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Altered cortical spectrotemporal processing with age-related hearing loss

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Trujillo M, Razak KA. Altered cortical spectrotemporal processing with age-related hearing loss. *J Neurophysiol* 110: 2873–2886, 2013. First published September 25, 2013; doi:10.1152/jn.00423.2013.—Presbycusis (age-related hearing loss) is a prevalent disability associated with aging that impairs spectrotemporal processing, but the mechanisms of such changes remain unclear. The goal of this study was to quantify cortical responses to frequency-modulated (FM) sweeps in a mouse model of presbycusis. Previous studies showed that cortical neurons in young mice are selective for the rate of frequency change in FM sweeps. Here single-unit data on cortical selectivity and response variability to FM sweeps of either direction and different rates (0.08–20 kHz/ms) were compared across young (1–3 mo), middle-aged (6–8 mo), and old (14–20 mo) groups. Three main findings are reported. First, there is a reduction in FM rate selectivity in the old group. Second, there is a slowing of the sweep rates at which neurons likely provide best detection and discrimination of sweep rates. Third, there is an increase in trial-to-trial variability in the magnitude and timing of spikes in response to sweeps. These changes were only observed in neurons that were selective for the fast or intermediate range of sweep rates and not in neurons that preferred slow sweeps or were nonselective. Increased variability of response magnitude, but not changes in temporal fidelity or selectivity, was seen even in the middle-aged group. The results show that spectrotemporal processing becomes slow and noisy with presbycusis in specific types of neurons, suggesting receptive field mechanisms that are altered. These data suggest neural correlates of presbycusis-related reduction in the ability of humans to process rapid spectrotemporal changes.

auditory cortex; hearing loss; aging; frequency-modulated sweeps; response variability

HUMAN AUDITORY PROCESSING abilities decline with age. Age-related deficits are seen in temporal fine structure processing and frequency-modulated (FM) sweep detection thresholds, phoneme discrimination, and word recognition (Fitzgibbons and Gordon-Salant 2001; Fitzgibbons et al. 2006; He et al. 1998, 2007; Hopkins and Moore 2011). These deficits are further compounded by hearing loss. Presbycusis (age-related hearing loss) affects ~35% of humans older than 65 yr (Gates and Mills 2005). It is the most prevalent form of hearing impairment, contributes to speech processing deficits and social isolation, and may lead to cognitive impairment (Frisina 2009; Gates and Mills 2005; Lopez-Torres Hidalgo et al. 2009; Weinstein and Ventry 1982).

Specific speech problems in presbycusis include difficulty in discriminating stop consonants or fricative-vowel speech syllables (Turner and Robb 1987). Compressed speech, with or without linguistic cues, is difficult to recognize (Gordon-Salant and Fitzgibbons 2001). Most of this difficulty can be explained by impaired recognition of compressed consonants. Rapid formant transitions are difficult to discriminate, contributing to a decline in speech processing (Blumstein and Stevens 1979; Dorman et al. 1985; Dubno et al. 1989; Gordon-Salant et al. 2007; Zeng and Turner 1990). Hearing aids amplify sounds but do not necessarily improve speech recognition (Hogan and Turner 1998), suggesting deterioration of central spectrotemporal processing. Physiological studies in humans indicate altered representation of time-varying speech cues, including reduced temporal precision and increased response variability of evoked responses (Anderson et al. 2012; Tremblay et al. 2003).

Physiological studies in rodents have characterized presbycusis-related change in spectral processing by measuring tonotopy (Willott et al. 1993) or tuning curves (Turner et al. 2005) and temporal processing using gap detection or amplitude-modulated (AM) signals (Barsz et al. 2002; de Villers-Sidani et al. 2010; Parthasarathy and Bartlett 2011; Simon et al. 2004; Walton et al. 1998, 2002, 2008). Only one study has addressed cortical spectrotemporal selectivity with aging at the single-neuron level (Mendelson and Ricketts 2001). There are currently no data on variability (temporal and response magnitude) of responses to repeated presentations of the same sound in aging auditory neurons that may be correlates of observed deficits in humans (Anderson et al. 2012; Tremblay et al. 2003). Gap detection and AM selectivity studies suggest longer temporal integration windows in older neurons, leading to the prediction of decreased selectivity for fast spectrotemporal cues. The goal of this study was to test this prediction directly by characterizing selectivity and response fidelity of neurons to FM sweeps with different directions and sweep rates in the aging C57BL/6 (C57) mouse cortex.

The C57 mouse presents certain advantages for this study. First, C57 mice show age-related hearing loss with a predictable time course (Ison et al. 2007; Spongr et al. 1997; Willott et al. 1993). Considerable background data on the time course of presbycusis and physiological effects in this strain are available (Taberner and Liberman 2005; Willott et al. 1993). Second, cortical FM sweep rate/direction selectivity data in young C57 mice before the onset of measurable hearing loss are available for comparison with older mice (Carrasco et al. 2013; Trujillo et al. 2011). Third, the excitatory/inhibitory receptive field mechanisms underlying FM sweep rate selectivity in the C57 cortex are known (Trujillo et al. 2013). Thus, if presbycusis-related changes in FM rate selectivity are found, the underlying mechanisms can be explored.

FM sweeps are relatively simple sounds to explore spectrotemporal processing. FM sweeps contribute to speech recognition (Stickney et al. 2005; Zeng et al. 2005). The auditory cortex of all species examined contains selectivity for the rate and direction of FM sweeps (Atencio et al. 2007; Brown and Harrison 2009; Godey et al. 2005; Heil et al. 1992; Mendelson and Cynader

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1985; Nelken and Versnel 2000; Razak and Fuzessery 2006; Shamma et al. 1993; Suga 1965; Tian and Rauschecker 1994, 2004; Trujillo et al. 2011; Washington and Kanwal 2012; Weeks et al. 2000; Zhang et al. 2003). Studies in rodents show that the auditory cortex is involved in rate-dependent FM sweep direction discrimination (Ohl et al. 1999; Wetzel et al. 1998).

We compared FM rate/direction selectivity and variability of response magnitude and timing in the core auditory cortex of C57 mice across three age groups: young (1–3 mo old), middle-aged (6–8 mo), and old (14–20 mo). We recorded responses to linear upward and downward sweeps with rates between 0.08 and 20 kHz/ms. This range includes the preferred rates of most neurons in the young C57 mouse (Trujillo et al. 2011). We report reduced FM sweep rate selectivity, increased selectivity for slow sweeps, and increased response variability in the old group compared with the young group. Response magnitude variability increases even in the middle-aged group, suggesting earlier onset of some presbycusis-related changes than others.

METHODS

All procedures were approved by the Institutional Animal Care and Use Committee at the University of California, Riverside. Mice were obtained from an in-house breeding colony that originated from Jackson Laboratory (Bar Harbor, ME). Two to five littermates were housed in each cage under a 12:12-h light-dark cycle and fed ad libitum. Two age groups were recorded in this study: the middle-aged group (6–8 mo, $N = 31$ mice) and the old group (14–20 mo, $N = 34$ mice). Comparison data from the young age group (1–3 mo) were obtained from our previous studies that used identical methods (Trujillo et al. 2011, 2013). These age ranges were chosen to study periods of relatively little hearing loss to moderate to profound loss (Keithley et al. 2004). Mice of either sex were used.

Surgical Procedure

A combination of ketamine (150 mg/kg) and xylazine (10 mg/kg) was injected (ip) to induce anesthesia for surgery and electrophysiology. Anesthesia was maintained throughout the experiment by supplemental dosage of ketamine-xylazine and/or isoflurane inhalation (0.2–0.5% in air). Preliminary comparisons showed there were no differences in selectivity or response magnitude between the different anesthetics. Data were therefore combined. Anesthetic state was assessed via the toe-pinch reflex test throughout the experiment, and supplemental anesthetic was administered as needed. After an areflexic state of anesthesia was reached, a midline scalp incision was made and the right temporalis muscle was reflexed. A dental drill was used to perform a craniotomy to expose the auditory cortex. At the end of electrophysiological recording, mice were euthanized with pentobarbital sodium (125 mg/kg).

Acoustic Stimulation

All the FM sweep stimuli used in this study were presented at 10–20 dB above each neuron's minimum response threshold. Most neurons in the old C57 auditory cortex are tuned below 25 kHz (Willott et al. 1993). Therefore, the focus across age groups was on neurons tuned below 25 kHz to facilitate comparison of FM sweep responses of neurons with similar characteristic frequencies (CFs). Although neurons in the young group show CF $>$ 25 kHz, we only used the neurons tuned $<$25 kHz for comparison.

Experiments were conducted in a sound-attenuated chamber lined with anechoic foam (Gretch-Ken Industries). Acoustic stimuli were driven and data were acquired by custom software (Batlab; Dr. Don Gans, Kent State University, Kent, OH). Sound intensities were controlled with programmable attenuators (PA5; Tucker-David Technologies, Gainesville, FL) prior to amplification by a stereo amplifier (Parasound HCA1100) or an integrated amplifier (Yamaha AX430). Sounds were delivered through a free-field ribbon tweeter (LCY-K100, Madisound) located 6 in. and 45° from the left ear, contralateral to physiological recordings. Frequency response of the acoustic stimuli system was flat within ±3 dB for frequencies between 6 and 40 kHz as measured by a 1/4-in. Bruel and Kjaer microphone and measuring amplifier. The roll-off at higher frequencies was smooth at ~20 dB/octave. A Krohn-Hite filter (Brockton, MA) was used to filter out frequencies below 5 kHz (Butterworth, 24 dB/octave). No evidence of distortions was seen across the intensity range used based on spectral analysis of recorded sounds.

Auditory Brain Stem Response

Auditory brain stem responses (ABRs) were acquired in a subset of mice [14 young (Y), 22 middle-aged (M), and 20 old (O)] to quantify hearing thresholds and ensure that the M and O mice showed hearing loss. Electrodes were placed subdermally along the midline of the scalp (active electrode), the left cheek (reference), and the tail (ground). Pure tones were presented from 7 to 50 kHz (5-ms duration, 0.5-ms rise/fall time, 10-Hz repetition rate, 256 repetitions) in 3- to 5-kHz increments. Evoked ABR waveforms were acquired in a 7.5-ms window relative to stimulus onset. Threshold at each frequency was obtained by stepping up intensity in 10-dB steps; 5-dB steps were used near threshold. The threshold was defined as the minimum intensity that produced at least three distinct peaks within 7.5 ms of tone onset.

Electrophysiology

A stereotaxic apparatus (Kopf model 930) and a bite bar (Kopf model 923B) were used to secure mice for electrophysiological recordings. Recordings were acquired with glass microelectrodes filled with 1 M NaCl (2- to 10-MΩ impedance). Electrodes were driven into the cortex with a Kopf direct drive 2660 micropositioner. Single-unit recordings were obtained at depths of between 124 and 728 μm (mean = 402 ± 114) in Y, between 111 and 714 μm (mean = 405 ± 125) in M, and between 102 and 724 μm (mean = 399 ± 116) in O mice. Single-unit responses were identified by constancy of amplitude and waveform as displayed on an oscilloscope and were isolated with a window discriminator. Data quantification consisted of counting the number of spikes elicited over 20 stimulus repetitions. The repetition rate was 1 Hz. Poststimulus time histograms (PSTHs) were obtained over a 300-ms window relative to stimulus onset. There was little to no spontaneous activity in this experimental preparation.

Data Acquisition

The primary auditory cortex (A1) of the young C57 mouse can be identified by robust, short-latency responses to tones, narrow and defined tuning curves, as well as increasing CF in the caudal to rostral direction (Cruikshank et al. 2002; Trujillo et al. 2011; Willott et al. 1993). The anterior auditory field (AAF) is located immediately rostral to A1 and exhibits a reversed tonotopy relative to A1. Narrow tuning and robust, short-latency tone responses also characterize AAF. Both A1 and AAF are considered core auditory cortex. The transition zone from A1 and AAF is relatively broad, and mirrored tonotopy becomes less useful as a boundary marker in the M and O mice because almost all neurons have CFs below 25 kHz (Willott et al. 1993). For these reasons, no attempt was made to distinguish neurons in A1 versus AAF, and data are reported as recorded from the core auditory cortex. In each mouse recorded, electrode locations

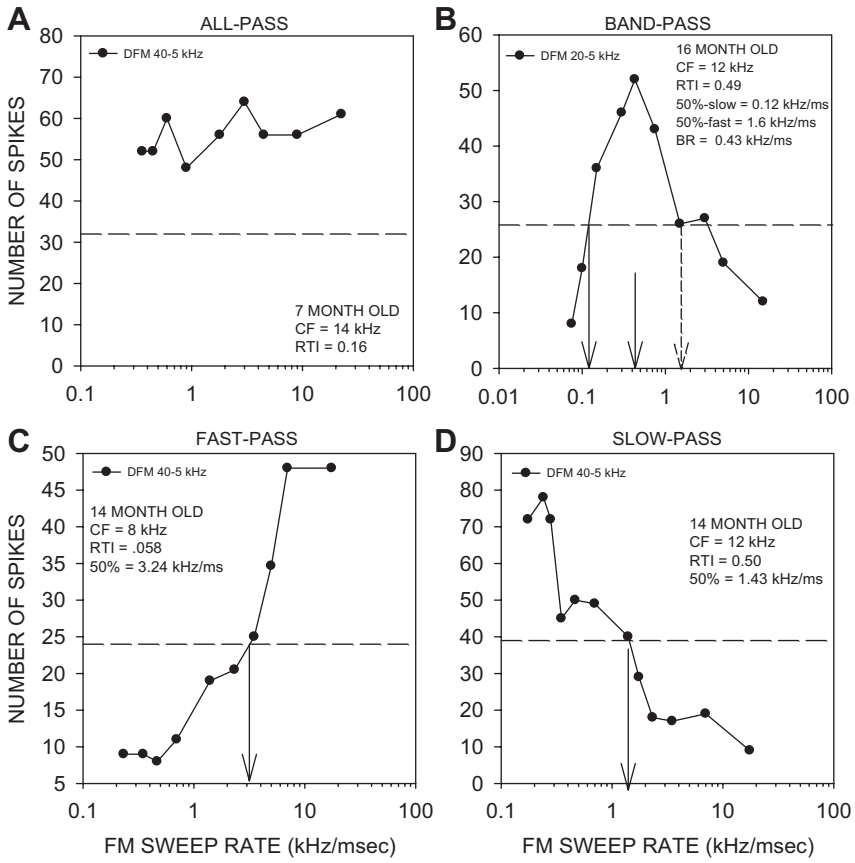

Fig. 1. Classification of frequency-modulated (FM) sweep rate tuning. *A*: all-pass (AP). *B*: band-pass (BP). *C*: fast-pass (FP). *D*: slow-pass (SP). Dashed line marks 50% of maximum response. "Number of spikes" on *y*-axis in this and subsequent graphs are in response to 20 repetitions of each stimulus. The age of the mouse and the bandwidth of sweep used are indicated in each panel. DFM, downward FM sweep; CF, characteristic frequency; RTI, rate tuning index; BR, best rate for BP neuron; 50%, 50% cutoff rate for BP, FP, and SP. Arrows in *C* and *D* represent the 50% cutoff rate. BP neurons have two 50% cutoff rates, one on the fast side of the peak and another on the slow slide of the peak. These are marked in *B* with dashed and solid arrows, respectively. The short arrow in *B* represents BR.

sampled the rostrocaudal extent of the core auditory cortex and thus covered both A1 and AAF.

Single neurons were isolated by using pure tones (5–40 kHz, 20–90 dB SPL, 1-ms rise/fall times, 10- to 30-ms duration, 1-Hz repetition rate), broadband noise, and up/down sweeps as search stimuli. Upon isolation, tone response properties were acquired. Pure tones with frequencies between 5 and 40 kHz (1- to 5-kHz resolution, 10- to 30-ms duration, 1-ms rise/fall time, 1-Hz repetition rate) were presented to determine excitatory frequency tuning curves. The CF was noted as the frequency at which the neuron responded to at least five consecutive presentations at the lowest sound intensity tested. The excitatory frequency tuning at 10 and 20 dB above the minimum threshold was then determined by increasing intensity in 10-dB steps and changing frequencies with 1-kHz resolution.

FM sweep rate selectivity. In the young mouse cortex, the vast majority of neurons are not direction selective (Trujillo et al. 2011). Initial data indicated that this was true in M and O mice as well (see RESULTS). Therefore, for sweep rate selectivity measures we focused only on downward FM sweeps. Rate selectivity for downward FM sweeps was assessed in 147 M and 163 O neurons. Y neuron rate selectivity data from Trujillo et al. (2011, 2013) were used for comparison.

Sweep rate selectivity was determined by presenting linear downward FM sweeps of fixed bandwidth and different durations (1-Hz repetition rate). The sweep rate, defined as the rate of change in kilohertz per millisecond, was determined by dividing the FM bandwidth (in kHz) by the duration (in ms). FM sweeps were presented at a single intensity, 10–20 dB above CF threshold. FM sweep bandwidths used were between 15 kHz (e.g., a 20 → 5 kHz sweep) and 45 kHz (e.g., a 50 → 5 kHz sweep) with the criterion that the bandwidth extended at least 5 kHz outside the tuning curve on the high-frequency side. This ensures that putative inhibitory sidebands, which abut the excitatory tuning curve in A1 and shape sweep rate selectivity (Trujillo et al. 2011, 2013), were included in the FM sweeps. Sweep durations between 2 and 200 ms (rise/fall time 1 ms) were used. This allowed FM rates between 0.08 and 20 kHz/ms to be presented. We have shown previously that core cortical neurons in the mouse respond selectively to FM sweep rate and not to sweep duration or sweep bandwidth (Trujillo et al. 2011).

Classifying FM sweep rate selectivity. Neurons were classified (Fig. 1) as all-pass (AP), band-pass (BP), fast-pass (FP), or slow-pass (SP) according to FM rate selectivity (Trujillo et al. 2011). AP neurons respond above 50% of maximum response for all rates tested

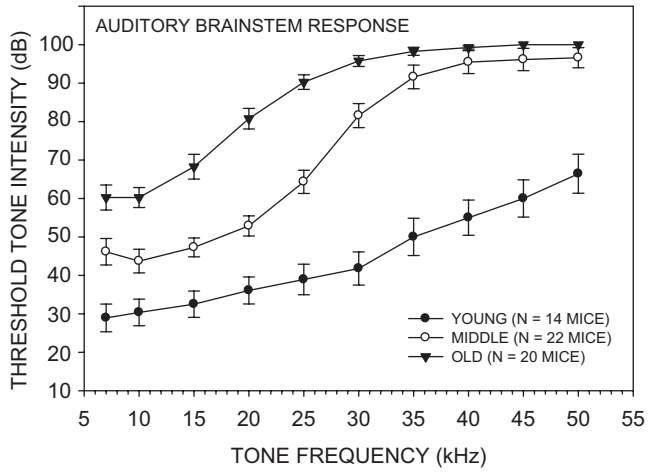

Fig. 2. Quantification of hearing loss in a subset of mice used. Auditory brain stem response (ABR) was assessed at frequencies between 7 and 50 kHz. The threshold for each frequency was defined as the intensity from which a 5-dB decrease eliminated the first peak of the ABR. Symbols represent mean ± SE threshold attenuation for young (Y), middle-aged (M), and old (O) mice.

(Fig. 1*A*). BP neurons were selective for a range of rates, with responses dropping below 50% of maximal response as FM sweep rate was decreased or increased beyond that range (Fig. 1*B*). FP neurons were selective for fast FM sweep rates, and responses decreased below 50% of maximal response as FM sweep rate was decreased (Fig. 1*C*). SP neurons were selective for slow FM sweep rates, and responses decreased below 50% of maximal response as FM sweep rate was increased (Fig. 1*D*).

FM sweep rate selectivity. The degree of selectivity was quantified with the rate tuning index (RTI) and is calculated as follows (Atencio et al. 2007; Brown and Harrison 2009):

$$\text{RTI} = (n/n - 1) \times [1 - (\text{mean}/\text{max})]$$

where n = the number of FM sweep rates assessed, "mean" is the average response across all rates tested, and "max" is the maximum response. RTI varies between 0 and 1, with a higher value indicating sharper rate selectivity. In addition to RTI, the 50% cutoff rate, defined as the rate at which the response declined to 50% of maximum response, was quantified for FP, BP, and SP neurons (e.g., Fig. 1, *B* and *C*). For BP neurons, the best rate (e.g., Fig. 1*B*) was also quantified as (Trujillo et al. 2011)

$$\text{BR} = \sum (\text{spikes} \times \text{FM rate})/\sum (\text{spikes})$$

FM sweep direction selectivity. In a smaller subset of neurons (65 M and 53 O neurons), both upward and downward sweeps were tested to study direction selectivity. Data from Trujillo et al. (2011) on Y mice were used for comparison. The upward and downward sweeps were of identical bandwidths and rates. To assess the degree to which neurons prefer upward or downward FM sweeps, the direction selectivity index (DSI) was calculated as follows:

$$\text{DSI} = (\text{D} - \text{U})/(\text{D} + \text{U})$$

where D and U are the trapezoidal area under the curve for downward and upward FM sweeps, respectively. DSI values closer to +1 indicate a preference for downward FM, and values closer to −1 indicate a preference for upward FM. Because direction selectivity varies with rate (Razak and Fuzessery 2006; Trujillo et al. 2011; Zhang et al. 2003), DSI was assessed at three different ranges of FM rate: 0.1–1 kHz/ms, 1.1–3 kHz/ms, and 3.1–10 kHz/ms.

Response variability. Response variability was quantified with the Fano factor [Fano factor = (variance/mean)] (Fu et al. 2012; Kara et al. 2000; Yang et al. 2009a). Fano factor was calculated for two different measures of responses to 20 repetitions of FM sweeps: the number of spikes per stimulus (magnitude variability) and variability in interspike interval (ISI variability). For each neuron, multiple sweep rates were repeated 20 times to determine rate selectivity functions. For the magnitude variability measure from each neuron, Fano factor was calculated for every sweep rate and averaged across sweep rates. Fano factor for response magnitude was also calculated at the sweep rate that elicited the maximum response. For the ISI variability measure, the median ISI was taken for each presentation of a sweep rate that elicited at least 3 spikes and the Fano factor across 20 repetitions was calculated based on the variability of the median ISI. The mean ISI Fano factor for the neuron was then calculated by averaging across the different sweep rates tested.

Data Analysis

Unless otherwise noted, one-way ANOVA with post hoc pairwise comparisons was used to compare response measures across age groups. $P < 0.05$ was taken as statistically significant.

RESULTS

The aim of this study was to compare FM sweep rate and direction selectivity in the core auditory cortex across three age groups in a presbycusis mouse model. Only neurons with CFs < 25 kHz were compared across age groups, because almost all neurons in the M and O group have CF < 25 kHz (Willot et al. 1993). Sounds could not be presented at a set intensity level across ages because the minimum threshold for tones was significantly different across the age groups. A one-way ANOVA of age group × threshold revealed a significant main effect on threshold [$F(2,216) = 44.05$, $P < 0.001$]. A Tukey honestly significant difference (hsd) post hoc test revealed that the O group had a significantly higher mean (±SE) CF threshold (53 ± 1.5 dB SPL) compared with the Y (32 ± 1.3 dB SPL) and M (31 ± 1.7 dB SPL) groups. No difference was observed between Y and M. Therefore, all response properties identified below were obtained at intensities between 10 and 20 dB above minimum threshold for each neuron. Because all neurons were tested at similar relative intensities above threshold, differences in neural detectability of sounds within the excitatory tuning curve are unlikely to be a factor in the analysis.

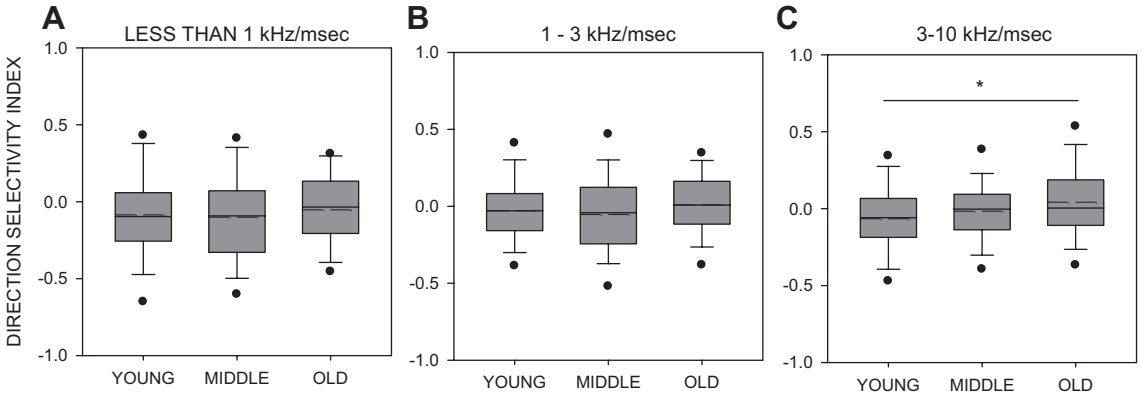

Fig. 3. FM direction selectivity and presbycusis. *A*: box plot of direction selectivity index (DSI) by age group for FM sweep rates <1 kHz/ms. *B*: box plot of DSI by age group for FM sweep rates between 1 and 3 kHz/ms. *C*: box plot of DSI by age group for FM sweep rates between 3 and 10 kHz/ms. Upper and lower edges of each box represent the 75th and 25th percentiles, respectively. Vertical bars represent standard deviation around the mean. The horizontal bar within each plot represents the median, and the dashed line represents the mean. A 1-way ANOVA did not reveal a significant effect of age group for <1 kHz/ms [*A*; $F(2,201) = 0.43$, $P = 0.65$] or 1.1–3 kHz/ms range [*B*; $F(2,201) = 0.94$, $P = 0.39$], indicating no presbycusis-related change in DSI at those FM sweep rate ranges. For the 3.1–10 kHz/ms range, 1-way ANOVA revealed a significant main effect of age on DSI [*C*; $F(2,201) = 3.23$, $^*P < 0.05$].

Table 1. *Distribution of FM sweep rate tuning type*

Tuning Type	Young (N = 194)	Middle-Aged (N = 147)	Old (N = 163)
All-pass	14%	19%	14%
Band-pass	46%	32%	35%
Fast-pass	26%	20%	18%
Slow-pass	14%	29%	33%

FM, frequency modulated.

Auditory Brain Stem Response

Figure 2 shows the average ABR thresholds from a subset of mice across the age groups. There was a significant hearing loss in the M and O groups compared with the Y group. A two-way ANOVA on threshold × age group × frequency revealed a significant main effect of age group [$F(2,559) = 429$, $P < 0.001$] and a significant main effect of frequency [$F(9,559) = 94$, $P < 0.001$]. There was a significant interaction between age group and frequency [$F(18,559) = 5.18$, $P < 0.001$]. A Tukey post hoc test revealed that at <40 kHz all three groups were different ($P < 0.01$). At >40 kHz, the Y group had significantly lower threshold than the M and O groups. The M and O groups were not different from each other at frequencies > 40 kHz. These results imply that moderate hearing loss was present in the M group and severe hearing loss was present in the O group.

Effects of Presbycusis on FM Direction Selectivity

Direction selectivity was assessed at three FM sweep rate ranges: <1 kHz/ms, 1.1–3 kHz/ms, and 3.1–10 kHz/ms (Fig. 3). On average, DSI was ~0 across the three groups. For the <1 kHz/ms range, a one-way ANOVA did not reveal a significant effect of age group [$F(2,201) = 0.43$, $P = 0.65$], indicating no presbycusis-related change in DSI at those FM sweep rate ranges. For the 1.1–3 kHz/ms range, one-way ANOVA did not reveal a significant effect of age [$F(2,201) = 0.94$, $P = 0.39$], indicating no presbycusis-related change in DSI at those FM sweep rate ranges. For the 3.1–10 kHz/ms range, one-way ANOVA revealed a significant main effect of age on DSI [$F(2,201) = 3.23$, $P < 0.05$]. A Tukey hsd post hoc test revealed that the Y and O groups were significantly different, with the Y group demonstrating a slight tendency toward upward sweeping FMs (mean DSI = −0.07) and the O group demonstrating a slight tendency toward downward sweeping FMs (mean DSI = 0.04). These results suggest a subtle shift toward preferring downward FM sweeps with age only at the fast sweep rates.

Neurons with DSI values greater than 0.3 and less than −0.3 were considered direction selective, and the prevalence of such

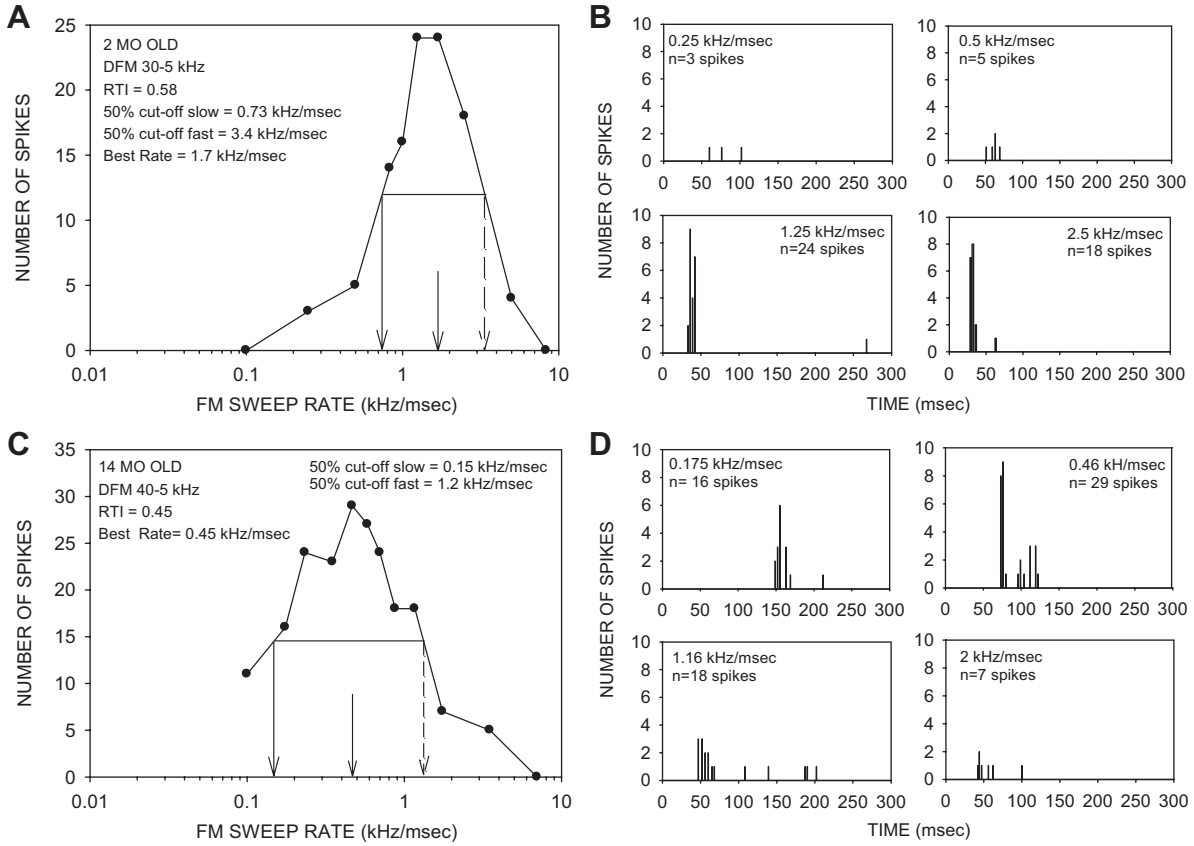

Fig. 4. Representative FM rate selectivity functions from the Y and O groups. *A* and *C*: FM rate selectivity functions from a 2-mo-old and a 14-mo-old cortical neuron, respectively. Short arrows in both panels point to the best rate. Long solid arrows point to the 50% cutoff rate on the slow rate side of the peak. Long dashed lines point to the 50% cutoff rate on the fast rate side of the peak. *B* and *D*: poststimulus time histograms of responses to selected (indicated in each panel) sweep rates for the neurons shown in *A* and *C*. Stimulus onset in these graphs is at 0 ms. The latency of response decreases with faster sweep rates because faster sweeps reach the excitatory tuning curve earlier. These neurons illustrate the general population trends shown in subsequent graphs. FM sweep selectivity is broader (RTI is smaller) in the O neuron. The 50% cutoff rates and best rate are shifted to slower rates in the O neuron.

direction-selective neurons was compared across the three age groups. Across different rate ranges and groups, <25% of neurons were direction selective (collapsed across rate ranges: Y = 20%, M = 15%, O = 23%) and the prevalence did not change with age ($\chi^2 = 4.382$, $P = 0.357$). Comparison of DSI across age only from these neurons also did not reveal an age-related change at any of the sweep rate ranges (1-way ANOVA, $P > 0.05$ for both neurons with DSI < -0.3 and neurons with DSI > 0.3 at all 3 rate ranges). Collectively, these results indicate weak FM sweep direction selectivity in the mouse auditory cortex with relatively little change with presbycusis.

Presbycusis-Related Change in FM Sweep Rate Selectivity

In contrast to direction selectivity, significant presbycusis-related change in FM sweep rate selectivity was found. Figure 1 shows the different types of rate-selective neurons. Table 1 provides the distribution of tuning type by age. A majority of Y neurons demonstrate BP and FP rate tuning. The percentage of BP and FP neurons decreased in the M and O groups ($\chi^2 = 14.46$, $P < 0.05$). The percentage of SP neurons increased in the M and O groups. This indicates a presbycusis-related decrease in neurons selective for fast and intermediate sweep rates.

Figure 4 shows representative BP FM selectivity functions and PSTHs from the Y (Fig. 4, *A* and *B*) and O (Fig. 4, *C* and *D*) groups. These two neurons represent the main population trends observed in terms of FM rate selectivity with age. Compared with the Y neuron, the O neuron has a smaller RTI, indicating broader FM rate selectivity. In addition, the 50% cutoff rate and best rate in the O neuron indicate tuning to slower sweep rates. BP neurons have two 50% cutoff rates, one on the slow side of the peak (termed "50% cutoff rate slow") and the other on the fast side of the peak (termed "50% cutoff rate fast"). In the example neurons shown, both the slow and the fast 50% cutoff rates of the BP neurons were shifted to slower rates. We compared RTI within each FM rate selectivity type (FP, BP, AP, and SP) across age groups (Fig. 5). There was a significant reduction in RTI in BP neurons across age groups [Fig. 5*B*; 1-way ANOVA $F(2,193) = 10.97$, $P < 0.001$]. A Tukey hsd post hoc test revealed that the O group had a significantly lower RTI than the Y group. There were no differences between the Y and M groups and the M and O groups for BP neurons. There was no difference in RTI in the FP, AP, and SP neurons across age (1-way ANOVAs, $P > 0.05$; Fig. 5, *A*, *C*, and *D*). These results indicate that the sharpness of rate selectivity decreases with presbycusis specifically in the BP neurons.

The 50% cutoff rates of FP, BP, and SP neurons as well as the best rate of BP neurons were compared across age groups (Fig. 6). Across the population of BP neurons, both 50% cutoff rates (slow, Fig. 6*A*; fast, Fig. 6*B*) and best rates (Fig. 6*D*) were significantly reduced with presbycusis [1-way ANOVAs: 50% cutoff-slow $F(2,193) = 15.94$, $P < 0.001$, 50% cutoff-fast $F(2,193) = 39.02$, $P < 0.001$; best rate $F(2,193) = 38.88$, $P < 0.00$]. A Tukey hsd post hoc test revealed that the O group had

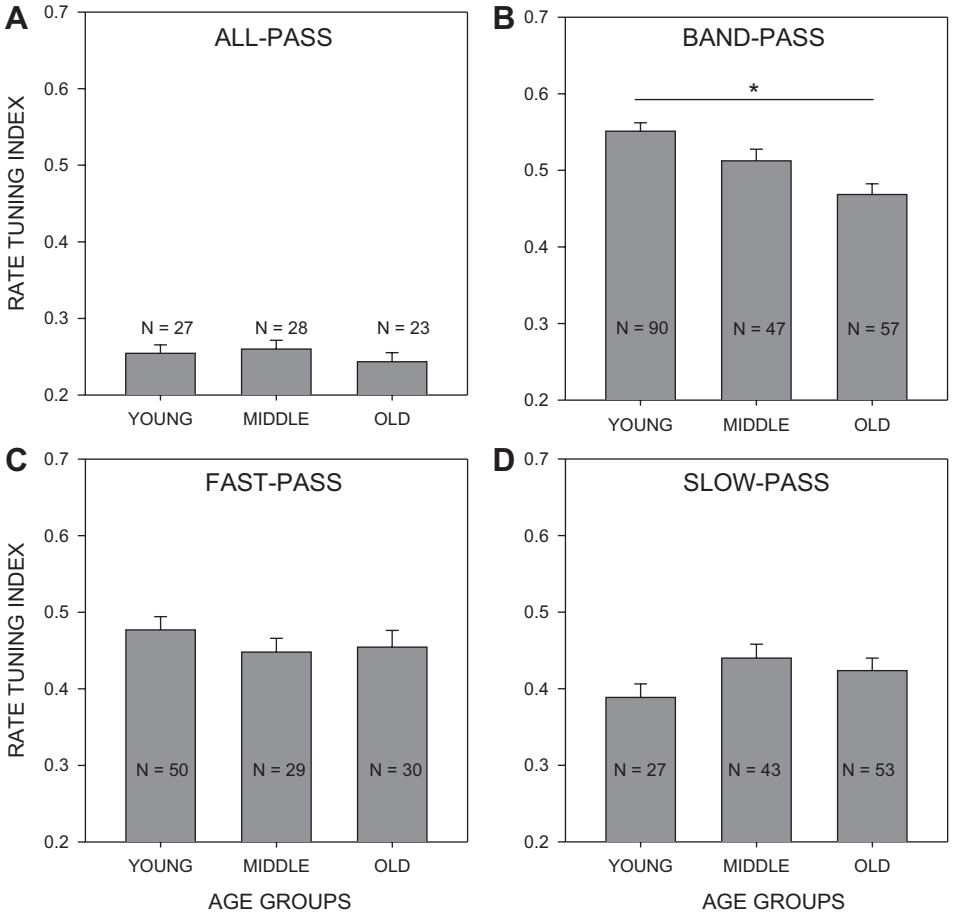

Fig. 5. FM sweep rate selectivity and presbycusis: RTI plotted according to rate tuning type: AP (*A*), BP (*B*), FP (*C*), and SP (*D*). Means ± SE are shown. Horizontal lines represent differences as revealed by a Tukey honestly significant difference (hsd) post hoc test. The sample size indicates number of neurons. *BP neurons show a significant decline in RTI. No changes were observed in other classes of neurons.

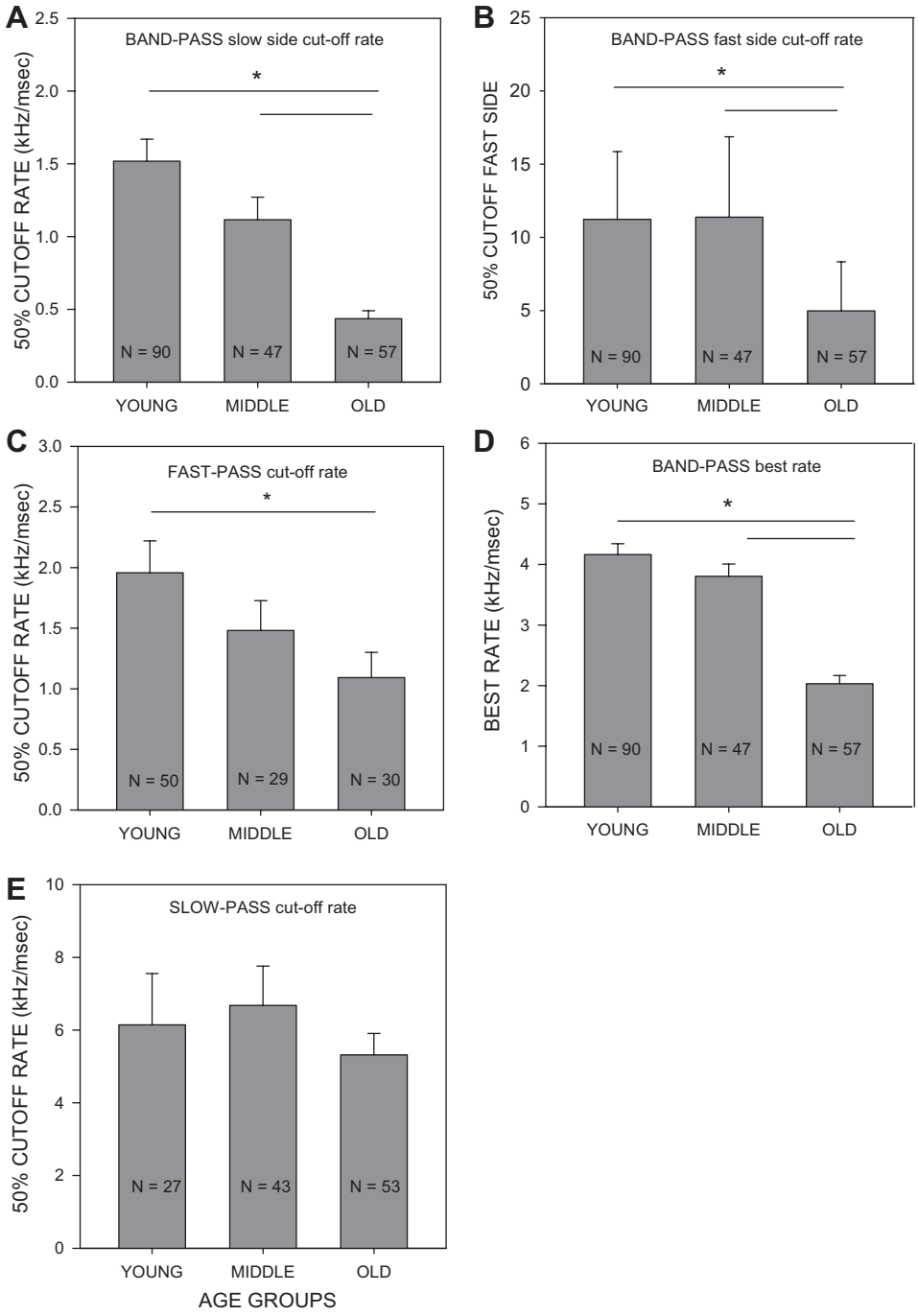

Fig. 6. FM rate selectivity slows with presbycusis: best rate and 50% FM cutoff rates of BP, FP, and SP neurons. Means ± SE are shown. Horizontal lines represent differences as revealed by a Tukey hsd post hoc test. In BP neurons, both 50% cutoff slow (*A*) and 50% cutoff rate fast (*B*) were significantly (*) reduced with age. In FP neurons as well, the 50% cutoff rate significantly shifted to slower sweep rates (*C*). The best rate of BP neurons shifted significantly to slower rates with age (*D*). No differences were found in SP neurons (*E*). Sample sizes indicate number of neurons.

significantly slower 50% cutoff rates (both fast and slow) and best rate than the Y and M groups. The 50% cutoff rate in FP neurons (Fig. 6*C*) also showed a significant presbycusis-related reduction [1-way ANOVA, $F(2,108) = P < 0.05$]. A Tukey hsd post hoc test revealed that the O group had a significantly slower 50% cutoff than the Y group. There was no change in SP neurons (Fig. 6*E*; $P > 0.05$). These results indicate that rate selectivity in FP and BP neurons shifts toward slower sweep rates with presbycusis.

If a relationship exists between CF threshold and sweep selectivity measures, the altered sweep selectivity in BP/FP neurons in the older mice may simply be a reflection of higher average thresholds. However, there was no significant correlation within each age group between CF threshold and either 50% cutoff rate (BP neurons: Y: $r = 0.006$, $P = 0.968$; M: $r = 0.37$, $P = 0.17$; O: $r = 0.044$, $P = 0.84$; FP neurons: Y: $r = -0.089$, $P = 0.74$; M: $r = 0.002$, $P = 0.99$; O: $r = -0.234$, $P = 0.485$) or best rate (BP neurons only: Y: $r = -0.003$, $P = 0.98$; M: $r = 0.408$, $P = 0.13$; O: $r = 0.04$, $P = 0.85$). This precludes the possibility that the observed reduction in rate selectivity resulted from the different neural thresholds with age.

Variability in Response to FM Sweeps with Presbycusis

The Fano factor is a measure of the variability in neuronal spiking in response to repetitions of the same stimulus. Figure 7

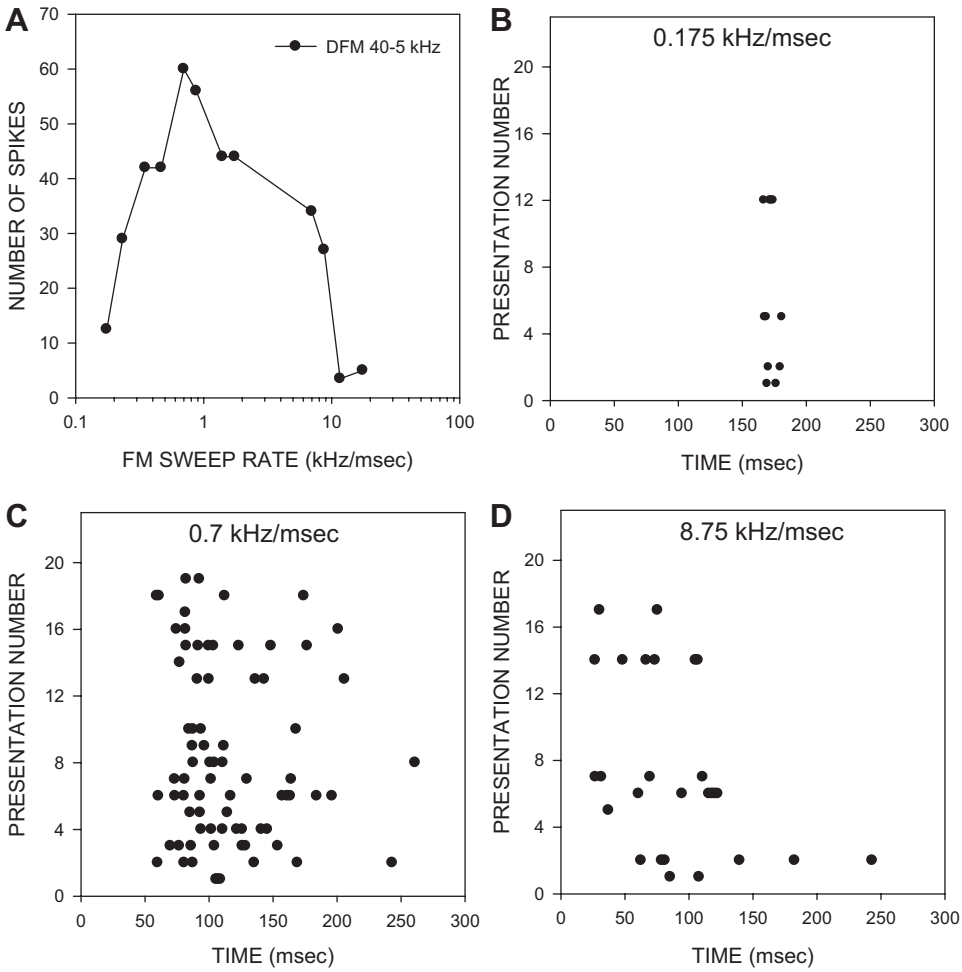

Fig. 7. *A*: example of FM sweep rate selectivity function in the O group. *B–D*: raster plots to illustrate variability in responses across repetitions of the same stimulus at 3 different sweep rates. Variability was quantified with the Fano factor calculated from the raster plot. Each stimulus was repeated 20 times. Each row of the *y*-axis of the raster plots represents 1 stimulus presentation. Fano factor was calculated from trial-to-trial variability in response magnitude, interspike interval (ISI), and response latency. Note that the latency of first spikes declines with increasing sweep rate because the excitatory tuning curve is reached earlier by faster sweeps.

shows an example BP neuron to illustrate the variability in response magnitude and ISI. Across the population, Fano factor for response magnitude increased with age in BP [1-way ANOVA, $F(2,193) = 12.69$, $P < 0.001$] and FP [1-way ANOVA, $F(2,108) = 4.83$, $P < 0.01$] neurons but not in AP and SP neurons (Fig. 8, 1-way ANOVA, $P > 0.05$). All three age groups were different from each other for BP neurons. In FP neurons, response magnitude variability increased in the M and O groups relative to the Y group. An additional comparison was made for the Fano factor of response magnitude at maximum response across the range of sweep rates tested for each neuron (data not shown). Once again, the Fano factor was not different for SP and AP neurons (1-way ANOVA, $P > 0.05$). However, for BP neurons the Fano factor was significantly lower in Y compared with both M and O groups (1-way ANOVA, $P < 0.001$; pairwise comparison Y vs. M: $P < 0.05$; Y vs. O: $P < 0.05$; M vs. O: $P > 0.05$). An identical pattern was found for Fano factor of response magnitude at maximum response in FP neurons as well (1-way ANOVA, $P < 0.001$; pairwise comparison Y vs. M: $P < 0.05$; Y vs. O: $P < 0.05$; M vs. O: $P > 0.05$). These data suggest that the fidelity of response magnitude across repeated presentations of the same sweep decreases with age, with significant differences observed even in the M group.

One potential mechanism of increased variability in response magnitude across 20 repetitions is a building up of adaptation toward the latter repetitions. To examine this possibility, we divided the sum of spikes for the last 5 repetitions of each sweep by the sum of spikes for the first 5 presentations. An average (across sweep rates) ratio close to 1 indicates low adaptation. The ratio was ~1 in BP (Y: 1.01 ± 0.04, M: 0.92 ± 0.05, O: 0.97 ± 0.04) and FP (Y: 1.11 ± 0.06, M: 1.05 ± 0.13, O: 1.1 ± 0.13) neurons, and there were no age-associated differences (1-way ANOVA, $P > 0.05$). There were also no differences in adaptation across the age groups regardless of whether the ratio of responses was measured for the first versus last 3 or 10 repetitions (data not shown). These analyses suggest that increased variability in FP/BP neurons is not due to increased adaptation across stimulus repetitions precluding possible mechanisms such as increased buildup of inhibition.

ISI variability provides information on temporal fidelity across stimulus repetitions. Fano factor for ISI was significantly higher in the O group compared with the Y group in FP and BP neurons (Fig. 9; 1-way ANOVA on ranks, $P < 0.05$). The increase in variability of ISI and response magnitude may arise from an increase in firing rate in the BP and FP neurons. A comparison of maximum firing rate (for the sweep rates tested) across age group shows that only in FP neurons was there an increase in the peak response magnitude with age (Fig. 10; FP neurons, 1-way ANOVA, $P < 0.05$). Together, these data indicate increased presbycusis-related variability in response magnitude and timing in the FP and/or BP neurons only. In BP neurons, increase in variability occurs without a significant

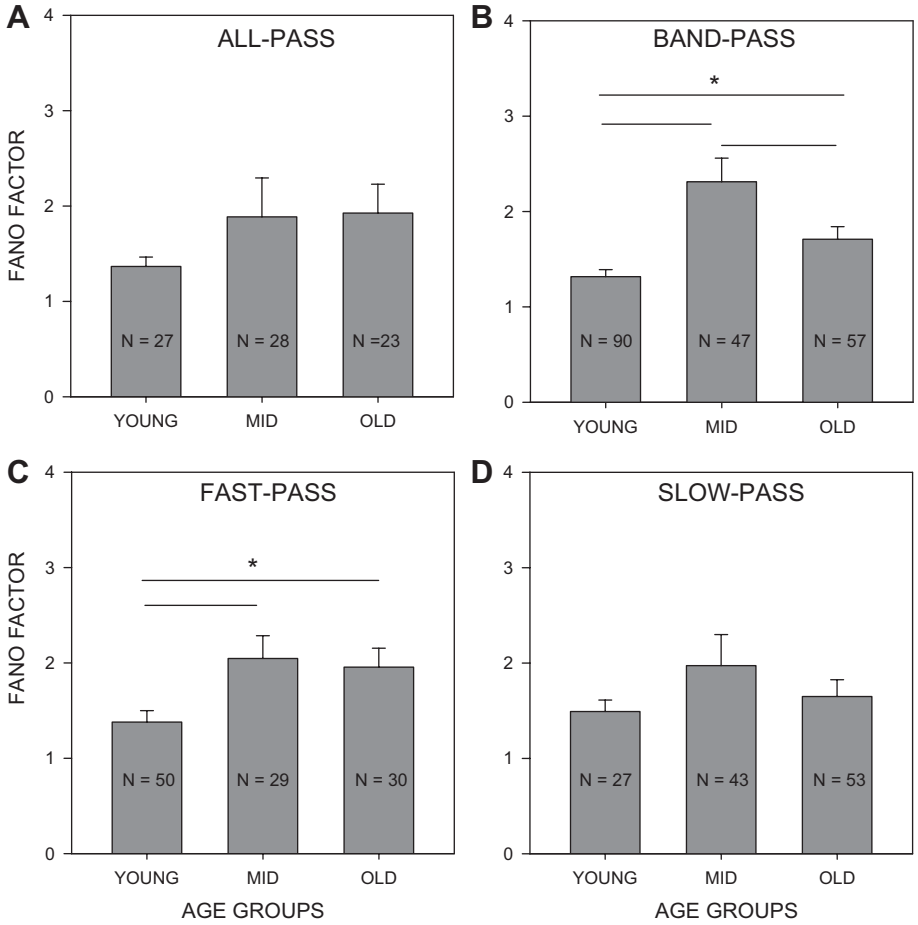

Fig. 8. Trial-to-trial variability in response magnitude increases with presbycusis: trial-to-trial variability in response magnitude for AP (*A*), BP (*B*), FP (*C*), and SP (*D*) is shown. Means ± SE are shown. Horizontal lines represent differences as revealed by a Tukey hsd post hoc test. As depicted in *B*, in BP neurons variability increased from Y to M group. Interestingly, the M group had increased variability relative to the O group. No significant differences (*) were observed in AP and SP neurons.

increase in peak response magnitude. In both FP and BP neurons, increased variability in response magnitude is seen even in the M group, indicating that the increased variability in timing occurs later in age than the increased variability in response magnitude.

DISCUSSION

There are significant changes in FM sweep selectivity with presbycusis in the C57 mouse core auditory cortex that specifically affect FP and/or BP neurons. The 50% cutoff and the best rate are shifted toward slower rates in FP and BP neurons. The 50% cutoff rate is approximately the center of the range of rates over which a neuron shows maximum decline in response magnitude and may be the sweep rate near which the neuron is maximally informative about rate of change of frequency. The best rate is a measure of the sweep rate that is best detected. This suggests that, with presbycusis, FP/BP neurons' sweep rates of best detection and discrimination shift toward slower rates. The Fano factor is a measure of variability of a neuron's response across repetitions of the same stimulus. Fano factors for response magnitude and ISI of FP and BP neurons were larger with age, indicating increased variability of response to repetitions of FM sweeps. Because the 50% cutoff rate and best rate decrease and variability increases with age, older neurons will be most informative about the stimulus for slower spectrotemporal changes (Butts and Goldman 2006). There will be a reduction in the number of neurons providing information for the fast spectrotemporal changes. The sparing of SP/AP neurons suggests that the observed effects are not a result of some nonspecific degeneration process. Collectively, these data suggest that selectivity of neurons representing intermediate to fast sweep rates show presbycusis-related vulnerability in the auditory cortex.

Behavioral and electrophysiological studies in humans with presbycusis show increased detection thresholds for FM signals, increased difficulty in processing rapidly changing acoustic cues, and reduced temporal precision of neural responses to speech syllables (Anderson et al. 2012; Buss et al. 2004; Dorman et al. 1985; Elliott et al. 1989; Ernst and Moore 2012; Fox et al. 1992; Gordon-Salant and Fitzgibbons 2001; Gordon-Salant et al. 2007; Lacher-Fougere and Demany 1998; Tremblay et al. 2003). Our data provide electrophysiological markers for two prominent theories that may explain such deficits: the noisy processing and speed of processing theories (Mahncke et al. 2006a, 2006b; Salthouse 1996). The noisy processing theory attributes age-related processing declines to unreliable and low-fidelity sensory representations that impair cognitive function. If a neuron becomes more variable in its spiking with age, extracting signal from noise may be impaired and fidelity of sensory representation reduced. In terms of FM sweep representation, the increased Fano factor for response magnitude and ISI is suggestive of increased noise in spectrotemporal processing. Theoretical studies have shown that increased variability increases detection thresholds and decreases discriminability of sensory stimuli (Chacron et al. 2001; Sadeghi et al. 2007; Shadlen et al. 1996). Thus declines in spectrotemporal process-

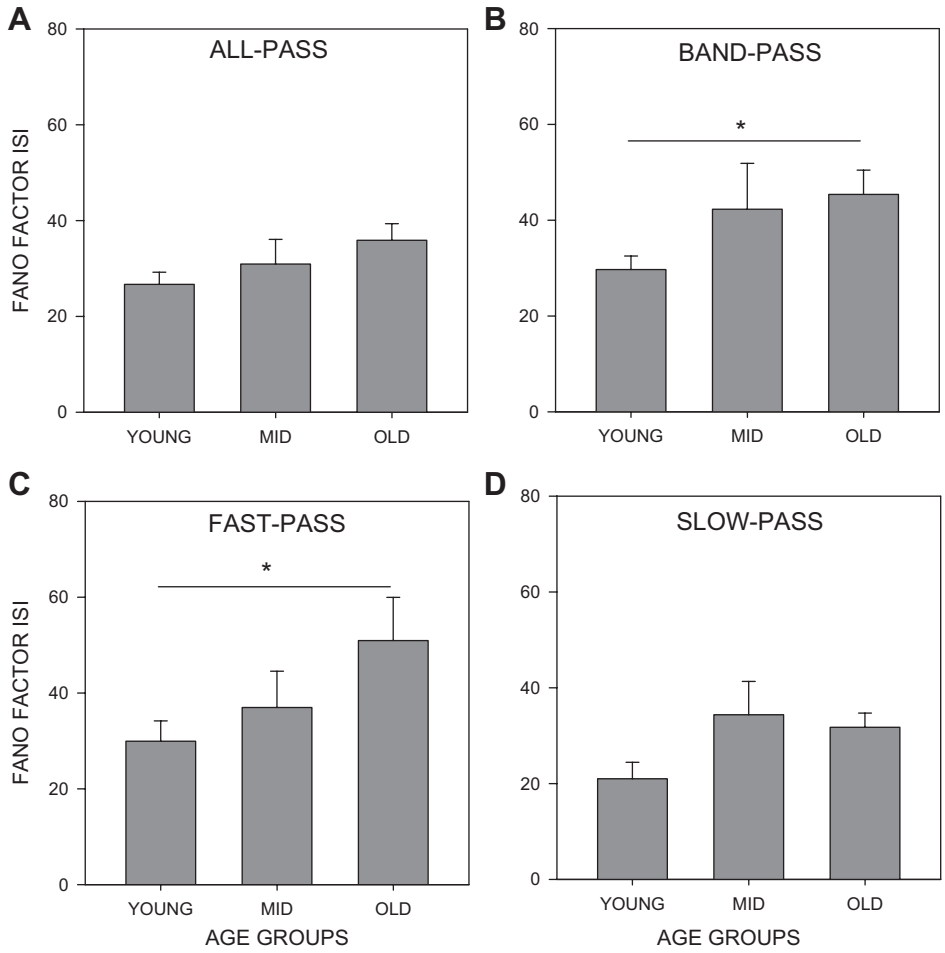

Fig. 9. Trial-to-trial variability in ISI increases with presbycusis: trial-to-trial variability in ISI for AP (*A*), BP (*B*), FP (*C*), and SP (*D*) is shown. Means ± SE are shown. The horizontal lines represent differences as revealed by a Tukey hsd post-hoc test. As depicted in *B* and *C*, in BP and FP neurons ISI variability increased from Y to O neurons. No significant differences (*) were observed in AP and SP neurons.

ing in humans with presbycusis may at least partly be explained by increased variability of responses. Our findings are consistent with those of Turner et al. (2005), who showed that frequency tuning curves in aged rat cortex were less consistent across stimulus repetitions. However, there are no prior data for comparison of response variability to spectrotemporally varying sounds. Thus it is unclear whether our finding of earlier onset (middle age) of increased variability in response magnitude compared with increased variability in ISI is a generalizable pattern across aging models.

The speed of processing theory attributes processing decline to a reduction in the speed at which processing can be carried out, impairing an individual's ability to perform cognitive operations on a stimulus that is rapidly changing. The leftward shift in rate selectivity functions with presbycusis toward slower rates suggests that neurons integrate sweep spectra over a longer time course to generate robust responses. These data are consistent with the findings of Mendelson and Ricketts (2001) in the rat cortex, in which an increase in percentage of neurons preferring slow sweep rates with age was reported. This is also consistent with age-related changes in temporal processing identified with gap detection (Walton et al. 1998, 2008) and AM selectivity (de Villers-Sidani et al. 2010; Walton et al. 2002), which predict longer temporal integration times with aging and therefore slowed spectrotemporal processing. The increase in integration time with presbycusis may underlie the deficits in processing consonants in speech, which can be alleviated by time expansion (Gordon-Salant and Fitzgibbons 2001; Gordon-Salant et al. 2007).

Possible Mechanisms Underlying Presbycusis-Related FM Sweep Processing Declines

Presbycusis-related changes in FM rate selectivity may be the functional manifestation of consistently identified changes in inhibitory circuits with age (Caspary et al. 2008; Leventhal et al. 2003; Suta et al. 2011) and hearing loss (Kotak et al. 2008). Because some of the mechanisms that shape FP/BP neuron rate selectivity functions are known (Trujillo et al. 2013), it is possible to generate hypotheses that relate altered inhibitory neurotransmission to specific receptive field changes. The two mechanisms that shape FM rate selectivity in the young mouse cortex are sideband inhibition and duration tuning (Trujillo et al. 2013). Sideband inhibition is present in most young BP/FP neurons. The temporal relationship between excitatory and sideband inhibitory inputs predicts rate tuning. FP/BP neurons with slower inhibition have slower 50% cutoff rate. Neurons without sideband inhibition are more likely to be AP/SP tuned. The observed changes in presbycusis suggest either a slowing down or a loss of sideband inhibitory inputs.

The cellular mechanisms of this change likely include reduced inhibition from parvalbumin-containing interneurons. Parvalbumin-containing inhibitory neurons are involved in processing auditory input with rapidly varying time cues (Atencio and Schreiner 2008) and with precise spike timing in general (Somo-

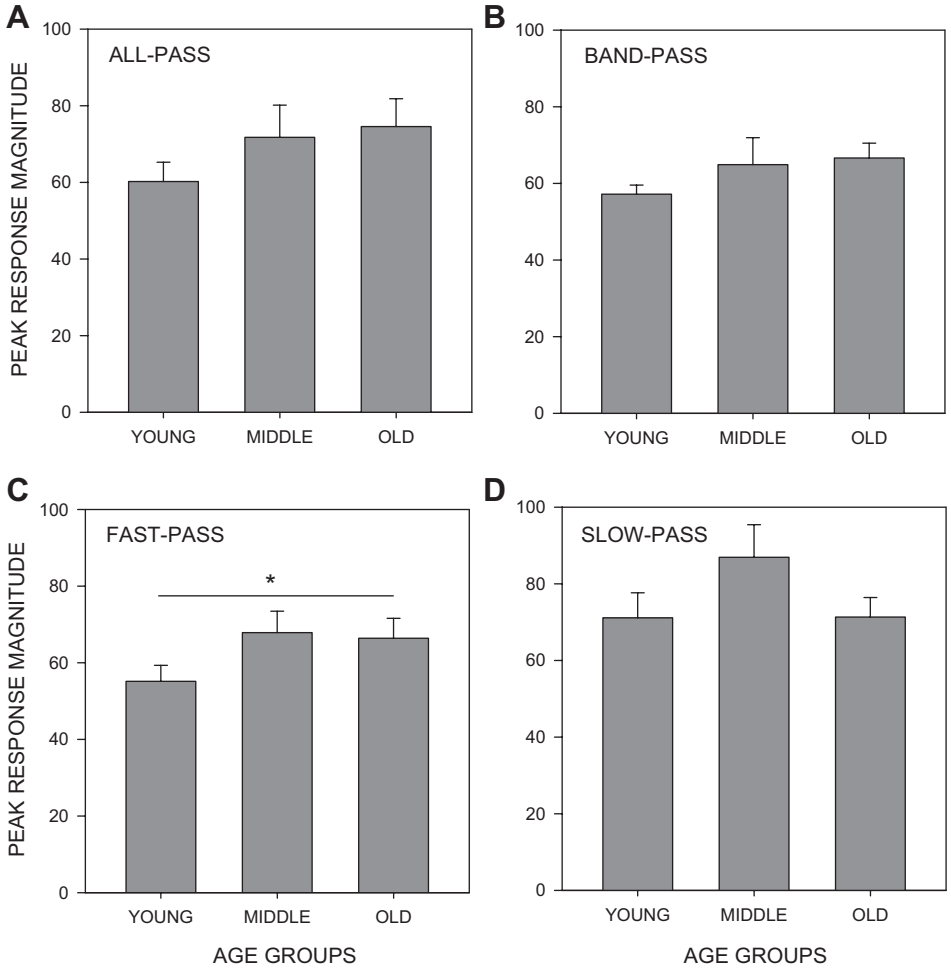

Fig. 10. The peak response magnitude for 20 repetitions of sweep rates between 0.08 and 20 kHz was calculated for each neuron and averaged within age groups. Comparison across groups reveals a difference (*) in FP neurons (*C*) but not for AP (*A*), BP (*B*), or SP (*D*) neurons. Means ± SE are shown.

gyi and Klausberger 2005). Rapid spiking neurons, presumably expressing parvalbumin, shape sideband inhibition (Wu et al. 2008). There is a reduction in the number of parvalbumin-expressing cells in the auditory cortex of rodents (Caspary et al. 2008; de Villers-Sidani et al. 2010; Ouda et al. 2008) including the C57 mouse (Martin del Campo et al. 2012). Reduction of parvalbumin expression in GABAergic neurons alters evoked inhibition (Lucas et al. 2010). Auditory training in aged rats can prevent processing decline with concomitant changes in cortical parvalbumin expression (de Villers-Sidani et al. 2010). These data implicate a role for parvalbumin-containing neurons in slowing down of the 50% cutoff and best rates, and a loss of precision in timing of responses. Future studies (e.g., optogenetic techniques) that decrease parvalbumin neuron activity in young neurons or enhance activity in old neurons will provide more direct insights on the role of parvalbumin neurons in FM sweep coding and slowed-down/noisy processing.

Duration tuning, which also depends on temporal interactions between excitatory and inhibitory inputs (Casseday et al. 2000; Ehrlich et al. 1997; Fuzessery and Hall 1999), may change with presbycusis to alter FM sweep selectivity. Models for duration tuning incorporate an early inhibitory input that is generated at sound onset and lasts the duration of the sound. In the coincidence model (Casseday et al. 2000), rebound from inhibition coincides with a delayed excitation at the preferred duration to enhance response magnitude. In the anticoincidence model (Fuzessery and Hall 1999), the early inhibition impinges on the delayed excitation for long-duration sounds, decreasing the probability of spiking. For short-duration sounds, the inhibition ends before the delayed excitation, increasing the probability of spiking. A common feature in both models is the early inhibition that lasts the duration of the sound. Altered duration tuning with age will result if properties of this early-onset inhibition and its temporal relationships with delayed excitation are altered. However, it is currently not known whether and how duration tuning mechanisms are affected by age. The cellular subtypes involved in shaping duration tuning are also not known. Future studies will test the hypothesis that sideband inhibition is slowed or lost and/or duration selectivity is reduced with presbycusis to cause changes in FM sweep rate selectivity.

To further understand the mechanisms of presbycusis-related decline in cortical FM processing, it is important to disambiguate the relative contributions of central auditory system aging and peripheral hearing loss. The similarity of changes in cortical FM sweep selectivity between the C57 mouse (this study) and the Long-Evans rat (Mendelson and Ricketts 2001) is interesting in this regard given the differences in hearing loss with age between these models. The Long-Evans rat undergoes presbycusis with relatively less hair cell loss compared with the C57 mouse, which undergoes sensorineural presbycusis with considerable hair cell loss. Similar changes in FM processing in these models suggest that central

changes may be the primary cause of the observed age-related plasticity. In the C57 cortex, almost all the changes observed were prominent in the Y versus O comparison, although hearing loss is evident in the M mice (Fig. 2). This also suggests that central aging mostly drives the observed plasticity. However, to address this issue directly requires a comparison of age-matched animals with and without hearing loss, ideally of the same genetic background and raised with similar auditory experience. The development of a congenic C57 mouse strain that does not undergo accelerated sensorineural hearing loss now provides an opportunity to disambiguate central aging and peripheral hearing loss in presbycusis-related change in auditory processing (Harding et al. 2005; Keithley et al. 2004).

Comparison of Age-Related Decline in Sensory Processing Across Modalities

FM rate selectivity is analogous to visual motion speed processing in that neurons code for speed of movement of stimulus across the sensory epithelium. Therefore, it is interesting to note that neurons in aging macaque monkey area middle temporal (MT) also prefer slower motion speeds and show increased response variability to repetitions of motion stimuli (Yang et al. 2009b). Moreover, analogous to results with time expansion of consonants in audition, thresholds for detecting visual motion speed improve with increasing stimulus duration to a larger extent in older participants (Raghuram et al. 2005). Similar receptive field mechanisms have been proposed to underlie FM rate selectivity and motion speed selectivity in auditory (Razak and Fuzessery 2008, 2009; Trujillo et al. 2013) and visual (Duysens et al. 1985; Razak and Pallas 2005) systems, respectively. The similar deficits observed in the respective areas with aging are suggestive of similar underlying causes. Indeed center-surround antagonistic interactions are weakened with aging (Betts et al. 2005), which in turn may be due to reduced GABAergic inhibition (Leventhal et al. 2003). Neuronal spike variability has also been explored in the visual cortex of aging monkeys. Fano factors for response magnitude in V1 and MT increased from ~1.5 in the young cortex to ~2.5 in the old cortex. Fano factors for response magnitude in the auditory cortex (present study) are within the range seen in visual cortex, and the level of change with age is also similar. In the somatosensory cortex as well, receptive field expansion and altered temporal properties (David-Jurgens et al. 2008; Godde et al. 2002) and an imbalance in excitation and inhibition (Hickmott and Dinse 2013) are seen with age. These changes are likely to impact receptive field mechanisms that shape tactile motion selectivity (Wilent and Contreras 2005). Together these findings suggest that similar mechanisms may be involved in increased response variability and decreased selectivity across sensory cortices with age.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

Author contributions: M.T. and K.A.R. conception and design of research; M.T. and K.A.R. performed experiments; M.T. and K.A.R. analyzed data; M.T. and K.A.R. interpreted results of experiments; M.T. and K.A.R. prepared figures; M.T. and K.A.R. drafted manuscript; M.T. and K.A.R. edited and revised manuscript; M.T. and K.A.R. approved final version of manuscript.

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