 3*A*,*C*), while most stimulus durations trended toward a significant difference between young and old neurons for tone-pip stimuli (e.g., 24, 36, and 42 ms conditions in Figure 3A; $P > 0.05$ with Bonferroni correction). Age-related influences on stimulus-driven activity also depended on cortical regions. We found that young core neurons had higher driven activity than young belt neurons at all stimulus durations of tone-pip stimuli only (P-values <0.0005), except for the 42 ms condition ($P > 0.05$ with Bonferroni correction). However, there was no activity difference between the 2 cortical areas for tone-pip or noise-burst stimuli for the old monkeys ($P > 0.05$). For nonsynchronized neurons, the effects of age were only present in 2 tone-pip conditions for core neurons (Fig. 3F). Nonsignificant results were found at other tone-pip conditions in the core and belt neurons (Fig. 3*E*,*F*), potentially due to the small sample size of nonsynchronized neurons available for the analysis. No activity difference by age or cortical areas was found in non-synchronized neurons for noise-burst stimuli (Fig. 3*G*,*H*, $P > 0.05$).

Our analysis of stimulus-driven activity was further divided into the 4 cycles of tone or noise on/off periods. Instead of starting from the sound onset, we measured normalized spike data from the time point of the median first-spike latency of a given neuron. Each cycle consisted of the same duration for stimulus -on and -off intervals (e.g., 6 ms tone-on and 6 ms tone-off for 1 cycle of a tone-pip stimulus). The average firing rate was normalized as before, and calculated at each of the 4 cycles. Similar to the previous results, old synchronized neurons showed higher-driven activity than the young neurons across cycles of different stimulus durations for both stimulus types, especially in the core (Supplementary Fig. 2 and Table S2 for details). There was a similar age-related trend for the non-synchronized neurons that did not reach statistical significance, likely due to the small sample size of this neuron group (results not shown). No cortical difference in stimulus-driven firing rate within each age group across the 4 cycles was

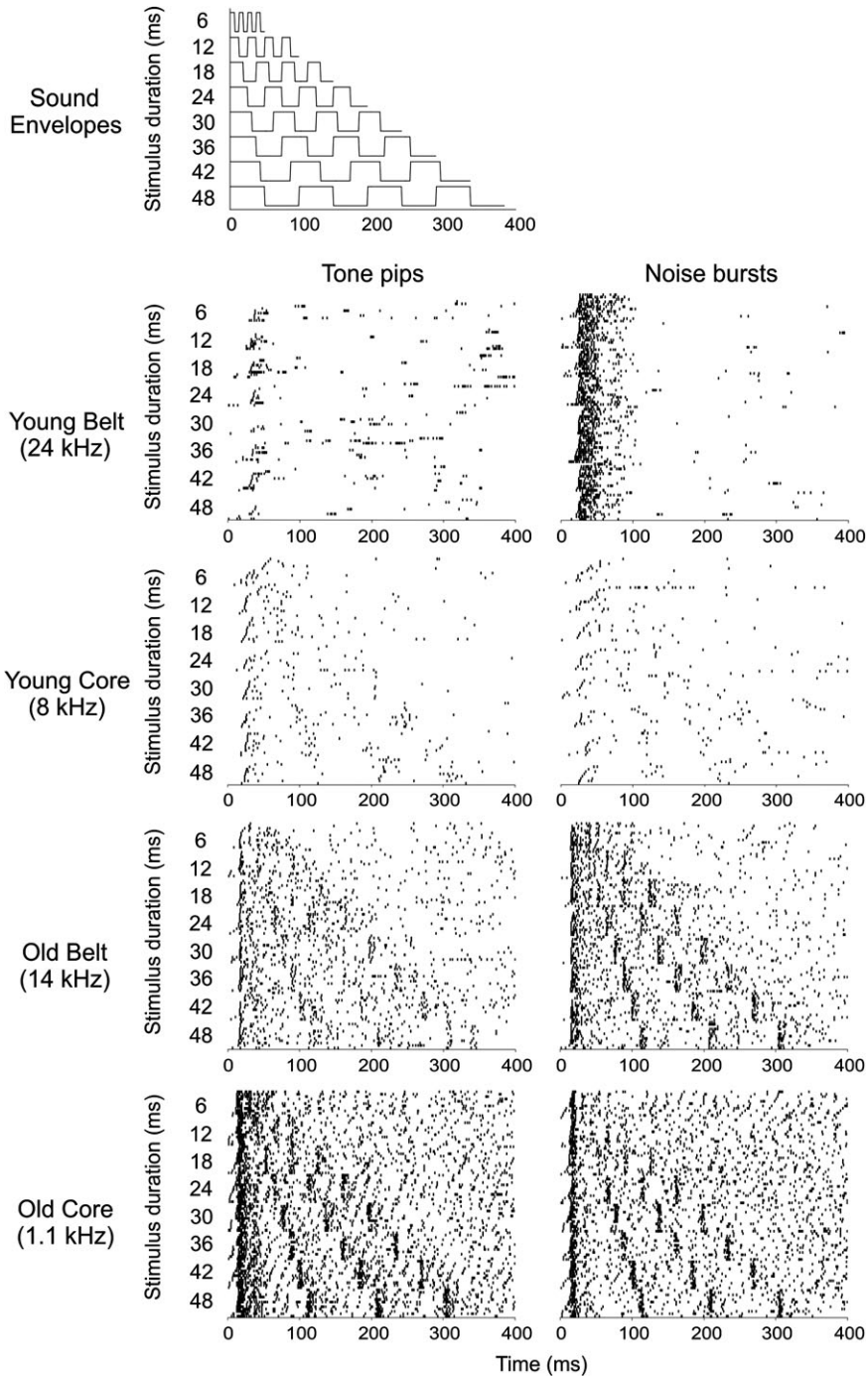

Figure 1. Auditory responses to tone pips and noise bursts varied by age and cortical region. The top graph displays the sound envelopes at 8 stimulus/interval durations, 6–48 ms. Raster plots display spike trains of tone pips (left column) and noise bursts (right column) in 4 example neurons, 12 repetitions for each stimulus. Characteristic frequency was specified for each example. The duration of stimulus-driven spike trains increased with increasing stimulus duration. Activity preferences of belt and core neurons in the young monkeys were associated with noise bursts and tone pips respectively, while those areas shared similar firing patterns in the old monkeys.

present in synchronized and nonsynchronized neurons. These cumulative findings indicate that higher-than-normal spike discharge, regardless of spontaneous and stimulus-evoked activities, was widely present in the old subjects, particularly for those units showing auditory synchrony.

Age-related decreases in SNRs of spike activity are often associated with increasing neural responsiveness to both optimal and nonoptimal stimuli, which introduce noise variance in visual and auditory coding (Leventhal et al. 2003; Zhang et al. 2008; de Villers-Sidani et al. 2010; Clinard and Cotter 2015). The SNR was calculated for each neuron by dividing the maximum evoked discharge rate by the spontaneous activity of that unit. This analysis revealed similar SNRs between the young and old subjects, regardless of the cortical region (Supplementary Table S3). Among the synchronized population for tone-pip stimuli, core neurons had higher SNRs than belt neurons in the

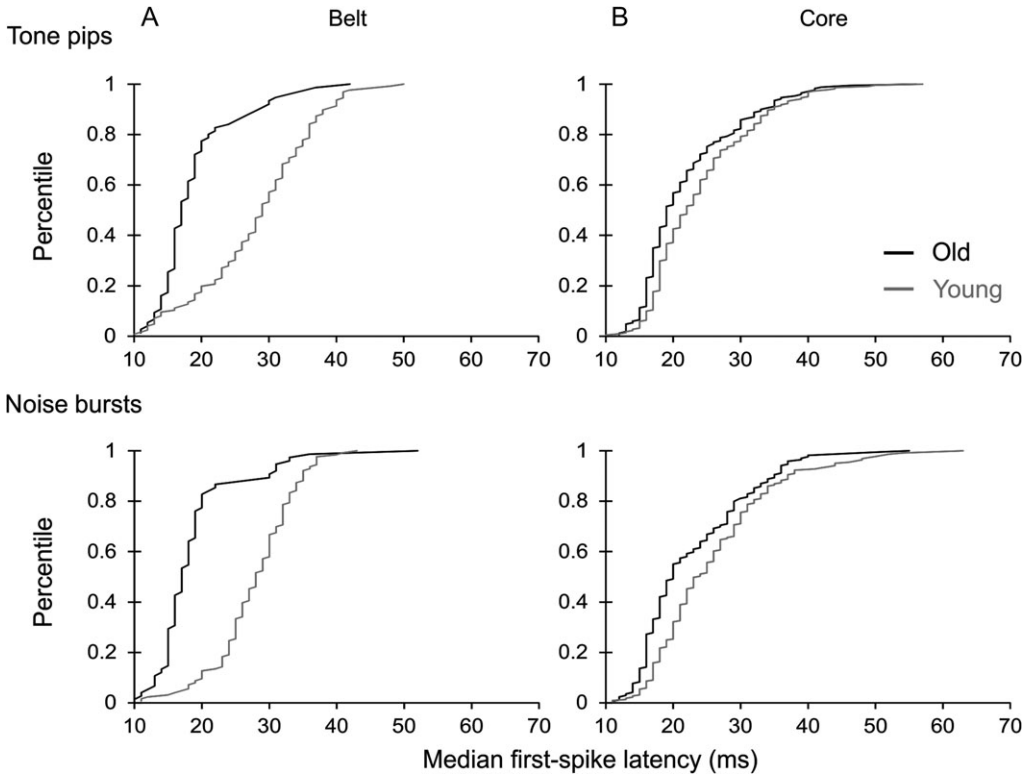

Figure 2. Short response latencies to sound sequences in old monkeys. The graphs depict cumulative distributions of the median first-spike response latency of belt (*A*) and core (*B*) neurons in young (gray lines) and old (black lines) monkeys. An age-related difference in response latencies was present in all cortical regions and stimulus types (K–S test, $P < 0.005$).

old animals (Wilcoxon rank-sum test, $P < 0.005$), but not in the young animals ($P > 0.05$). Parallel to other findings, neither age nor cortical differences in SNRs were present in the nonsynchronized population.

Effects of stimulus adaptation on spike discharge were found across various stimulus conditions (see Fig. 4) in that neural responses to the first temporal cycle of sound sequences appeared to be the highest compared to the responses to other cycles for a given stimulus duration, except for those of young belt neurons. Here, the study focused on synchronized neurons only when examining adaptation effects on spike discharge across the 4 temporal cycles. This was because these neurons were more likely to respond to multiple temporal cycles, and allowed us to compare spike discharge across successive temporal cycles, in contrast to nonsynchronized neurons. We did not include synchronized young belt neurons because they normally showed weak, tonic activity during the remaining sound presentations in contrast to young core neurons. Regardless of stimulus type or age, a reduced response following the sound onset was more prevalent in synchronized neurons whose normalized discharge rate was the highest at the first temporal cycle for stimulus durations of 24 ms or above, compared to the remaining 3 temporal cycles (Wilcoxon rank-sum tests, *P*-value <0.0001). In the old monkeys, synchronized core and belt neurons show similar adaptation effects between the 2 stimulus types.

Age-Related Differences in Processing Rapid Temporal Features

Our previous study revealed that the periodicity of core auditory responses was enhanced with increasing temporal duration (i.e., decreasing temporal frequency; Phan and Recanzone 2007), and the current findings support this observation. Figure 4 shows the population responses across all neurons studied to each of the different stimuli in young and old monkeys. Young core neurons (Fig. 4, the left 2 columns, blue lines) exhibited clear synchronous firing to sound envelopes of tone pips and noise bursts at longer duration lengths. In contrast, young belt neurons (Fig. 4, the right 2 columns, blue lines) primarily responded to the sound onset of tone pips or noise bursts, and maintained low, residual firing to the remaining stimulus presentations. Old neurons (red lines), regardless of cortical regions, showed isomorphic-like activity patterns to the presented sounds. These age-related observations in temporal coding were further confirmed by examining the proportion of synchronized neurons in each region. A greater proportion of young core neurons showed significant VS for both stimulus types relative to young belt neurons (Fig. 5*A*,*C*, Chi-square statistics: 11.41–36.00, $P < 0.0005$). In contrast, this cortical difference in the proportion of synchronized neurons was absent in the old monkeys (Fig. 5*B*,*D*).

One drawback in the current analysis was that spike activity during the onset of tone-pip or noise-burst sequences could heavily contribute to the resultant VS and Rayleigh statistics. A neuron with strong spike activity only to the onset of a sound sequence would yield a high Rayleigh statistic, even though this neuron did not synchronize with the stimulus envelope of the remaining sound (i.e., the second through fourth cycles). Therefore, the VS analysis was repeated and focused on only responses from the second cycle to the end of a sound presentation (i.e., 3-feature-cycle analysis), and excluded spike data within the first tone (noise) on/off cycle. Parallel to the prior

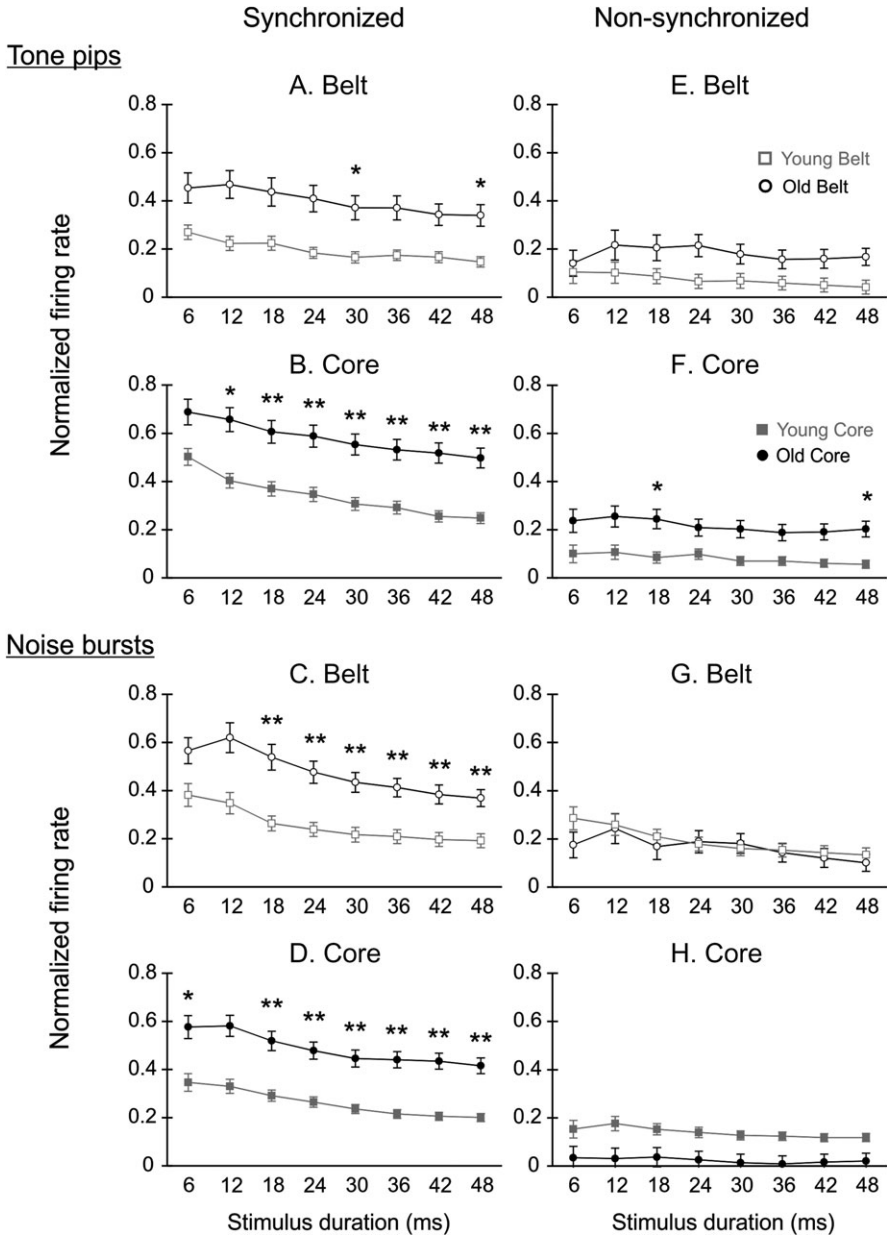

Figure 3. High stimulus-driven firing rates in old, synchronized neurons. Squares and circles denote young and old monkeys, and open and filled symbols represent belt and core neurons. Asterisks denote significant age-related difference for a given stimulus condition (Wilcoxon rank-sum test, *P < 0.0005, **P < 0.0001). Among synchronized neurons (*A–D*, left column), age-related differences were present in both cortical regions for noise bursts, while the same effect was predominantly seen only in the core for tone pips. For nonsynchronized neurons (*E–H*, right column), only 2 tone-pip conditions (*F*) showed age-related difference for core neurons, while others (*E* and *H*) were only trends towards significance at some stimulus durations. In young monkeys, response preference of core over belt existed in synchronized neurons at tone pips only (*A* vs. *B* in gray lines for 6, 12, 18, 24, 30, 36, 48 ms; Wilcoxon rank-sum test, *P* < 0.0005), but was absent in old monkeys.

findings based on the entire spike trains, there was still a greater proportion of synchronized neurons in the core relative to the belt in the young monkeys (Fig. 5*E*,*G*, Chi-square statistics 19.82–59.34, $p < 0.0001$), but such a cortical difference was absent in the old monkeys.

Previous analysis of the responses to AM noises showed that young core neurons had significantly greater VSs (i.e., better phase-locking) compared to aged core neurons (Overton and Recanzone 2016). Consistent with that report, our comparisons of the VSs among the synchronized neurons showed that young core neurons had higher VS values at long stimulus durations (30–48 ms) than old core neurons for both stimulus types (Fig. 6*C*,*D*), while no age-related difference in VS was found in belt neurons (Fig. 6*A*,*B*). Age-related differences of phase-locking also varied with the cortical region. For the young neurons, core neurons had higher VS at long stimulus durations (30–48 ms) than belt neurons for tone pips and noise bursts (Fig. 6*E*,*F*), and this difference in VS between cortical areas was again absent in the old monkeys (Fig. 6*G*,*H*). We repeated this analysis using the second through fourth cycles as described above. Although the adjusted VS and Rayleigh statistics of young belt neurons were greatly reduced in the 3-feature-cycle analysis, the corresponding findings remained the same as in the original analysis. These VS findings depict a

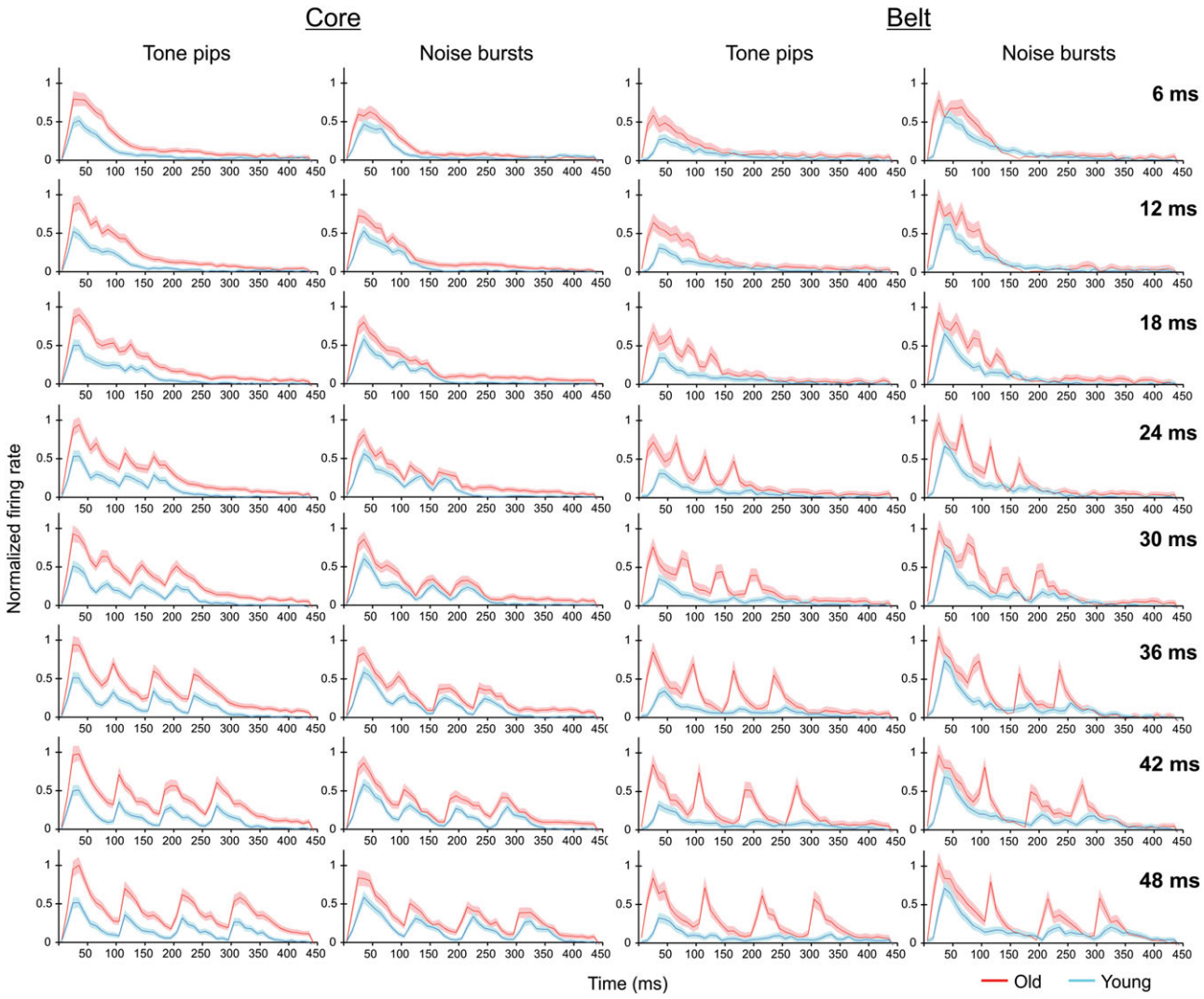

Figure 4. Elevated, isomorphic-like representation of sound sequences in old monkeys. Normalized spike activity was pooled from core and belt neurons across stimulus conditions, and are depicted in PSTHs from 6- to 48-ms stimulus durations for young (blue lines) and old (red lines) monkeys. PSTHs were constructed with 10-ms time bins without smoothing, and shaded bands represented mean standard errors. Note that phase-locking discharge patterns of population activity improved with increasing stimulus durations in most conditions, except for the young belt neurons. Young belt neurons (right columns, blue lines) mainly showed clear onset responses to the first cycle of tone-pip or noise-burst stimuli. In old monkeys (red lines), population activity of both regions followed the stimulus envelopes.

reduced phase-locking capability in neurons of the core in aged monkeys compared to those in young monkeys, indicating that functional preference in temporal coding is altered in the old monkeys, consistent with what was observed in the responses to AM noise (Overton and Recanzone 2016).

The preceding analysis of VS described the extent of temporal precision of the responses with respect to the presence of sound features. To evaluate how well neural discharge patterns would mimic stimulus envelopes, we performed a cross-correlation analysis between the 2 continuous signals. The analysis estimated the highest correlation coefficient (i.e., peak correlation) when peaks and/or troughs of spike activities and sound envelopes were best aligned. The RMS method estimated the overall degree of similarity between the 2 signals. Figure 7 shows the peak (A, the left 2 columns) and average (B, the right 2 columns) correlation coefficients of synchronized neurons as a function of stimulus durations for tone-pip stimuli. In both cortical areas, the old synchronized neurons showed higher peak and average correlation coefficients than the young neurons at numerous stimulus durations of all 4 cycles, and the effect was more prevalent in the core. There were also similar age-related differences for core and belt neurons for noise-burst stimuli, as the old synchronized neurons better mimicked stimulus envelopes of noise-burst sequences than the young neurons throughout the 4-cycle of a noise sequence (see Supplementary Table S4 for details). No cortical difference was revealed within each age group for the synchronized neuron population (results not shown). Although there was no observable difference of age within non-synchronized neurons, core neurons had higher peak and average correlation coefficients than belt neurons for tone pips only in the young subjects, but this was absent from the old subjects (see Supplementary Table S5 for details). The analysis of time lags associated with peak correlation coefficients between spike trains and sound stimuli did not reveal any age-related difference in any neuron group. These findings suggests that functional changes in temporal processing are associated with normal aging. The auditory cortex of the young animals exhibited better temporal

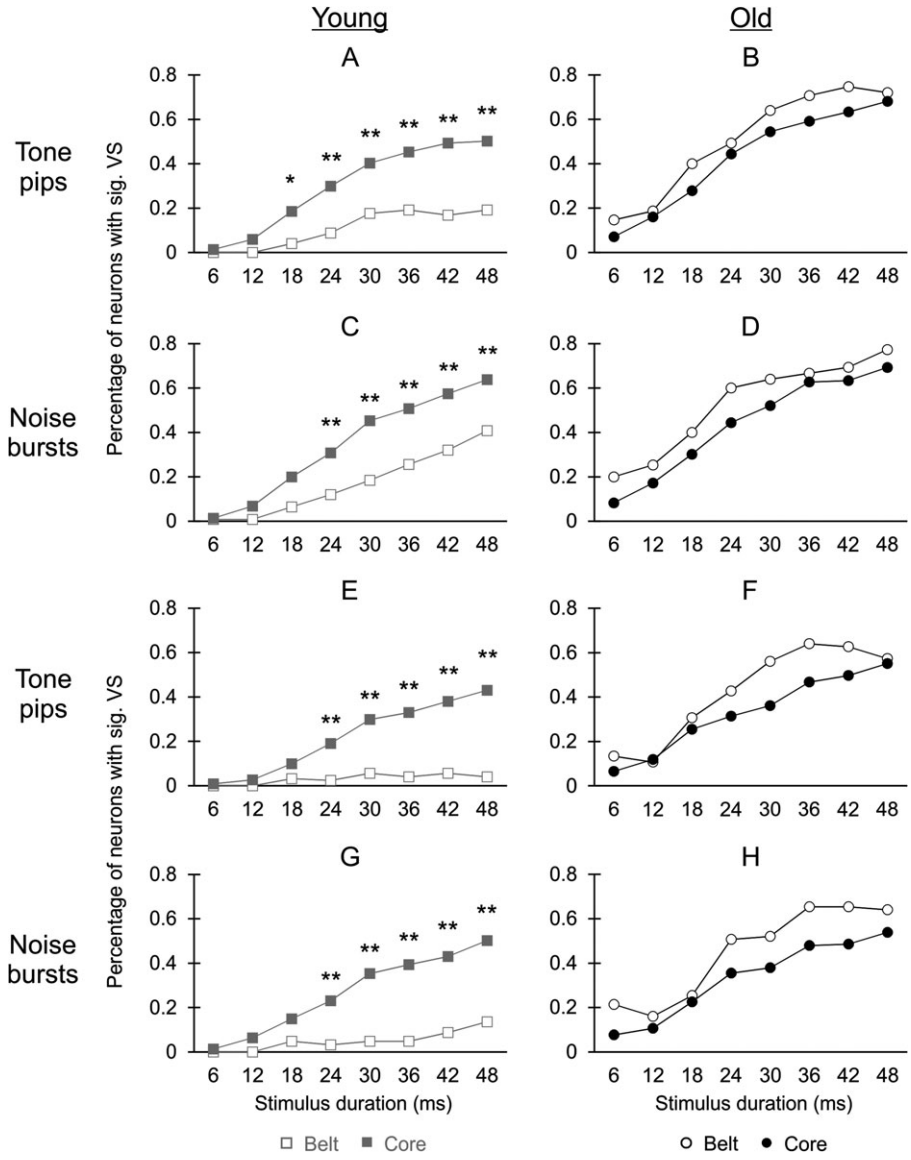

Figure 5. An absence of cortical difference in phase-locking responses present in the old monkeys. Panels *A* to *D* were based on spike data along the entire sound duration, and panels *E* to *H* were based on spike data from only the second to fourth temporal feature cycles of each sound duration (i.e., 3-feature-cycle analysis). Asterisks denote significant cortical difference for a given stimulus condition (Chi-square test, *$P < 0.0005$, **$P < 0.0001$). Regardless of whether the analyses were based on 3 or 4 stimulus cycles, there was a greater proportion of core neurons than belt neurons associated with significant VS in the young monkeys (*A*, *C*, *E*, and *G*). This cortical difference was absent in the old monkeys.

precision in their neural responses, particularly at the auditory core. Further, the higher precision of the core responses compared to the belt responses in the young monkeys was absent in the old monkeys. Instead, the aged auditory neurons demonstrated isomorphic-like representations of sound sequences in both cortical areas.

Age-Related Changes in Population Activation During Sound Representations

The present findings reveal a functional change in the representation of the temporal features of sounds as a consequence of normal aging. Aged auditory cortical neurons showed reduced phase-locking proficiency, and yet better isomorphic-like responses, bearing a resemblance to sound envelopes at all temporal frequencies. This raises the question of auditory cortical neurons respond to a range of fast- and slow-paced sound sequences in the young and old monkeys. We therefore computed a temporal sensitivity index (1-*n*/16, where *n* is the number of stimulus sequences a neuron synchronized to; see Materials and Methods section) to assess the neuronal responses to a variety of stimulus durations (based on 3-feature-cycle analysis), collapsed for both tone and noise stimuli. The closer this value is to 1, the less sensitive (i.e., more selective) the neuron responds to this set of stimuli. The results of this analysis are shown in Figure 8*A*, and revealed a clear shift in the temporal sensitivity of the belt neurons with age in which old belt neurons showed lower temporal sensitivity indexes than young belt neurons (Wilcoxon rank-sum test, $P < 0.0001$). Such a difference was not apparent for neurons in the

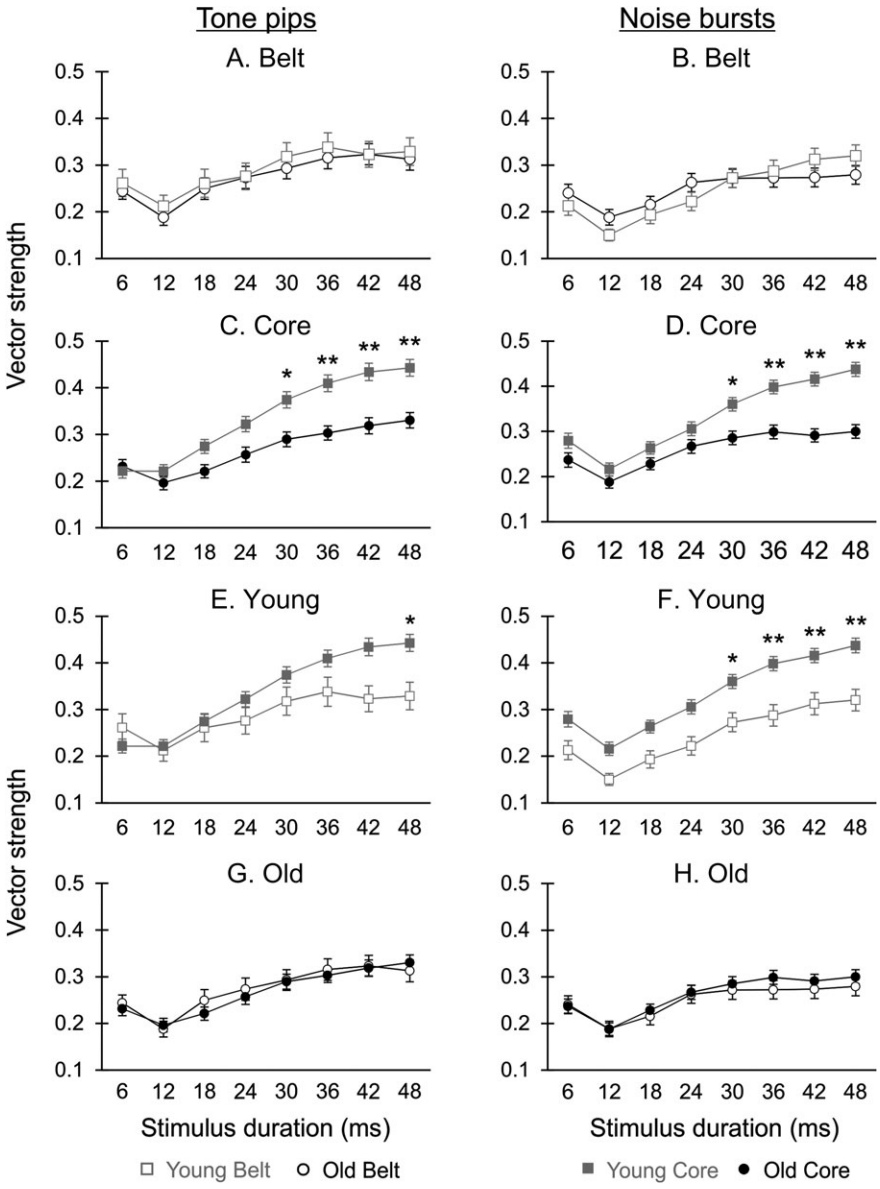

Figure 6. Age-related difference and cortical preference in phase-locking. Data are plotted to demonstrate VS differences by age (*A–D*) or by cortical region (*E–H*). Asterisks denote significant age-related difference for a given stimulus condition (Wilcoxon rank-sum test, *P < 0.0005, **P < 0.0001). Age-related differences in VS were present at long stimulus durations in the core for both stimulus types (*C* and *D*), but not in the belt (*A* and *B*). For the young subjects, core neurons had higher VS than belt neurons, predominantly for noise-burst conditions (*F*) and one tone-pip condition (*E*). This cortical preference in phase-locking was absent in the old subjects (*G* and *H*). The VS analysis based on 3 stimulus cycles (second to fourth cycles) yielded the similar results shown here for the entire sound duration (results not shown).

core (Fig. 8*B*). For the young monkeys, the majority of core neurons had temporal sensitivity indexes between 0.3 and 0.9 (median temporal sensitivity index = 0.69), while the majority of belt neurons showed a sudden peak at the index value of 0.8 and above (median temporal sensitivity index = 0.94). As a result, the belt was more temporally selective than the core in the young animals (Wilcoxon rank-sum test, $P < 0.0001$). Surprisingly, old belt neurons (median temporal sensitivity index = 0.56) were less temporally selective than old core neurons (median temporal sensitivity index = 0.69; Wilcoxon rank-sum test, $P = 0.014$). These findings indicate that age-related changes in temporal sensitivity were present in the auditory belt, where belt neurons in the old monkeys showed a broad tuning to a wide range of slow to fast temporal rates.

When inspecting trial-average spike activity of each neuron at different stimulus durations, we observed several response patterns qualitatively different between the young and old animals. Figure 9 illustrates examples of spike activity at stimulus durations of 12, 30, and 48 ms. In young monkeys, most of the stimulus-evoked responses occurred during the sound onset period (first temporal cycle; "Onset only"). Some neurons fire at the sound onset, and also at the second, third and/or fourth cycles ("Onset plus"). Only a small number of neurons showed sustained firing throughout all 4 temporal feature cycles ("Sustained"). We also encountered 2 other types of cells, those that did not fire in phase with the stimulus ("Out of phase") and those that did not have an appreciable response. For old monkeys, neurons with sustained

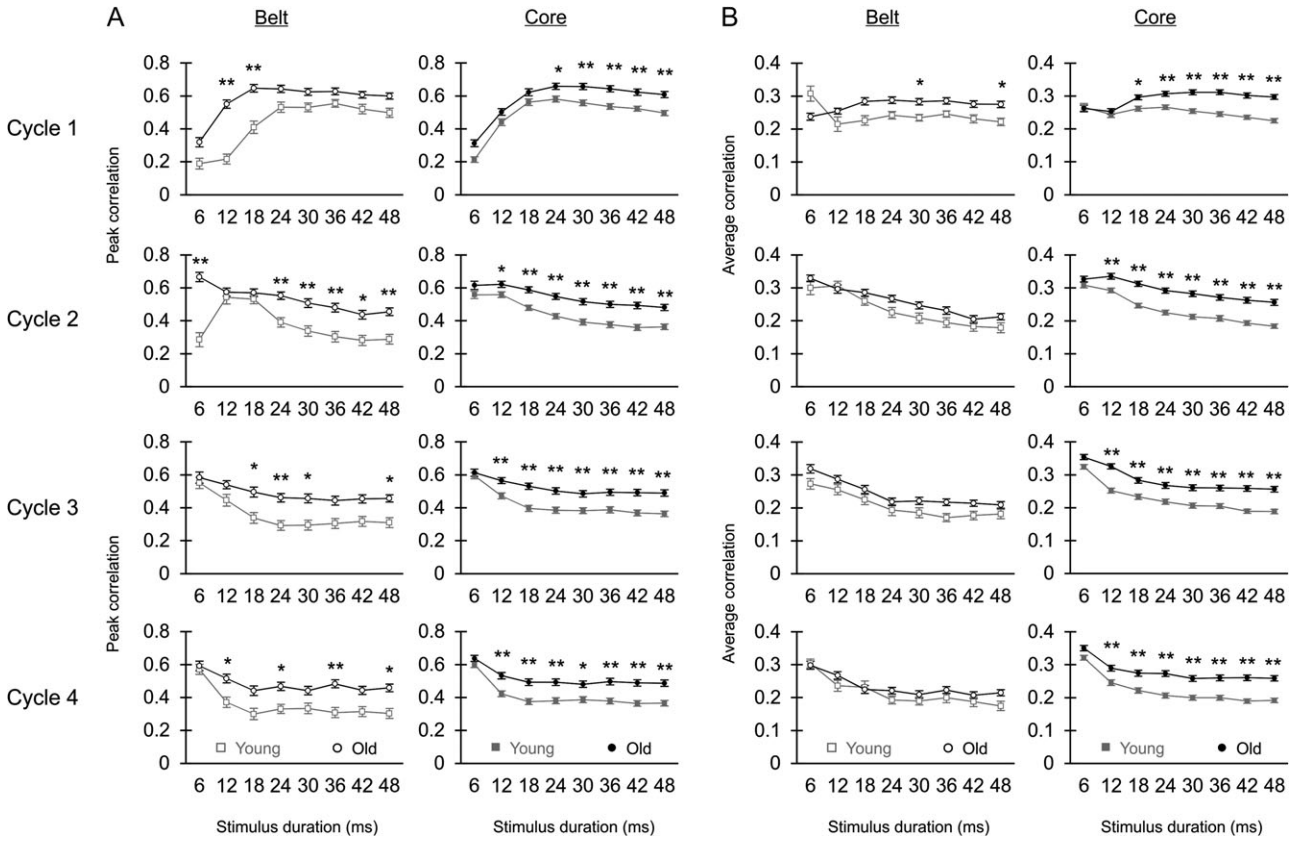

Figure 7. Age-related difference in signal similarity between tone pips and synchronized spike activity. Asterisks denote significant age-related difference for a given stimulus condition (Wilcoxon rank-sum test, *$P < 0.0005$, **$P < 0.0001$). Panels *A* and *B* depict peak and average estimates (RMS-derived) of signal similarity between spike trains and sound sequences, respectively. In both measures, the cross-correlation analysis indicates that a higher degree of signal similarity mainly exists in old core neurons relative to the young neurons. The corresponding results of synchronized neurons regarding noise-burst stimuli were also similar to the present findings based on tone pips, and are summarized in Supplementary Table S4.

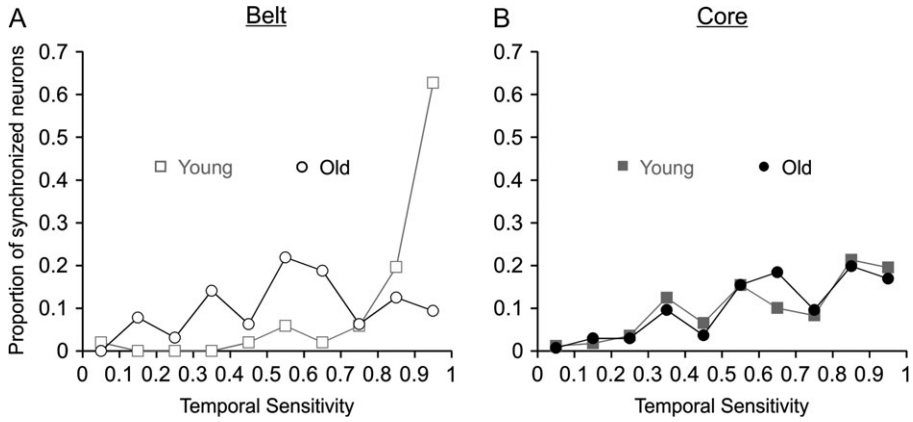

Figure 8. Age-related changes in temporal-feature representations in non-human primates. In panel *A*, an increase in temporal selectivity of the young belt region showed that over half of the young belt neurons responded and phase-locked to 3 stimuli or less (equivalent to a sensitivity index ≥ 0.81), while there was a wide range of old belt neurons synchronizing at various stimulus durations. No age difference was found in the core neurons (Panel *B*).

activity were commonly observed in the auditory cortex. Based on 48-ms sound sequences, the majority of young auditory neurons were either "Onset only" or "Onset plus", which comprised of over 60% of recorded units (Table 2). "Out of phase" neurons were very rare, with only 3 neurons encountered in the auditory cortex of young monkeys. For the old animals, over half of the neurons in both the core and belt exhibited sustained firing to sound stimuli throughout all temporal feature cycles, relative to those in the young monkeys (Table 2: ~31% and 20% in core and belt areas, respectively). This evidence suggest a contrast in neural representation of sounds between sparse and selective versus homogenous and broad coding strategies for the young and aged auditory cortex, respectively.

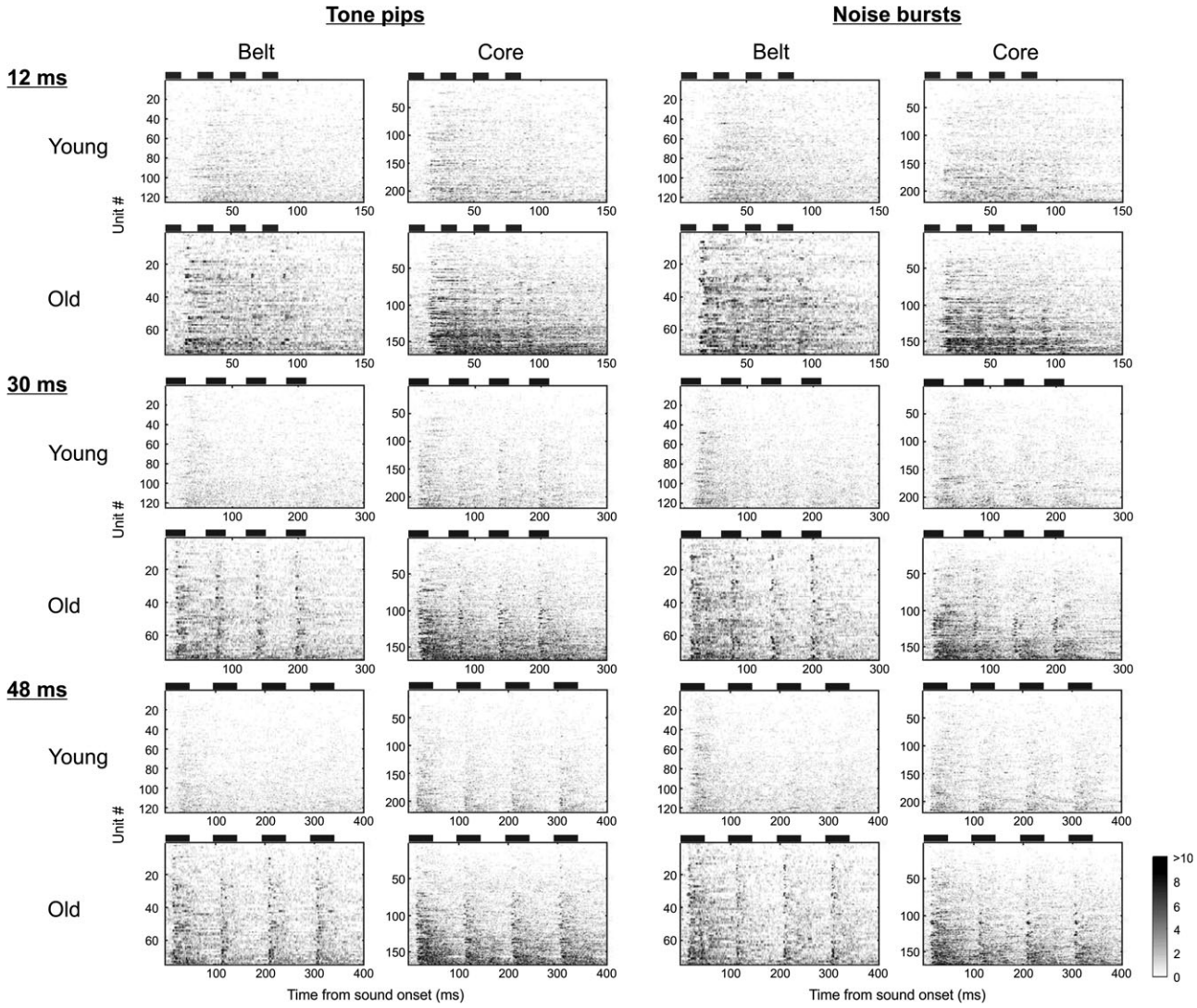

Figure 9. A transition from sparse to homogenous representations of sound stimuli in aged auditory cortex. Raster plots, sorted for all units in the ascending order of total spike counts, show trial-average discharge patterns of all units at 3 stimulus durations (12, 30, and 48 ms). Raster plots at each stimulus duration differ in the x-axis due to increasing stimulus durations from 12 to 48 ms. Stimulus timings of sound envelopes are shown in black blocks above each raster plot, started at time 0 from sound onset. The color bar shows average firing rates in spikes per second with the white color indicating zero average firing rate. Each plot illustrates the trial-average spike activity of all neurons of a cortical region as a function of time. Neurons in the young animals displayed a sparse representation of sound sequences in that only a few neurons had strong stimulus-driven activity beyond sound onset (i.e., the first temporal cycle). This was in contrast to the old animals in that their trial-average spike activity mainly showed sustained firing patterns distributed across the neural population.

Table 2. A distribution of auditory response profiles in relation to sound envelopes

Type	Belt		Core	
	Young	Old	Young	Old
Onset only	0.32	0.13	0.32	0.17
Onset plus	0.30	0.26	0.23	0.12
Sustained	0.20	0.51	0.31	0.64
Out of phase	0.02	0.04	0.01	0.02
No/negligible response	0.16	0.06	0.13	0.05

Proportions of neurons here were based on neuronal responses to the 48-ms tone pips and noise bursts only.

In order to further investigate the effects of age and cortical area on auditory coding revealed by our univariate measures, we performed a multivariate pattern analysis. This analysis examined whether the activation patterns of the auditory cortex could convey information about the sound properties of tone versus noise, and the duration of on/off intervals. We compared this analysis between core and belt neurons of young and old monkeys in order to illustrate potential differences along these 2 dimensions. Figure 10A describes the data construct of a RDM. Pattern dissimilarities are shown in color pixels and are sorted by the order of cycles (first through fourth) at each of the 8 stimulus durations (6–48 ms) for tone pips and noise bursts, and result in 64 stimulus conditions (4 cycles $*$ 8 stimulus durations $*$ 2 sound types). The diagonal line indicates the stimulus pairing of a given stimulus to itself, where the correlation distance is zero. The upper half area along the diagonal line is the mirror image to the lower half area, thus we can simply focus on the upper half area for data illustration. The off-diagonal areas reflect values denoting the pattern dissimilarity between neural activities evoked by a given pair of stimulus

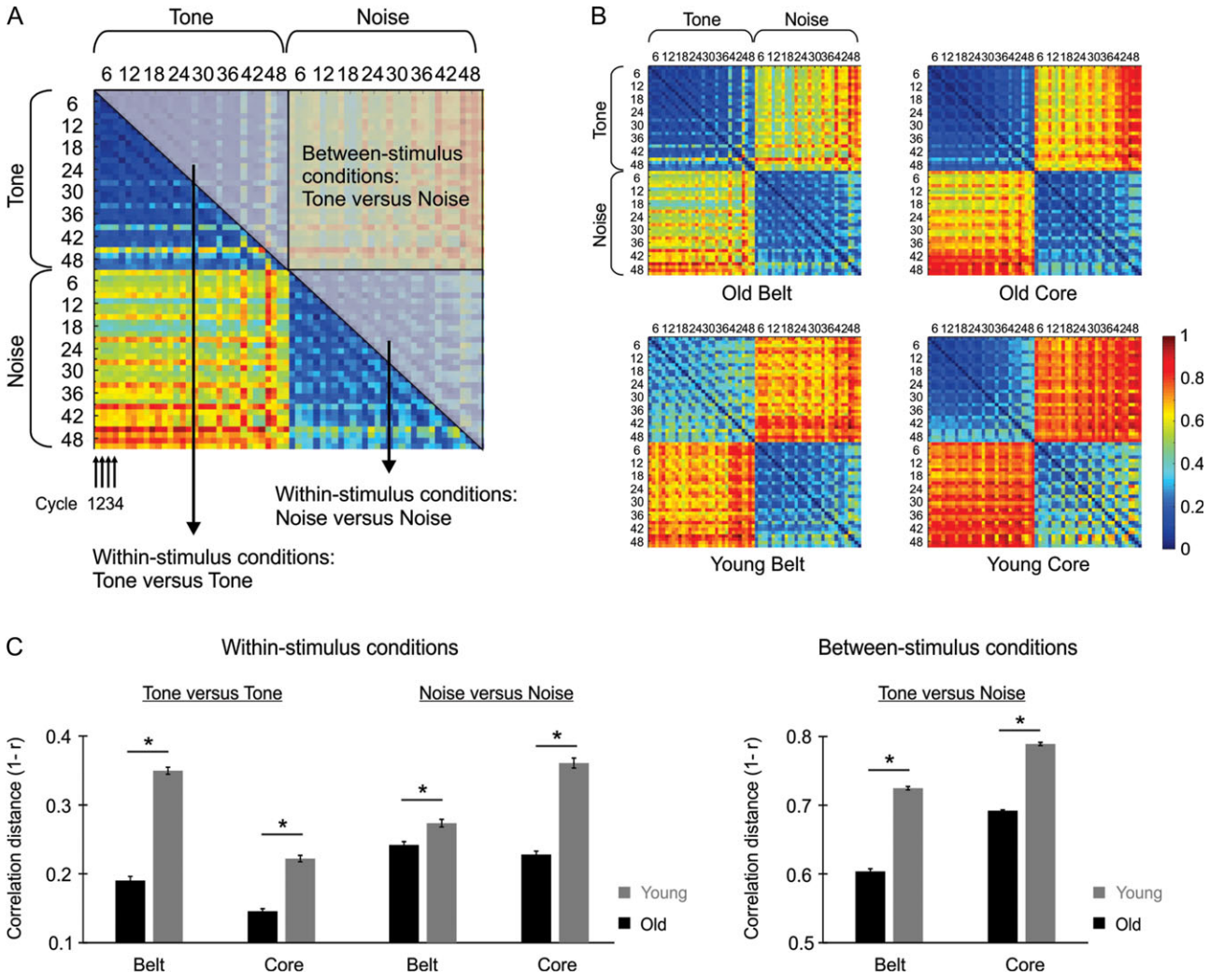

Figure 10. RDMs of auditory-evoked patterns in belt and core neurons varied by age. Normalized, average responses of recorded neurons were transformed into linear vectors of activation across the 64 stimulus conditions, separated by age and cortical region. Panel A shows a RDM of the old belt neurons, constructed by linear vectors of neuronal activation patterns (i.e., correlation distance 1–*r*). They were sorted into stimulus type (tone and noise sequences), stimulus duration (6–48 ms), and cycle (1–4). The color bar shows correlation distances in a scale between the most similar (dark blue) to the most dissimilar (dark red) activation patterns for a given pair of stimulus conditions. Pixels of the upper right half of the matrix are the mirror image to the lower left half of the matrix along the diagonal line. The upper and lower triangular areas (the 2 shaded triangles) show pattern dissimilarities between tone stimuli only or noise stimuli only (within-stimulus conditions), while the upper right square quadrant (the shaded square) shows pattern dissimilarities between tone and noise stimuli (between-stimulus conditions). In panel *B*, neuronal activation patterns of both age groups clearly distinguished the conditions between tone pips and noise bursts (orange/red color pixels for between-stimulus conditions), compared to those within a given stimulus type only (light and dark blue color pixels for within-stimulus conditions). Panel C. Asterisks denote significant age-related difference for a given comparison (permutation t-statistics, 10 000 samplings without replacement; *$P < 0.0001$). For within-stimulus conditions, neuron of the young monkeys processed stimuli more differently than those of old monkeys for both stimulus types, regardless of cortical regions. In processing differences between tone and noise sequences (i.e., between-stimulus conditions), neuron of the young monkeys, regardless of regions, were better able to show pattern dissimilarity between the 2 stimulus types than those in old monkeys. Population activation patterns also varied by cortical regions within each age group. When comparing activation patterns associated with at least one noise stimulus (i.e., within-stimulus noise-only conditions and between-stimulus conditions), young core neurons showed higher pattern dissimilarity than young belt neurons, and vice versa for within-stimulus tone-only conditions. There were similar findings in old neurons, except that an absence of cortical difference existed in pattern activation for within-stimulus noise-only conditions (for details, also see Table 3).

conditions. The upper-left and lower-right triangles (highlighted in shaded areas) above the diagonal line display pattern dissimilarities within the stimulus type of tone pips or noise burst only (within-in stimulus conditions), while the upper-right square quadrant reflects pattern dissimilarities between tone pips and noise bursts (between-stimulus conditions). The observed RDMs were all significantly different from chance, as verified by a random shuffling procedure repeated in 10 000 times (see Supplementary Table S6).

Visual inspection of RDMs revealed a clear contrast between the within-stimulus conditions (tone or noise, the 2 shaded triangular areas in dark and light blue pixels) and the between-stimulus conditions, regardless of age or cortical region (Fig. 10*B*). For the within-stimulus condition, neurons of the young monkeys, regardless of cortical regions, processed stimuli more differently than those of old monkeys for both stimulus types (Fig. 10C; for statistics, see Table 3). Between the 2 cortical regions, belt neurons in both age groups showed a greater degree of dissimilarity between different temporal rates compared to the core neurons for tone pips (Fig. 10C; also see Table 3). In contrast, for noise burst stimuli young core neurons showed greater dissimilarity across temporal rates compared

Table 3. Age-related changes in activation pattern dissimilarities for within-stimulus conditions (tone pips or noise bursts only) and between-stimulus conditions

Stimulus	Comparison	Condition	*t*-statistics	97.5% confidence interval
Tone only	Old vs. Young	Belt	−20.28*	−2.71 to −1.30
		Core	−13.06*	−2.86 to −1.29
	Belt vs. Core	Old	6.37*	−2.68 to −1.32
		Young	18.63*	−2.87 to −1.32
Noise only	Old vs. Young	Belt	−4.32*	−2.77 to −1.27
		Core	−15.29*	−2.85 to −1.32
	Belt vs. Core	Old		Not Sig.
		Young	−9.73*	−2.81 to −1.28
Tone vs. Noise	Old vs. Young	Belt	−26.52*	−2.13 to 1.96
		Core	−24.96*	−1.96 to 1.93
	Belt vs. Core	Old	−17.98*	−1.84 to 1.88
		Young	−18.52*	−2.09 to 1.97

Statistical results were verified in non-parametric permutation statistics (sample *t*-test, 10 000 samples without replacement). Asterisks indicate significant difference for a given comparison at $P < 0.0001$.

to young belt neurons. This difference was not as obvious for neurons from old monkeys. For the between-stimulus conditions, neurons of the young monkeys, regardless of regions, yielded a higher degree of pattern dissimilarity than those in old monkeys. Within each age group, core neurons processed stimuli more differently than the belt neurons (Table 3). The later findings may be due to the fact that it was difficult to evoke belt neurons in the young monkeys relative to the high activity of core neurons (i.e., see Fig. 4). Neuronal activation at the belt was less variant, and thus more similar at between-stimulus conditions.

Based on the same correlation distance matrices, we created dendrograms to visualize whether there would be a change in hierarchical organization of pattern activations in the aged auditory cortex. Observed clustering shown in dendrograms were significant at for all ROIs (see Supplementary Table S6). Regardless of age or cortical region, the largest degree of pattern separation was between tone and noise stimulus types (Fig. 11; the first branch point at the top). In young monkeys, the activation patterns of the core and belt during sound onset (first temporal cycle) were closely clustered together (the left-most first-level cluster tree, axis labels highlighted in red and red brackets) compared to other stimulus conditions, regardless of the stimulus type. There were also sub-clusters containing stimuli associated with short or long stimulus durations (Young belt and core in Fig. 11*B*,*D*, green for stimulus durations between 6 and 24 ms; blue for stimulus conditions between 30 and 48 ms). These observations revealed that the auditory cortex effectively distinguished between tone pips and noise bursts, and also employed a mixture of coding principles based on the stimulus onset and stimulus duration. Old neurons showed a different clustering of pattern dissimilarity relative to the young neurons. Observed neuronal activity patterns were the most similar within tone-pip stimuli in old belt and core neurons (Fig. 11*A*,*C*), as a reversal of cluster trees depicted by young belt and core neurons. A similar clustering of the first temporal cycle (red brackets) was preserved in noise-burst sequences for old belt and core neurons. But for tone pips, major clusters were composed of stimuli with either short or long stimulus durations. For example, neuronal activity patterns were mainly clustered together with stimulus conditions between 6–24 ms (axis labels highlighted in green and green brackets) that included 15/16 and 14/16 conditions at the left-most of the x-axis for old belt and core neuron populations, respectively. The remaining half of the stimulus conditions were at least 30 ms or above (axis labels highlighted in blue and blue brackets). The later findings indicated the hierarchical organization of auditory coding for tone pips was altered in our old monkeys, particularly for fast-paced tonal stimuli.

These overall findings reveal striking functional differences in the auditory cortex between young and old neurons. Old core and belt neurons vigorously responded to tone pips and noise bursts in a continuous, synchronous discharge fashion. In contrast, the auditory cortex in the young animals mainly showed transient onset responses, coupled with some sparse, strong sustained-firing neurons. RSA showed that the old neuron population had been altered, and demonstrated reduced coding proficiency in distinguishing temporal features between different stimulus sequences. The results from our univariate and multivariate measures illustrate that coding differences of population responses varied by age and cortical region. Taken together, the aged auditory cortex exhibited a homogenous, distributed coding of temporal sound features, compared to a diverse and sparse coding strategy present in the young auditory cortex.

Discussion

The present study revealed 3 main effects of natural aging on temporal rate coding in the macaque auditory cortex. The first finding was the increase in spontaneous and stimulus-driven activity in the old monkeys, while their SNRs were comparable to the young animals. The old neurons also had short onset response latencies, and the latency difference between the core and belt found in the young monkeys was reversed in the old monkeys. Second, there was a decrease in phase-locking precision in the old neurons in the core auditory cortex, and the synchronous response preference of core neurons compared to belt neurons disappeared in the old animals. Surprisingly, the involvement of the belt neurons during synchronization was enhanced in the old animals, to a comparable level as the core neurons in the same monkeys. Third, we demonstrated age-related changes in the cortical representation of sound stimuli. This change was from sparse, selective responses into dense, homogeneous activity patterns within a cortical region. The aged auditory cortex exhibited altered, weakened neural coding

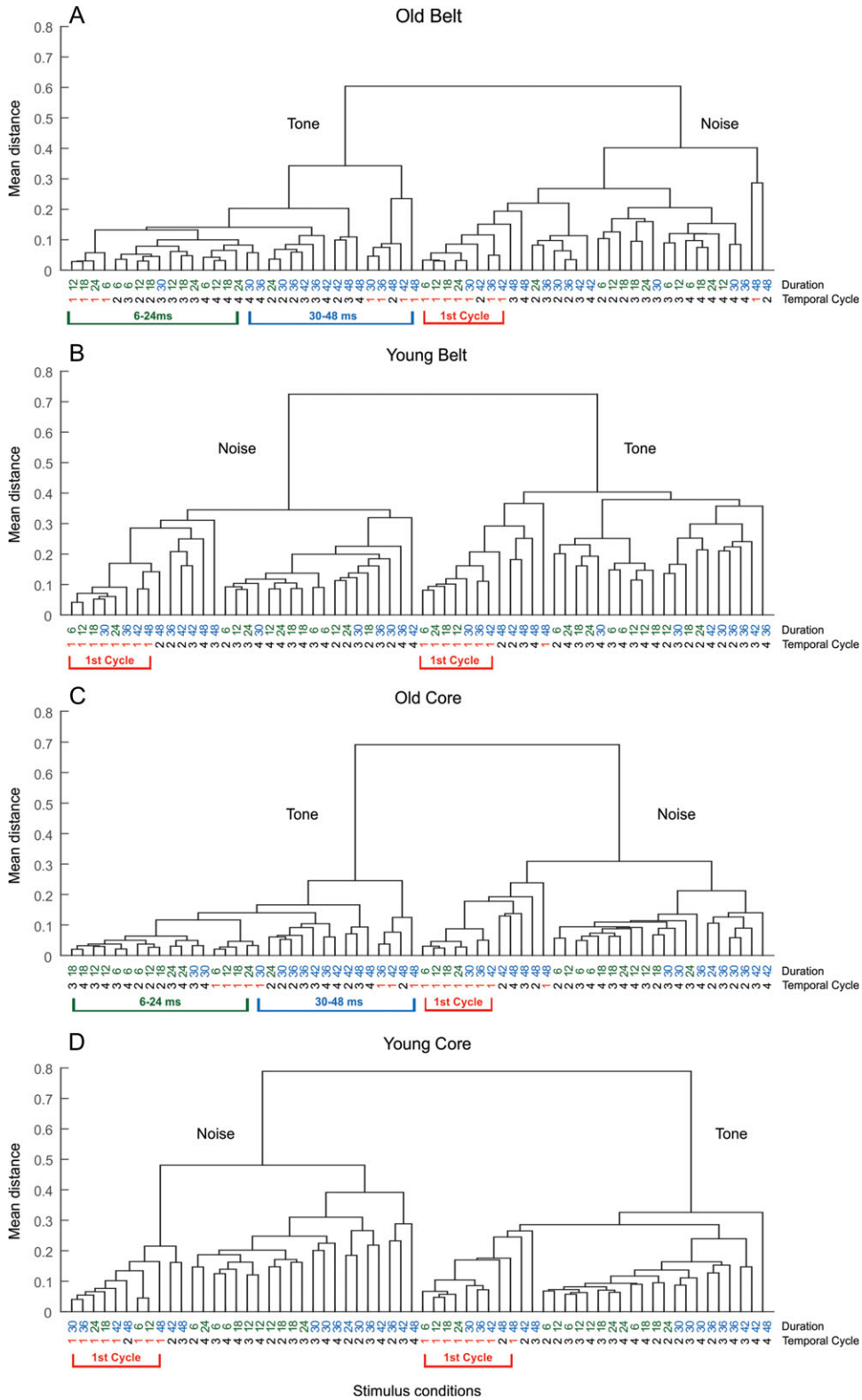

Figure 11. Hierarchical organization of population activity patterns differed in old and young monkeys. On each *x*-axis, the top-row labels represent stimulus durations (6–48 ms) and the bottom-row labels specify temporal cycles (1–4). Dendrograms illustrate that activity patterns of the same stimulus type (tone pips or noise bursts) were more similar, while those activity patterns between the 2 stimulus types were the most apart from each other (the first branch from the top). Population activation during the first temporal cycle (labeled as "1", highlighted in red texts and brackets) formed major clusters in young monkeys (*B* and *D*), and were commonly present in tone pips and noise bursts, regardless of the cortical area. The observed clustering by the first temporal cycle was also present in noise bursts in old monkeys (the right half branches, *A* and *C*). However, the major clusters of old belt (*A*) and core neurons (*C*) were associated with a high proportion of short- or long-stimulus durations (the left half branches: green texts and brackets for 6–24 ms; blue texts and brackets for 30–48 ms) in tone pips, relative to those in noise bursts.

while processing various acoustic features. These findings are in conjunction to the observation that the majority of old neurons showed isomorphic-like, sustained firing to the stimulus envelope. This cumulative evidence indicates a degradation of the temporal precision of responses and a modification in the coding mechanisms of acoustic events during normal aging, in both the primary auditory core and the lateral belt.

Hyperactive, Short-Latency Neuronal Responses in the Old Monkeys

The most striking observation was the increase in spike discharge in the old monkeys, regardless of the spontaneous and sound-evoked activity. This finding is consistent to our prior reports in these same animals on age-related changes in spatial tuning functions (Juarez-Salinas et al. 2010; Engle and Recanzone 2013) and temporal tuning of AM noise (Overton and Recanzone 2016), as well as with other studies of mammalian auditory and visual cortical areas in rodents, felines, and nonhuman primates (Schmolesky et al. 2000; Hua et al. 2006; Yu et al. 2006; Hughes et al. 2010). Enhanced auditory-evoked responses (e.g., P1, N1, and object-related negativity) are also associated with the superior temporal plane of elderly humans, particularly those with mild hearing impairments (Alain et al. 2012, 2014). Rodent studies clearly demonstrate that aging is linked to an imbalance between increased excitatory drive and reduced GABA-mediated inhibitory modulation along the ascending auditory pathway, for example the cochlear nucleus, the inferior colliculus, the auditory thalamus, and the auditory cortex (Caspary et al. 1990, 2002; Palombi and Caspary 1996; Walton et al. 2002; Ling et al. 2005; Richardson et al. 2013). Hyperactive neural responses, mediated by a loss of cortical inhibition, are commonly present in visual (V1 and V2; Schmolesky et al. 2000; Leventhal et al. 2003; Yu et al. 2006) and auditory cortices (Juarez-Salinas et al. 2010; Engle and Recanzone 2013; Overton and Recanzone 2016) of aged nonhuman primates. Recent imaging studies also demonstrate a link between a reduction in GABA levels within the primary auditory cortex in elderly humans with hearing loss (Profant et al. 2013; Gao et al. 2015). This cumulative evidence across mammalian species strengthens the pivotal role of inhibitory mechanisms in shaping sensory processing.

The diminished influence of GABA-mediated inhibition could also account for the reduced response latencies shown in the core and belt neurons of the old monkeys. Longer response latencies of the belt neurons present in our young monkeys is consistent with the serial and hierarchical organization of auditory processing pathways from the core to the adjacent belt (Rauschecker 1998; Kaas et al. 1999; Recanzone, Guard, Phan 2000; Recanzone, Guard, Phan, Su 2000). Intracortical inhibitory projections from the core to the belt are weakened in old animals, and thus disrupt the response delay from the core to the belt (Engle and Recanzone 2013), and contribute to the short onset response latencies seen in our old monkeys. Though differences between recording studies (e.g., behavioral state, sensory modality and animal species) yield mixed effects of aging on response latency upon sensory events (e.g., Mendelson and Ricketts 2001; Turner et al. 2005; Wang, Zhou, et al. 2005; Hughes et al. 2010), there is substantial evidence of GABAergic influences in shaping response latencies and response timing at cortical and subcortical levels (Park and Pollak 1993; Simon et al. 2004). Future studies are required to clarify the experimental and neurochemical conditions that would selectively shorten or lengthen the response latency of cortical sensory neurons.

Age-related changes in neural responses are also dependent on the cortical region and the stimulus type. The auditory core neurons showed age-related effects in neuronal activity for both tone-pip and noise-burst conditions across several neural measures. In contrast, differences in the belt neurons were primarily to noise-burst stimuli, which belt neurons are normally more sensitive to (Rauschecker et al. 1995; Recanzone, Guard, Phan 2000; Tian et al. 2001). Reduced sound-driven activity following sound onsets was also observed in synchronized neurons at slow-rate sound sequences, regardless of age and stimulus type. This was consistent with the effects of response attenuation or adaptation when a sound stimulus was repeated at interstimulus intervals up to 5 seconds (Evans and Whitfield 1964; Calford and Semple 1995; Brosch and Schreiner 1997; Ulanovsky et al. 2004; Werner-Reiss et al. 2006). The major findings reported here were largely based on synchronized neurons, even though non-significant, trending results were often seen for the non-synchronized neurons. This lack of age-related changes of non-synchronized neurons may be explained by the decreased sample size, and the corresponding reduction in statistical power during pairwise comparisons. The GABA-mediated inhibitory mechanism is also known to affect the SNR of auditory neural responses during normal aging (Schmolesky et al. 2000; Leventhal et al. 2003; Turner et al. 2005), but the present study demonstrated no age-related difference in SNR. This could be due to an overall heightened activity level in the aged auditory cortex to each stimulus tested. A lack of diversity in the population response is a key contributor to the homogeneous activation patterns seen across different acoustic attributes, suggesting that noise variance could be associated with a change in the population coding.

Increased Functional Role of Belt Neurons in the Temporal Coding of Old Monkeys

A decline in temporal processing to sounds with periodic and dynamic features is well-known in aged mammals. Elderly humans show a reduction in phase-locking and an increased peak variability in ABRs when listening to speech syllables in a quiet or a noisy background (Anderson et al. 2012, 2013). In aged Fisher Brown Norway rats (31–33 months old), the dorsal cochlear nucleus shows a reduction in VS at the best modulation frequencies of AM tones for various modulation depths (Schatteman et al. 2008). Applications of inhibitory neurotransmitters (e.g., GABAergic and glycinergic) or their antagonists (e.g., strychnine) can effectively enhance or weaken response synchrony to AM stimuli in the cochlear nucleus and the inferior colliculus (Koch and Grothe 1998; Backoff et al. 1999; Caspary et al. 2002). These results show that the temporal precision in processing rapidly-changing sound features is mediated, at least in part, by inhibitory mechanisms. Degraded response timing along the ascending auditory pathway would likely be transferred to the cortical level, as indicated by the decrease in phase-locking for the core neurons in the aged animals, even when excluding the responses to the first stimulus cycle, which would favor neurons with robust onset responses commonly seen in young animals.

Another age-related change is the difference between core and belt neurons in how well they are able to phase-lock to these stimuli. In the young monkeys, the core neurons had more synchronized units and overall better phase-locking

compared to belt neurons. This indicates that in young animals accurate temporal timing of neural responses is predominantly achieved by the core neurons. In contrast, we found a similar proportion of old belt neurons that exhibited synchronous activity as good as the old neurons in the core. Age-related differences in phase-locking were primarily associated with core neurons at slow-rate sound sequences with stimulus durations at 30 ms (33 Hz) or longer. The current findings are parallel to our previous reports in macaques that response periodicity of core neurons were poor to very face-paced tone pips at 6- and 12-ms durations (Phan and Recanzone 2007), and age-related differences in temporal coding were present up to an AM-rate of 32 Hz (Overton and Recanzone 2016). This cumulative evidence all indicates that synchronous core neurons of the same old monkeys have reduced phase-locking capability and weakened response dynamic to sound sequences, particularly for slow-rate acoustic features.

A loss of cortical inhibition discussed above can obviously undermine the sensitivity of the auditory belt neurons in temporal tuning. The enhanced enrollment of the auditory belt and the isomorphic-like coding strategy at these areas also demonstrate a potential compensation for reduced temporal precision of synchronized neurons in the aged auditory cortex. This decreased precision is likely due, at least in part, by the decreased inhibition throughout the ascending auditory axis, consistent with anatomical studies in both rodents and macaques (Caspary et al. 2008; Gray et al. 2013, 2014a, 2014b; Engle et al. 2014). Though more old core and belt neurons collaborate to track acoustic dynamics, this strategy can be counterproductive if they are too broadly-tuned with overlapping receptive fields. Apart from degraded temporal resolution in the responses, redundant information from a population of hyperexcitable, highly-responsive neurons may lower the ability to detect and resolve subtle temporal dynamics, consistent with temporal processing deficits seen in aged animals and humans.

The mammalian central auditory system, upstream to the auditory cortex, exhibits a variety of age-related changes in neural coding of sounds. Increased spontaneous rate, stimulus-evoked activity, or both are not always associated with old animals in the rodent cochlear nucleus, inferior colliculus and auditory thalamus (e.g., Walton et al. 1998; Palombi et al. 2001; Mendelson and Liu 2004; Schatteman et al. 2008), and yet these central auditory regions clearly show a gradual loss of frequency selectivity and temporal precision or an increase in gap detection threshold to tone/noise bursts and AM noises (Leong et al. 2011; Cai et al. 2016; Brecht et al. 2017). Age-related increases in rate coding in the inferior colliculus can be found at sound onset (Herrmann et al. 2017) or extend to the rest of the periodic cycles of AM noises for slow-rate stimulus conditions (Walton et al. 2002). Recent studies also reported similar age-related changes in temporal coding of sinusoidal AM noises in rats. Aged neurons in the auditory thalamus have a weak effect of reduced phase-locking at the AM-rate of 16 Hz (Cai et al. 2016), and aged neurons of the inferior colliculus exhibit better neural synchronization (spikes and local field potentials) to a 45-Hz AM noise (Herrmann et al. 2017). Although age-related deficits in neural coding are expressed differentially between the central auditory neuroaxis and the auditory cortex, pharmacological studies show a common, diminished efficacy of GABA-mediated neurotransmission in these structures, which contribute to a net down-regulation of functional inhibition (Caspary et al. 2008). In short, hyperactive neural responses with degraded temporal fidelity can originate at auditory regions upstream to the auditory cortex, the cortex itself, or both, consistent to the serial and parallel networks of auditory information pathway observed in the macaque auditory nervous system (Hackett 2011).

Age-Related Difference in the Population Representation of Sounds

Sparse coding of sensory events has been demonstrated across sensory modalities in various species, for example audition in insects, avians, and rodents (Hromádka et al. 2008; Clemens et al. 2012; Schneider and Woolley 2013), vision in monkeys (Rolls and Tovee 1995; Vinje and Gallant 2000), olfaction in insects (Laurent 2002), and touch in mice (Crochet et al. 2011). It is proposed that such sparse coding is an efficient mechanism for encoding sensory inputs in which only a small subset of neurons within a population respond actively to an incoming stimulus, while the remaining population is inactive or at a sub-threshold activity level (Laughlin 2001; Willmore and Tolhurst 2001; Olshausen and Field 2004). Thus, if the neuronal response profiles are highly selective and diverse, a combination of different neural subsets will facilitate extraction for a broad spectrum of sensory features, flexibly convey information variance, and detect small changes between sensory events. The present results shown in our young monkeys are consistent with typical examples of sparse coding in rodent and avian auditory systems (Hromádka et al. 2008; Bartho et al. 2009; Carlin and Elhilali 2013; Schneider and Woolley 2013). Auditory neurons, particularly in the core, had low spontaneous and stimulus-evoked discharge rates with better temporal precision. There was also an increase in temporal selectivity from core to belt in the young monkeys. The majority of auditory neurons in these 2 regions had transient onset responses, and a low percentage of them showed out-of-phase or sustained firing activity across temporal feature cycles. A few neurons with sustained firing activity can represent a non-isomorphic, rated-based transformation of a stimulus, and track the continued presence of a sound, with a background of a silent or moderately active population (Wang, Lu, et al. 2005). The collaboration between a subset of preferentially driven neurons and a population of transient, onset-response neurons portrays a coding mechanism for detecting and identifying acoustic events over time in a dynamic listening environment, and therefore maintaining a stable perceptual representation (Carlin and Elhilali 2013).

In the old monkeys, however, response characteristics of auditory neurons reflect a change in coding mechanisms. The majority of old neurons, regardless of the cortical region, showed sustained firing and broad synchronization to stimuli with different temporal rates. The cross-correlation analysis showed that the spike discharge patterns of the old core and belt neurons largely mimicked sound envelopes at different stimulus durations. The VS analysis clarified this isomorphic-like auditory coding with weakened temporal precision in the spike firing. A change in sparse coding within the auditory cortex can be attributed to a change in inhibitory mechanisms as discussed above. Highly-responsive interneurons showed sparse firing characteristics in the awake rodent auditory cortex (21–30 days old; Hromádka et al. 2008). Strong inhibitory projections onto excitatory pyramidal cells in the auditory cortex, often deteriorated during normal aging, are essential for mediating response heterogeneity and population sparseness of sound-evoked activity (Hromádka et al. 2008), and a decrease of this inhibitory drive could underlie the observed differences between young and old neurons.

Examining population activity helps to elucidate the underlying coding principles of perceived stimuli in a given brain region, for example visual categorical representations in the macaque inferior temporal cortex (Kriegeskorte et al. 2008) and subjective valence in the human amygdala (Jin et al. 2015). The multivariate pattern analysis (e.g., RSA) is primarily employed in fMRI studies to evaluate voxel-based activation patterns across multiple brain regions, and is widely incorporated into the design of imaging studies across sensory and cognitive domains. A few studies employed this analytical method when single-unit recordings were conducted in mammals. These studies reported how a given neural population would encode and represent stimuli differently, according to stimulus identity, category or affective social valence (Kiani et al. 2007, inferior temporal cortex in macaque monkey, face versus non-face images; Matsumoto et al. 2016, amygdala in rats, self versus conspecific ultrasonic vocalizations). Here, cortical activity during sound presentations showed a common coding scheme in both age groups, for example stimulus type (tone vs noise sequences), sound onset (the first temporal cycle of a sequence), and short/long stimulus durations. RSA revealed that the neural activity patterns in both age groups were capable of distinguishing between tone and noise stimuli. Population activations in the old monkey neurons, however, were less distinguishable in all conditions relative to neurons in the young monkeys. Their coding principle of tone-pip sequences was also altered in the aged auditory cortex. Short/long stimulus durations, instead of sound onsets, preferentially describes cluster organizations of population activity in the old monkeys. The multivariate pattern analysis offers additional support for age-related effects on neural representation of fast-paced tonal stimuli in geriatric monkeys. Current results shown in the agglomerative hierarchical cluster analysis are stimulus-dependent in that auditory features exemplified by clusters of pattern responses will vary by sound type, spectrotemporal parameter or ethological significance (Romanski et al. 2005). The present findings therefore suggest that the auditory cortex is able to extract and utilize a series of sound attributes embedded within tone/noise sequences during auditory coding. The use of multivariate pattern analysis will be fruitful for auditory neuroscience to evaluate various coding strategies of the human and macaque auditory nervous systems, from purely sound stimulation to auditory-oriented behavior or cognition. This approach offers an innovative, complementary measure of auditory processing relevant to acute or chronic hearing deficits, alongside with traditional audiometric test batteries.

The increased neural excitability, reduced temporal selectivity, and increased cell numbers in sustained firing, were the hallmarks of response profiles in our old monkeys. Individual neural responses were more broadly-tuned to different temporal rates, and the resultant distributed coding may not be optimal for processing subtle acoustic differences embedded within rapidly-changing sounds. In addition to internal noise (Schmolesky et al. 2000; Turner et al. 2005; Clinard and Cotter 2015), the altered coding mechanism provides another explanation why aged animals have a degraded ability to process complex sounds, and for the more specific case that elderly humans have difficulties in understanding dynamic speech stimuli in a noisy environment. A loss of cortical inhibition, both within the cortex as well as inherited from subcortical processing, may precipitate the age-related changes in the sparse representation of sounds.

Previous comparisons between different auditory cortical areas have revealed that, compared to the core, complex sound stimuli are required to elicit neural responses in lateral belt areas. For example, the caudal belt area (where most of the neurons reported here resided) have been shown to be highly spatially selective relative to the core or other lateral belt areas (Rauschecker et al. 1995; Recanzone, Guard, Phan, Su 2000; Tian et al. 2001; Woods et al. 2006; Miller and Recanzone 2009; Juarez-Salinas et al. 2010; Engle and Recanzone 2013). In contrast, rostral belt areas are more selective for non-spatial information such as vocalizations (Rauschecker et al. 1995; Tian et al. 2001). The hierarchical nature of auditory processing from simple to complex sound sensitivity is also present in humans (Chevillet et al. 2011). Only a few reports examined the extent of the macaque auditory core and belt simultaneously within the same behavior paradigm. Recent studies showed changes in spike rate and phase-locking to AM noise present in both core and belt neurons when macaque monkeys discriminated AM noises, but the task-induced plasticity appeared to be stronger or longer-lasting in the belt region (Niwa et al. 2013, 2015). Comparing pattern dissimilarity between behavioral and neural measures in future experiments will enable an evaluation of how such compromised auditory coding could underlie age-related hearing deficits.

Macaques as an Animal Model for ARHL

The present study extends our understanding of temporal coding in nonhuman primate, as an integral part of our continuous effort to examine the effects of aging on the auditory nervous system of the same species. Extending the results of Phan and Recanzone (2007), we elucidated functional differences in spike discharge and temporal synchronization between the auditory core and belt, and their implications on coding tone- and noise-generated sound sequences. Electrophysiological evidence such as this is crucial to distinguish stimulus coding between the young and old monkeys. The present findings are consistent to our prior studies, as well as those reported on other sensory modalities and animal models. Here, we propose an altered processing mechanism from sparse coding to dense, distributed coding in the aged auditory cortex. Reduced GABAergic inhibitory mechanisms at the peripheral and central auditory sites, which crucially contributes to several animal models of human presbycusis, underlines detrimental effects on hearing and processing rapidly-changing acoustic features. The present study reveals a profound impact of aging on the higher-order auditory region in phase-locking, while the same area is equally susceptible to aging in degraded spatial tuning functions (Engle and Recanzone 2013). Effects of aging on higher-order sensory cortical areas have only been addressed by a few studies in nonhuman primates (e.g., V2 and MT: Wang, Zhou, et al. 2005; Yang et al. 2009; lateral belt: Juarez-Salinas et al. 2010; Engle and Recanzone 2013), with little attention to the potential changes in population coding mechanisms as a result of normal aging. Age-related changes in population coding mechanisms could account for a loss of acoustic details in the incoming sound streams, which limits the proficiency of other brain areas to extract and utilize essential information for behavioral and cognitive functions. Such processing deficits could be the neuronal bases of the age-related deficits in speech comprehension and short-term verbal memories commonly found in older adults.

Supplementary Material

Supplementary data are available at *Cerebral Cortex* online.

Notes

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