



Research paper

Development of response selectivity in the mouse auditory cortex

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ABSTRACT

The mouse auditory system contains neurons selective for tone duration and for a narrow range of frequency modulated (FM) sweep rates. Whether such selectivity is developmentally regulated is not known. The main goal of this study was to follow the development of neuronal responses to tones (frequency and duration tuning) and FM sweeps (direction and rate selectivity) in the core auditory cortex (A1 and AAF) of ketamine/xylazine anesthetized C57bl/6 mice. Three groups were compared: postnatal day (P) 15–20, P21–30 and P31–90. Frequency tuning bandwidth decreased during the first month indicating refinement of the excitatory receptive field. Duration tuning for tones did not change during development in terms of categories of tuning types as well as measures of selectivity such as best duration and half-maximal duration. FM rate and direction selectivity were developmentally regulated. Selectivity for linear up and down FM sweeps (0.06–22 kHz/ms) was tested. The best rate and half-maximal rate of neurons categorized as fast- or band-pass selective shifted toward faster rates during development. The percentage of fast-pass selective neurons also increased during development. These data suggest that cortical neurons' discrimination and detection abilities for relatively faster sweep rates improve during development. Although on average, direction selectivity was weak across development, there was a significant shift toward upward sweep selectivity at slow rates. Thus, the C57bl/6 mouse auditory cortex is not adult-like until at least P30. The changes in response selectivity can be explained based on known developmental changes in intrinsic and synaptic properties of mouse auditory cortical neurons.

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1. Introduction

Response properties in the auditory cortex show developmental changes and such changes are influenced by experience (Barkat et al., 2011; de Villiers-Sidani et al., 2007; Insanally et al., 2010; Oswald and Reyes, 2008; Razak et al., 2008; Vater et al., 2010). The mouse is a useful model to tease apart activity-dependent and -independent factors in the development of response selectivity (Barkat et al., 2011; Demyanenko et al., 2011; Gianfranceschi et al., 2003; Intskirveli et al., 2011; Ranson et al., 2012; Sugiyama et al., 2008; Torii et al., 2012; Xu et al., 2011). The focus of the present study was to determine the normal developmental time course of spectral, temporal and spectrotemporal selectivity in the mouse auditory cortex. This will provide baseline measures for investigations in transgenic models of diseases with auditory communication

implications. We focused on developmental time periods between post-natal (P) days 15–30 and compared the responses with those found in adult (P31–P90) because *in vitro* studies show changes in intrinsic and synaptic properties in the mouse auditory cortex between P15 and P30 (Oswald and Reyes, 2008, 2011).

The first goal of this study was to follow the development of responses to pure tones with a focus on frequency and duration tuning in the core auditory cortex (both primary auditory cortex, A1 and the anterior auditory field, AAF) of the mouse (strain C57bl/6) auditory cortex. Sharp frequency tuning is a defining feature of core auditory cortex and it develops relatively early compared to temporal processing features of the cortex (see Froemke and Jones, 2011 for review). Duration tuning for tones is found in auditory systems across vertebrate taxa and is likely to be important in temporal (Brand et al., 2000; Casseday et al., 1994; Chen, 1998; Fuzessery and Hall, 1999; Perez-Gonzalez et al., 2006; Wang et al., 2006) and spectrotemporal processing (Fuzessery et al., 2006) of behaviorally relevant sounds. Whether duration tuning in the mouse auditory cortex is similar to that found in the mouse inferior colliculus (IC, Brand et al., 2000) is unknown. Duration tuning arises from precise temporal interactions of inhibition and excitation generated by a single tone (Casseday et al., 1994; Fuzessery and

Abbreviations: A1, primary auditory cortex; AAF, anterior auditory field; AP, all-pass; BP, band-pass; BW, bandwidth; CF, characteristic frequency; DSI, direction selectivity index; FP, fast-pass; FM, frequency modulated; MT, minimum threshold; P, postnatal day; RTI, rate tuning index; SP, slow-pass.

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Hall, 1999). Whether duration tuning changes during development is unknown in any species, and such studies will provide insights on the development of temporal interactions. We studied the development of frequency and duration tuning between P15–90 in the core auditory cortex of mice.

The second goal was to investigate the development of selectivity for frequency modulated (FM) sweeps. FM sweeps are relatively simple sounds to investigate basic mechanisms and development of spectrotemporal selectivity. FM sweeps are ubiquitous components of vocalizations, including human speech and rodent calls. Both rate and direction of change of frequencies are relevant cues in discrimination of vocalizations (Vignal and Mathevon, 2011; Zeng et al., 2005). Physiological and behavioral studies show sensitivity to FM sweeps in rodents (Wetzel et al., 1998; Zhang et al., 2003). The auditory cortex is necessary for behavioral FM sweep discrimination in rodents (Ohl et al., 1999). In both bats and chinchillas, FM sweep rate selectivity is adult-like at the time of hearing onset, but FM direction selectivity develops slowly (Brown and Harrison, 2010; Razak and Fuzessery, 2007a). A recent study of the core auditory cortex of mice demonstrated strong FM rate selectivity (Trujillo et al., 2011), but it is not known whether this selectivity is developmentally regulated. This study investigated the development of FM sweep rate and direction selectivity between P15 and P90 in A1 and AAF of the C57 mice. Results indicate that the core auditory cortex of C57 mice is not adult-like until around P30. The significant developmental changes observed were sharper frequency tuning and changes in selectivity for FM sweep rates between P15 and P30. There was a moderate but significant change in FM sweep direction selectivity and no observable change in duration tuning for tones.

2. Methods

The Institutional Animal Care and Use Committee at the University of California, Riverside approved all procedures. Mice (C57bl/6J strain, henceforth referred to as C57) were obtained from an in-house breeding colony that originated from breeding pairs purchased from Jackson Laboratory (Bar Harbor, Maine). Mice were weaned at P21 and housed with 2–3 littermates under a 12/12 h light/dark cycle and fed *ad libitum*. Three age groups were studied: P15–20 (17 mice), P21–30 (18 mice), P31–90 (34 mice).

2.1. Justification of mouse strain and for pooling data from P31–P90 as the adult group

The C57 strain was chosen because it is a commonly used background strain for many genetic models of disease with auditory communication disorders (e.g., presbycusis, Fragile X Syndrome). The data from this study can serve as the baseline for available disease models. This mouse strain shows accelerated age-related hearing loss with audiometric evidence for hearing loss from around P90 (Henry and Chole, 1980; Hunter and Willott, 1987; Mikaelian, 1979; Spongr et al., 1997; Willott, 1986). Comparison of cochlear morphology, auditory brainstem responses and distortion-product otoacoustic emissions shows that the C57 strain is similar to the CBA/CaJ strain at 1 month, and begins to deviate at 3 months (Park et al., 2010). Auditory cortical responses and gross tonotopy appear to be normal in the 1 month old C57 mice and start to show plasticity from 3 months of age (Willott et al., 1993). Taberner and Liberman (2005) compared auditory nerve fiber responses between C57 (~4 month) and CBA strains (age between 2 and 4 month) and found no differences in spontaneous rates, tuning curves, rate *versus* level functions, dynamic range, response adaptation, phase-locking, and the relation between spontaneous rate and response properties. The only difference found in the 4 month

old C57 mice was the expected elevation in high-frequency hearing threshold. Trujillo et al. (2011) showed no differences in cortical FM sweep selectivity between 1–2 mo old mice and 2–3 mo old mice. Taken together, these studies show most changes in the C57 auditory system compared to the CBA strain begins to happen around 3 months of age and becomes more pronounced between 3 and 6 months. Therefore, the data for adult mice (ages between P31 and P90) were pooled.

2.2. Surgical procedures

Mice were anesthetized with i.p. injections of ketamine (150 mg/kg) and xylazine (10 mg/kg) mixture. Anesthetic state was monitored throughout the experiment using the toe-pinch reflex test and supplemental dose of the ketamine/xylazine mixture was given as needed. Once an areflexic state of anesthesia was reached, a scalp incision was made along the midline, the skull was cleaned and a craniotomy was performed. The auditory cortex was exposed based on skull and vascular landmarks identified in Willott et al. (1993). Acute electrophysiology recordings were performed on each mouse.

2.3. Acoustic stimulation

Acoustic stimulation and data acquisition were driven by custom written software (Batlab, developed by Dr. Don Gans, Kent State University) and a Microstar digital signal processing board. Programmable attenuators (PA5, Tucker-Davis Technologies, Florida) allowed control of sound intensities before amplification by a stereo power amplifier (Parasound, HCA1100) or an integrated amplifier (Yamaha AX430). Sounds were delivered through a free field speaker (LCY-K100 ribbon tweeters, Madisound, Wisconsin) located 6 inches and 45° from the left ear, contralateral to the recording site. Frequency response of the sound delivery system was measured using a ¼ inch Bruel and Kjaer microphone and measuring amplifier and found to be flat within ±3 dB for frequencies between 7 and 40 kHz. Frequencies <5 kHz were filtered out (Butterworth, 24 dB/octave, Krohn-Hite).

2.4. Electrophysiology

Mice were placed in a Kopf stereotaxic apparatus (model 930, Tujunga, CA) and secured in a mouse bite-bar adapter (Kopf model 923B). Experiments were carried out in a heated (~80 °F), sound-attenuated chamber lined with anechoic foam (Gretch-Ken Industries, Oregon). Electrophysiological recordings were obtained with glass electrodes filled with 1M NaCl (2–10 MΩ impedance). Electrodes were driven orthogonally into the cortex using a Kopf direct drive 2660 micropositioner. Single unit recordings were obtained between 100 and 700 μm from the cortex surface, with ~90% of neurons recorded between 200 and 500 μm. For depth measurements, 'zero' was defined as the point when the electrode first touched the surface of the cortex indicated by changes in recording trace and audio monitor output. The consistency of the zero point was also verified when the electrode was pulled out from a penetration. Single unit recordings were identified by the constancy of amplitude and waveform displayed on an oscilloscope and isolated using a window discriminator. Poststimulus time histograms were obtained relative to stimulus onset. Action potentials that occurred within 400 ms of stimulus onset were included in the poststimulus time histograms. The number of spikes that were elicited over 20 stimulus repetitions was used for quantification of response properties. There was no spontaneous activity in the vast majority of recordings. In a few neurons with spontaneous activity, the response of the neuron in the absence of stimulus over the 400 ms

response window was subtracted from the number of spikes for each stimulus.

2.5. Data acquisition

The primary auditory cortex (A1) of the C57 mouse can be identified via vascular landmarks (Willott et al., 1993) and increasing characteristic frequencies (CF) in a caudal to rostral direction (Stiebler et al., 1997; Trujillo et al., 2011). The AAF is located just rostral to A1 and shows a mirror reversed tonotopic map to A1. Both A1 and the AAF are considered core auditory cortex based on inputs from the thalamus, frequency selectivity and response latency (Lee and Winer, 2011; Linden et al., 2003; Rouiller et al., 1991). Electrophysiologically, the core fields can be distinguished from surrounding areas based on robust (consistent across stimulus repetitions) and narrowly tuned responses to tones and short latency responses. The focus of this study was on development of response properties in these core auditory fields. No attempt was made to distinguish between these two core fields. Other areas such as AII, while also present in young C57 mice (Willott et al., 1993), were not sampled. Search stimuli consisted of tones, broadband noise and FM sweeps of either direction. Once a neuron was isolated, the following response properties were determined:

2.6. Frequency tuning curves

The objective was to determine the width of excitatory tuning curves at 10, 20 and 30 dB above threshold and to compare tuning widths across development. First, the range of sound frequencies producing spikes to at least five successive presentations was determined at a supra-threshold intensity. The range of frequencies tested was between 5 and 50 kHz with 1 kHz resolution. This frequency range was chosen because almost all neurons in the adult C57 mouse core auditory cortex are tuned in this range (Trujillo et al., 2011). This is unlikely to be due to hearing loss because in other strains without hearing loss, the vast majority of neurons in the core auditory cortex (Stiebler et al., 1997) and central nucleus of the inferior colliculus also have CFs <50 kHz (Holmstrom et al., 2010; Portfors and Felix, 2005). The tone duration used was optimized to maximize response as neurons in the mouse auditory system show duration selectivity (Brand et al., 2000). Search tones with durations between 2 and 30 ms were used to determine duration of maximum response to test frequency tuning. In 76% of the neurons, frequency tuning was tested with 5 ms duration tones and the remaining neurons were tested with 10 ms duration tones (1 ms rise/fall time). Although the duration of stimulus influences stimulus energy, it is unlikely that 5 versus 10 ms duration impacted measurements of tuning curves. The intensity was then reduced in 5 dB steps to determine the frequency at which the neuron was excited (defined as producing spikes to at least five successive repetitions) at the lowest sound intensity. This step served to determine the CF and minimum threshold (MT). The intensity was then increased to determine the range of excitatory frequencies (bandwidth, BW) at 10, 20 and 30 dB above MT; termed BW10, 20 and 30, respectively.

2.7. Duration tuning

CF tones of 2–300 ms duration were used to classify neurons according to their duration tuning functions as all-pass, band-pass, short-pass and long-pass (Casseday et al., 1994; Fuzessery and Hall, 1999). All-pass neurons responded above 50% of maximum response at all the durations tested. Band-pass neurons responded selectively to a particular range of tone duration, with responses

declining below 50% of the maximum response on both sides of the peak. Short-pass neurons responded better to relatively short durations and their responses declined below 50% for longer durations. Long-pass neurons responded better to the longest tones presented and their response decreased below 50% of maximum as tone duration is decreased. The best duration of band-pass neurons was defined as the geometric center of durations that elicited >80% of the maximum response. The 50% cutoff duration is the duration at which the response decreased to 50% of maximum.

2.8. FM rate selectivity

A1/AAF neurons in the adult mouse auditory cortex exhibit selectivity for a narrow range of FM sweep rates (Trujillo et al., 2011). The objective here was to quantify the development of such selectivity. FM sweep rate selectivity was determined by presenting linear FM sweeps of fixed bandwidth and different durations. The sweep rate (in kHz/ms) of the stimulus is the FM bandwidth (in kHz) divided by the duration (in ms) of the sweep. Upward (5 → 50 or 40 kHz) and downward (40 or 50 → 5 kHz) FM sweeps were presented at a single intensity, 10–20 dB above the minimum threshold for FM sweep response. Because these studies were not guided by a prior knowledge of the behaviorally-relevant range of sweep rates for an auditory generalist like the mouse, a broad range of FM sweep rates (0.06–22 kHz/ms) were tested. These sweep rates were generated using sweep durations between 2 and 300 ms. Although it is possible some neurons treat very short duration sweeps as clicks, most mouse auditory cortical neurons respond to short duration sweeps in a rate-selective manner (Trujillo et al., 2011).

Neurons were classified (e.g., Fig. 1) as all-pass (AP), slow-pass (SP), band-pass (BP) or fast-pass (FP) according to their FM rate selectivity (Felsheim and Ostwald, 1996; Mendelson et al., 1993; Poon et al., 1991; Razak and Fuzessery, 2006; Ricketts et al., 1998; Tian and Rauschecker, 1994; Trujillo et al., 2011). Note that the classification scheme for rate selectivity is similar to the one used for duration tuning. Henceforth, the abbreviations AP, BP, SP and FP will only be used to describe FM rate selectivity types, while the expanded term will be used to describe duration tuning types. This FM rate classification scheme only applies for the range of rates (0.06–22 kHz/ms) tested here and may differ if a different range of FM rates were used. AP neurons responded above 50% of maximum response at all rates tested. SP neuron responses decreased below 50% of maximum with increasing FM rates. FP neuron responses decreased below 50% of maximum as rates were decreased. BP neurons were selective for a range of rates, with responses decreasing below 50% of maximum for slower and faster rates.

The 50% cutoff rate, defined as the FM rate at which the response declines to 50% of maximum response was measured for FP, BP and SP neurons (Fig. 1). FP and SP neurons have a single 50% cutoff rate (Fig. 1A and B, respectively). BP neurons have two such values, on either side of a peak, 50% cutoff-slow and fast (Fig. 1C). For BP neurons, the best rate was also quantified (Fig. 1C). This was defined as the center of the range of rates producing >80% maximum response.

The degree of rate selectivity was quantified using the rate tuning index (RTI), calculated for each neuron as follows:

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

where n = the number of FM sweep rates assessed, 'mean' is the average response across all rates tested and 'max' is the maximum response. The RTI is also called speed tuning in the literature (Atencio et al., 2007; Brown and Harrison, 2009).

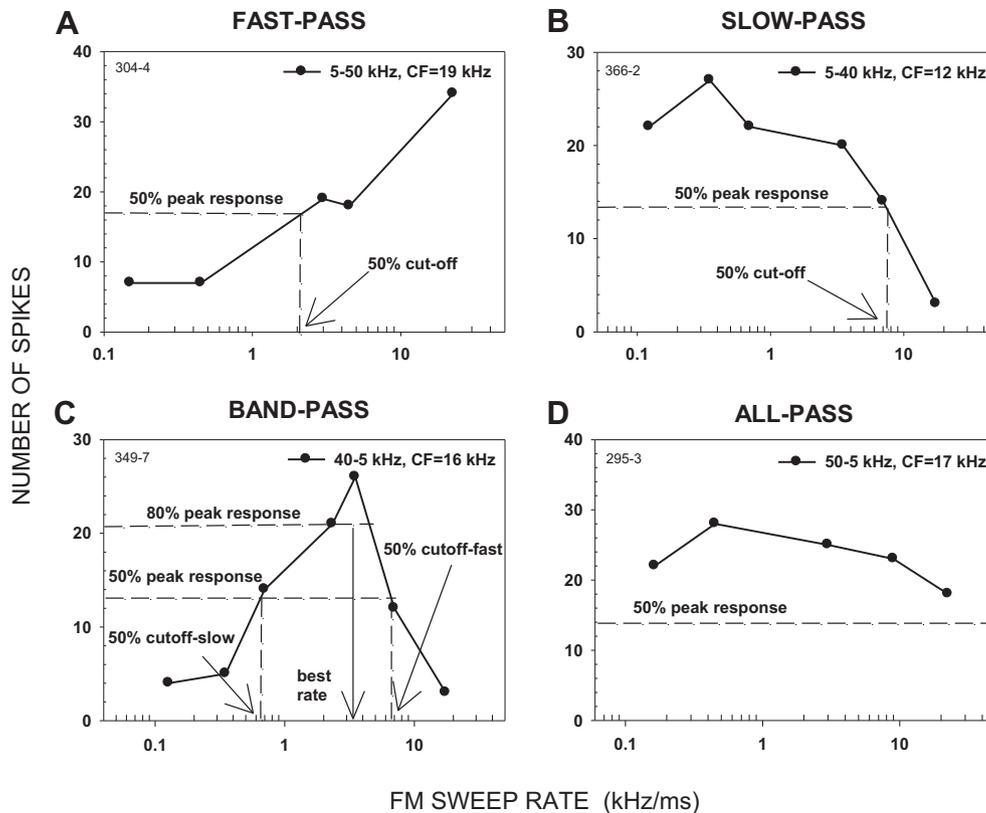


Fig. 1. Definition of 50% cutoff values and best rate for rate tuning functions. The ‘number of spikes’ measure in this and subsequent figures is the total number of spikes over a 400 ms window from stimulus onset and summed over 20 stimulus repetitions. A) Fast-pass neuron. The 50% cutoff is the rate at which neurons respond at less than 50% of peak response as sweep rate was slowed down. The dashed line marks 50% of maximum response. B) Slow-pass neuron. The 50% cutoff rate is the rate at which the neuron responded at less than 50% of maximum as sweeps rate is increased. C) Band-pass neuron. The best rate is the geometric center of the range of rates producing >80% of peak response. The ‘50% cutoff rate-slow’ is the rate at which response declines below 50% of maximum when sweep rates are decreased below the best rate. The ‘50% cutoff rate-fast’ is the rate at which response declines below 50% of maximum when sweep rates are increased above the best rate. D) All-pass neuron. CF: characteristic frequency. The bandwidth and direction of sweep used is indicated in each panel. For example, 5–50 kHz indicates an upward sweep in that frequency range. 50–5 kHz indicates a downward sweep.

2.9. FM direction selectivity

To assess a preference for upward or downward FM sweeps of the same bandwidths and rates, a direction selectivity index (DSI) was calculated as follows:

$$DSI = (D - U)/(D + U)$$

where D and U are the trapezoidal area under the curve for downward and upward FM sweeps (modified from O’Neill and Brimijoin, 2002; Razak and Fuzessery, 2006; Trujillo et al., 2011). DSI values near 1 indicate a preference for downward FM sweeps and values near -1 indicate preferences for upward FM sweeps. Because DSI is sweep rate-dependent (Razak and Fuzessery, 2006; Zhang et al., 2003), DSI was obtained at three different ranges of FM rates: ≤ 1 kHz/ms, 1.1–3 kHz/ms, and 3.1–10 kHz/ms.

3. Results

Neuronal response properties of A1 and AAF of C57 mice were compared across three different age groups during development: P15–20 (96 neurons), P21–30 (95 neurons) and P31–90 (230 neurons). The FM sweep selectivity data for the P31–90 neurons were reported in a previous publication (Trujillo et al., 2011) and are used here for comparison. The tone response properties (frequency and duration tuning) of P31–90 neurons from C57 core auditory region have not been previously described.

3.1. Responses to tones

3.1.1. Excitatory tuning curves become narrow during development

The characteristic frequency (CF) of the neurons across all three age groups was mainly in the relatively low-frequency range (7–30 kHz), consistent with previous reports that most neurons in the core auditory cortex (Trujillo et al., 2011) and central IC of mice exhibit CF below 50 kHz (Holmstrom et al., 2010; Portfors et al., 2009, 2011). More than 85% of the neurons had CFs between 10 and 25 kHz, regardless of the age group. Potential effects of hearing loss on CF distribution were not apparent in the P30–90 group (Table 1). The width of tuning curves of neurons was quantified across the three age groups (Fig. 2). BW10 and BW20 of the P15–20 and P21–30 groups were significantly broader compared to those of the P31–90 mice (ANOVA on Ranks, $p \leq 0.001$). BW30 of the P15–20 mice was also broader compared to that of the P31–90

Table 1

Distribution of CF across age group. Each cell shows the percentage of neurons with CF in the different frequency ranges.

	Percentage of neurons					
	6–10 kHz	11–15 kHz	16–20 kHz	21–25 kHz	26–30 kHz	31–35 kHz
P15–20	1	48	44	7	0	0
P21–30	0	35	53	12	0	0
P31–90	9	29	40	17	4	1

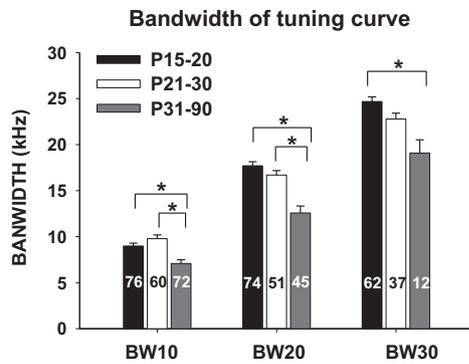


Fig. 2. Excitatory frequency tuning curves become narrower during development in the core auditory cortex of the mouse. * indicates significant differences (ANOVA on Ranks, Dunn's test $p < 0.05$). The number of neurons tested is shown inside each bar.

group (ANOVA on Ranks, $p \leq 0.001$). These results show refinement of the frequency tuning curve of neurons in the core auditory cortex during development.

3.1.2. Adult-like duration tuning is established early in development

Duration tuning was determined by presenting the CF tone at a single intensity, 10–20 dB above MT and with different durations ranging between 2 and 300 ms. Fig. 3 shows examples of short-pass, band-pass and long-pass neurons. Across the population (Fig. 4A), the vast majority of neurons across the three age groups were all-pass or long-pass neurons. No significant differences were found in the distribution of duration tuning categories across development (Chi-square test for independence, $p = 0.342$, Fig. 4A). Best duration of band-pass neurons did not significantly change with age: P15–20: 28.9 ± 8.85 ms; P21–30: 26.3 ± 7.35 ms; P31–90: 46.1 ± 12.9 ms (One-Way ANOVA, $p = 0.370$). There was no difference in the 50% cutoff duration in long-pass, short-pass and band-pass neurons across development (Fig. 4B, ANOVA on Ranks, $p > 0.05$, see Fig. 3A, B, and C for definition of 50% cutoff values). These results show that adult-like duration tuning is established relatively early in development in the mouse core auditory cortex.

Fig. 3D, E and F illustrate post stimulus time histograms (PSTHs) for five different tone durations from the short-pass, band-pass and long-pass neurons shown in Fig. 3A, B and C, respectively. Whether a duration-tuned neuron responds at stimulus onset or offset has important implications for underlying mechanisms (Covey and Casseday, 1999; Fuzessery and Hall, 1999). The response latency of offset duration-tuned neurons will increase with tone duration. It can be seen from the PSTHs in Fig. 3 that the latency of response was not tied to stimulus offset in these neurons. These responses were triggered at stimulus onset. In fact, offset responding neurons were not found in the core auditory cortex across all age groups in this study.

3.2. Development of FM rate selectivity

3.2.1. Distribution of FM rate selectivity types

Fig. 5 shows the distribution of neurons according to FM rate tuning category during development. The percentage of AP and FP neurons increased during development at the expense of SP neurons. The percentage of BP neurons remained relatively stable. This trend occurred for both, downward and upward sweeps. The category distribution was different during development for downward (Chi-square test for independence, $p < 0.001$) and upward FM sweeps (Chi-square test for independence, $p = 0.002$). These results suggest that an adult-like distribution of FM rate tuning types emerges after the first post-natal month in the core auditory cortex of the mouse.

3.2.2. The best rate of band-pass FM rate selective neurons increases throughout development

Although the percentage of BP neurons remained stable during development, the selectivity of BP neurons changed. The best rate of BP neurons was defined as the center of FM rates that produced $>80\%$ of maximum response (Fig. 1C). For downward FM sweeps, the percentage of neurons with best rates between 1.1 and 3 kHz/ms and >3 kHz/ms increased significantly with age (Fig. 6A, Chi-square test for independence, $p < 0.05$, z-tests, $p < 0.05$). This was also reflected in a significant increase (ANOVA on Ranks, $p < 0.05$) in the mean best rate of neurons with age (Fig. 6B, P15–20: 1.41 ± 0.21 kHz/ms; P21–30: 1.86 ± 0.38 kHz/ms; P31–90: 2.60 ± 0.19 kHz/ms). For upward sweeps, the proportion of neurons tuned to the different ranges of rate did not significantly change with age (Fig. 6C, z-tests, $p > 0.05$). Although a trend for increasing mean best rate was seen with age, these values were not significantly different (Fig. 6D, P15–20: 1.81 ± 0.308 kHz/ms; P21–30: 2.39 ± 0.348 kHz/ms; P31–90: 2.58 ± 0.331 kHz/ms, ANOVA on Ranks, $p > 0.05$). These data show a developmental increase in preferred sweep rates of core auditory cortex neurons for downward sweeps. These data also suggest different time courses for development of rate selectivity for upward versus downward sweeps.

3.2.3. The 50% cutoff rate of fast-pass and band-pass neurons increases throughout development

In both FP and BP neurons, responses decline as the sweep rate decreases below some optimal range. The 50% cutoff rate is used to quantify the rate at which response declines below 50% of maximum response for slower sweeps in both FP and BP neurons (see Fig. 1). The 50% cutoff rate increased during development for downward sweeps (Fig. 7A, P15–20: 0.362 ± 0.03 kHz/ms; P21–30: 0.663 ± 0.14 kHz/ms; P31–90: 0.841 ± 0.08 kHz/ms, ANOVA on Ranks, $p < 0.001$). The 50% cutoff rates for upward sweeps followed a similar trend (Fig. 7B, P15–20: 0.521 ± 0.09 kHz/ms; P21–30: 0.943 ± 0.19 kHz/ms; P31–90: 1.17 ± 0.18 kHz/ms). For upward sweeps, only the P15–20 and P31–90 data were different from each other (ANOVA on Ranks, $p < 0.001$).

For BP neurons, two 50% cutoff rates are present (one on the fast rate side and the other on the slow rate side, Fig. 1C). Fig. 7C shows the 50% cutoff rate on the fast rate side for BP neurons. For downward sweeps, the 50% cutoff rate on the fast side increased during development (P15–20: 5.22 ± 0.71 kHz/ms; P21–30: 6.78 ± 0.91 kHz/ms; P31–90: 8.29 ± 0.48 kHz/ms). The data for P15–20 and P31–90 were significantly different from each other (ANOVA on Ranks, $p < 0.05$). For upward sweeps, there was no developmental difference in the 50% cutoff rate on the fast side (Fig. 7D, ANOVA on Ranks, $p = 0.261$). Taken together, these data show that for downward sweeps, FP and BP neuron rate selectivity functions shift toward faster rates during development. Although the data for upward sweeps were mixed, a similar trend exists in terms of selectivity functions shifting to faster rates.

3.2.4. The 50% cutoff values of SP neurons decreases during development

The 50% cutoff rate of SP neurons is the rate at which response declines below 50% of maximum for increasing sweep rates (e.g., Fig. 1B). For downward sweeps, there was a developmental decrease in 50% cutoff rate of SP neurons (Fig. 7E, P15–20: 5.54 ± 0.8 kHz/ms; P21–30: 3.86 ± 0.703 kHz/ms; P31–90: 2.74 ± 0.37 kHz/ms). The data from P15–20 and P31–90 were different from each other (ANOVA on Ranks, $p < 0.05$). No significant differences were found for upward sweeps, but there was a trend of the 50% cutoff value to decrease in SP neurons (Fig. 7F, P15–21: 5.78 ± 0.93 kHz/ms;

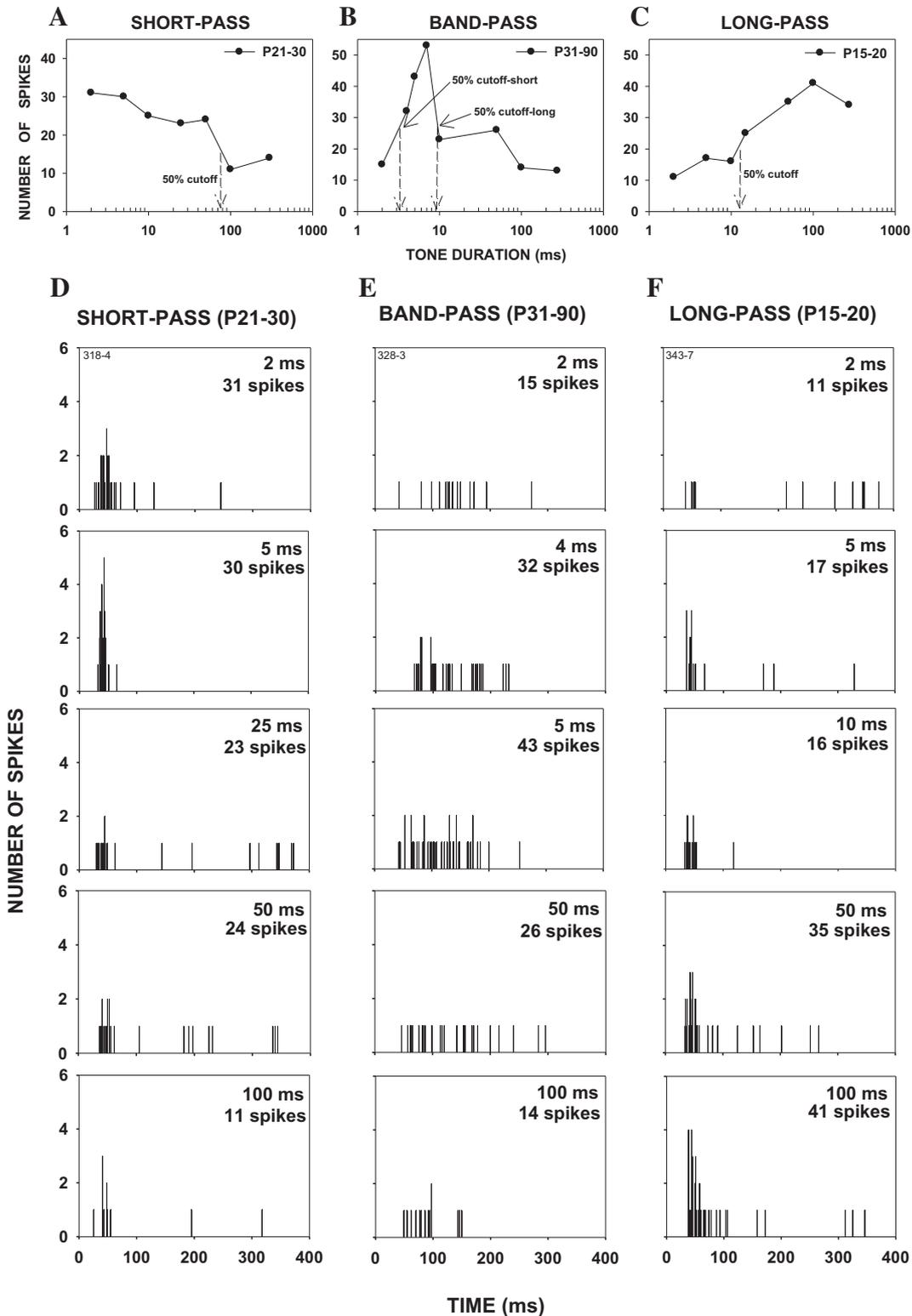


Fig. 3. Classification of duration tuning. A), B) and C) Examples of single neuron duration tuning functions tested with the CF tone at a single intensity, 10–20 dB above minimum threshold. D), E) and F) PSTHs (1 ms bin width) for five different tone durations corresponding to short-pass, band-pass and long-pass neurons shown on A, B and C, respectively. Stimulus onset is at 0 ms.

P21–30: 3.53 ± 0.84 kHz/ms; P31–90: 3.57 ± 0.65 kHz/ms, ANOVA on Ranks, $p > 0.05$). These data suggest that the rate selectivity functions of SP neurons shift leftward, toward slower sweeps, during development.

3.2.5. Rate tuning index does not change during development

The rate tuning index (RTI) was calculated to quantify the degree of rate selectivity (Fig. 8). The mean RTI value of BP, FP and SP neurons did not change across the age ranges for either downward

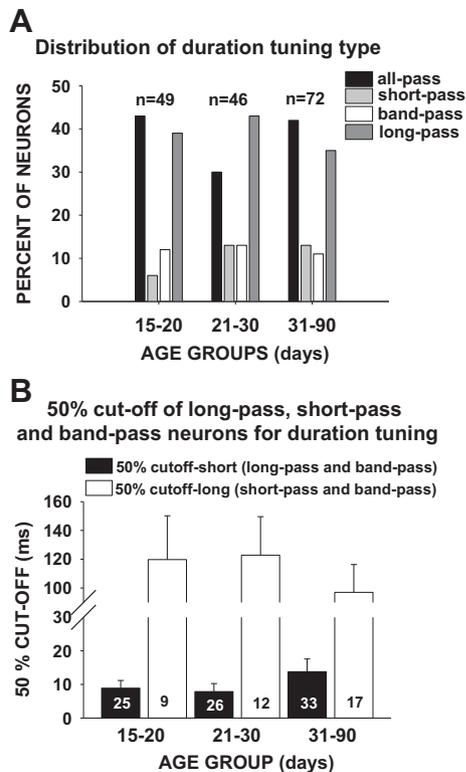


Fig. 4. Development of duration tuning. The distribution (A) of duration tuning types and 50% cutoff values (B) did not change with development (Chi-square test for independence, $p > 0.05$). 50% cutoff values are defined on Fig. 3A, B and C.

or upward sweeps (band-pass and fast-pass: downward (Fig. 8A): P15–20: 0.533 ± 0.02 ; P21–30: 0.493 ± 0.02 ; P31–90: 0.493 ± 0.01 ; upward (Fig. 8B): P15–20: 0.546 ± 0.02 ; P21–30: 0.488 ± 0.02 ; P31–90: 0.547 ± 0.02 ; slow-pass: downward (Fig. 8C): P15–20: 0.485 ± 0.0237 ; P21–30: 0.506 ± 0.0200 ; P31–90: 0.458 ± 0.0165 ; upward (Fig. 8D): P15–20: 0.511 ± 0.0240 ; P21–30: 0.556 ± 0.0224 ; P31–90: 0.481 ± 0.0187 , ANOVA on Ranks, $p > 0.05$). These data indicate that overall selectivity of neurons did not change, but the rate selectivity functions of BP and FP neurons shifted toward faster rates, and those of SP neurons shifted toward slower rates.

3.2.6. Development of direction selectivity

The development of direction selectivity was quantified by comparing DSI values across the three different age groups. DSI values were obtained for three sweep rate ranges: ≤ 1 kHz/ms, 1.1–3 kHz/ms and 3.1–10 kHz/ms for each neuron. Values of DSI lie between +1 and –1, with positive values indicating a preference for downward sweeps, zero indicating no preference and negative values indicating a preference for upward sweeps. Fig. 9 shows examples of neurons that responded similarly to downward and upward sweeps (Fig. 9A) and neurons that were selective for upward sweeps (Fig. 9B). Distribution of DSI is shown in Fig. 9C as histograms for each rate range and age analyzed. Although some neurons prefer downward or upward sweeps, on average the DSI values are centered near zero (dotted line) across the three ages. The distribution, particularly at the slowest rate tested, shifted toward negative DSI during development. The mean DSI values are shown in Fig. 9D. There is a tendency for neurons in the two youngest groups to prefer downward sweeps on average. This changed to an average DSI near zero or preferring upward sweeps in the adult mice. This trend was significant for the slowest sweep

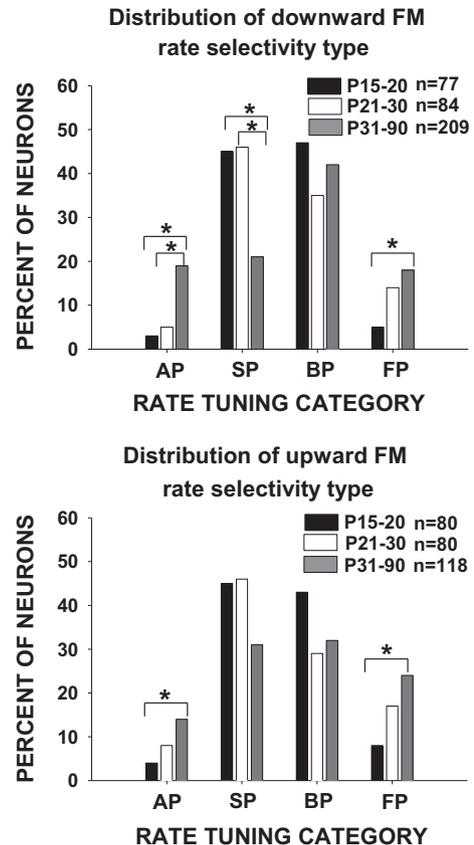


Fig. 5. Distribution of FM sweep rate tuning categories changes with age. The percentage of all-pass (AP), slow-pass (SP), band-pass (BP) and fast-pass (FP) neurons is shown for downward (top) and upward FM sweeps (bottom). The distribution of rate selectivity types varied among age groups for both downward and upward sweeps (Chi-square test for independence, $p < 0.05$). Differences across ages are indicated by * (z-tests, $p < 0.05$). n = number of neurons per age group.

rates. The DSI value of P31–90 was significantly lower compared to that of P21–30 for the ≤ 1 kHz/ms rate range (P21–30: 0.0992 ± 0.0281 ; P31–90: -0.0464 ± 0.0288 , ANOVA on Ranks, $p < 0.001$).

4. Discussion

This study examined the development of response selectivity in the core (A1/AAF) auditory cortex of the C57 strain mouse with emphasis on frequency tuning, duration tuning, FM sweep rate and sweep direction selectivity. The main finding was that frequency tuning, FM sweep rate and direction selectivity changed during development. Tone duration tuning was adult-like from the earliest age examined.

4.1. Frequency tuning development

The refinement of tuning curves or receptive fields is a ubiquitous process during the development of sensory systems, at least in altricial species (Carrasco et al., 2005; Fagioli et al., 1994; Hubel and Wiesel, 1963; Inan and Crair, 2007; Katz and Shatz, 1996; Stern et al., 2001; Zhang et al., 2001). In the chinchilla, a precocious mammal, tuning widths of auditory cortex neurons of P3 animals are similar to those in adults (Pienkowski and Harrison, 2005). On the other hand, in the rat, the pallid bat and the mustached bat, the bandwidth of tuning curves of neurons in the auditory cortex progressively refine during the first postnatal month (Razak and

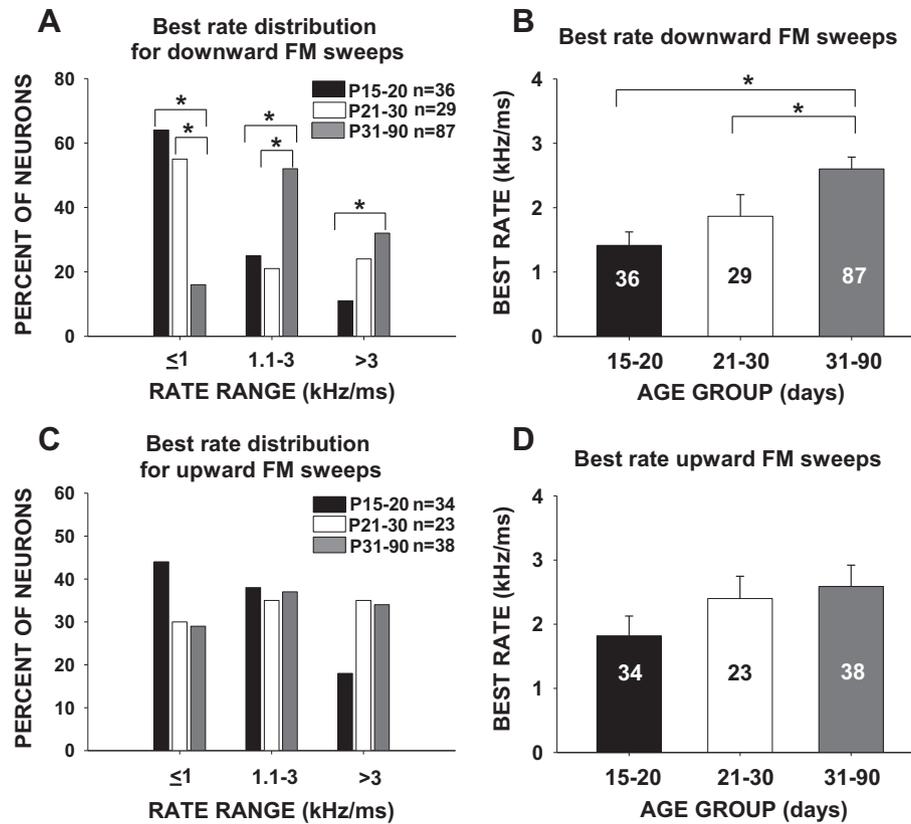


Fig. 6. Best rate of band-pass neurons increased significantly with age for downward sweeps. (A, C) Distribution of best rates across development for downward and upward sweeps. (B, D) The mean (\pm SEM) best rate for downward and upward sweeps. * indicates significant difference. Numbers inside the bars represent the number of neurons tested.

Fuzessery, 2007b; Vater et al., 2010; Zhang et al., 2001). The mouse core auditory cortex showed a similar trend as in other altricial species and was consistent with the sharpening of tuning curves in the mouse IC and cochlear nucleus, where frequency tuning becomes adult-like around P20–25 (Ehret and Romand, 1992; Saunders et al., 1980). Thus, refinement of cortical frequency tuning may simply reflect the developmental fine-tuning of subcortical neurons. Alternately and/or concomitantly, the refinement may depend on the modulation of the strength of inhibitory and excitatory intracortical connections (Chang et al., 2005). Sharpening of the excitatory tonal receptive fields of auditory cortex neurons after hearing onset with respect to the inhibitory receptive fields occurs in rat A1 (Sun et al., 2010), suggesting that changes of the strength of excitatory connections may be involved in tuning curve refinement.

4.2. Duration tuning development

Across development, most cortical neurons were either not selective for tone duration or responded best to long duration tones. The distribution of duration tuning categories (all-pass, short-pass, band-pass and long-pass) and selectivity of neurons did not change during the developmental period examined suggesting that the mechanisms responsible for duration tuning in the cortex are established at least around hearing onset. In the adult mouse IC as well, only \sim 10% of the neurons are short-pass or band-pass tuned; most neurons are non-selective (all-pass) or long-duration tuned (Brand et al., 2000). Results from the chinchilla IC yielded a similar pattern: 46% of the neurons are un-tuned to duration and 7% are band-pass (Chen, 1998). Thus, band-pass and fast-pass duration selective neurons appear to be relatively rare in the

auditory system of rodents compared to the midbrain of bats (Fremouw et al., 2005; Fuzessery and Hall, 1999; Luo et al., 2008). The preponderance of neurons responding to long duration sounds may reflect the long-durations (100–200 ms) of individual vocalizations in mice (Grimsley et al., 2011; Liu et al., 2003; Rotschafer et al., 2012). Duration tuning in the core auditory cortex has been examined only in the pallid bat and the little brown bat (Galazyuk and Feng, 1997; Razak and Fuzessery, 2006). Only \sim 8% of the neurons in the pallid bat A1 tuned in the echolocation range were band-pass or short-pass selective. Most neurons were non-selective or responded best to long durations. This was the case in the dorsal zone of the auditory cortex of cats as well (He et al., 1997). Thus, while comparative A1 data on duration tuning is sparse, the available data indicate relative rarity of band-pass and short-pass neurons in auditory cortex. This is true across development in the mouse.

Tone duration tuning arises through precise temporal interactions between inhibitory and excitatory inputs generated by single tones (Ehrlich et al., 1997). In the present study, neither the distribution of duration tuning categories nor the 50% cutoff values for the duration tuning functions changed across the examined ages. Our findings suggest that the temporal interactions between inhibitory and excitatory inputs driven by the CF are already mature a few days after hearing onset.

4.3. Development of FM sweep rate selectivity

One of the main effects of age found in this study was for the development of rate selective responses to FM sweeps (Fig. 10, schematic summary of results). Compared to the youngest group, adult mice (P31–90) had a higher proportion of fast-pass and

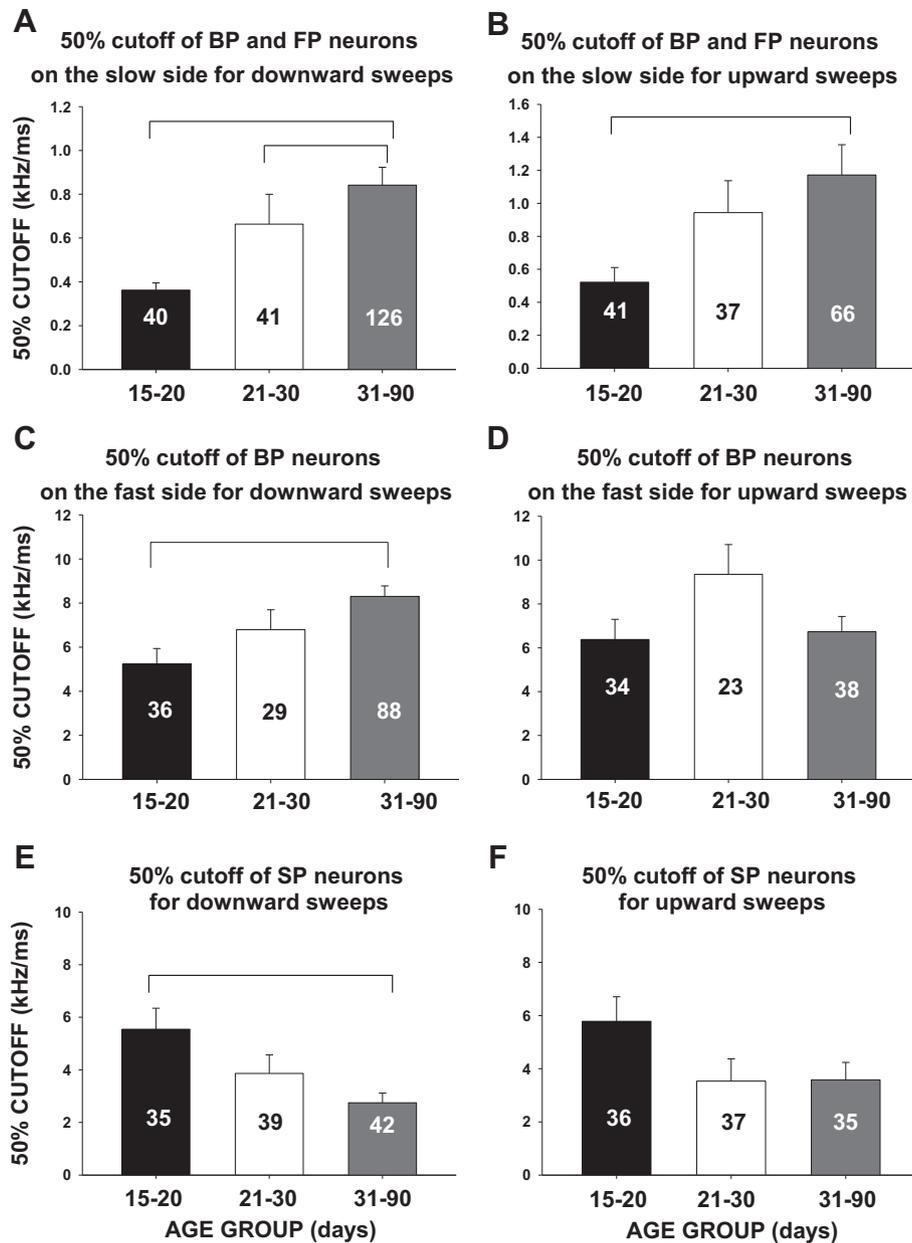


Fig. 7. The 50% cutoff rates change throughout development. 50% cutoff values are defined in Fig. 1. A) and B) 50% cutoff-slow values of BP and FP neurons increased with age for downward and upward sweeps (ANOVA on Ranks, Dunn's test, $p < 0.05$). C) 50% cutoff-fast value of BP neurons increased for downward sweeps (ANOVA on Ranks, Dunn's test, $p < 0.05$) but did not significantly change for upward sweeps (D, ANOVA on Ranks, $p > 0.05$). E) Slow-pass neurons presented a significant decrease in their 50% cutoff rate for downward sweeps (ANOVA on Ranks, Dunn's test, $p < 0.05$) but not for upward sweeps (ANOVA on Ranks, $p > 0.05$). Data shown as mean \pm SEM. * indicates significant difference. Numbers inside the bars represent the number of neurons tested.

all-pass neurons. This occurred mainly at expense of slow-pass neurons. The best rate of BP neurons shift toward faster rates during development. The 50% cutoff rate in fast-pass and band-pass neurons also shifts toward faster rates. The 50% cutoff rate is typically the middle of the range of sweep rates over which a neuron's response shows maximum change and therefore is the stimulus value around which the neuron will provide maximum information (Harper and McAlpine, 2004). The increase in best rate and 50% cutoff rate during development, together with the increased percentage of fast-pass neurons, indicates that core auditory neurons become more informative at faster sweep rates. The integration of frequencies over time to elicit robust responses in FP and BP neurons occurs over shorter durations with development. For slow-pass neurons, the 50% cutoff rate shifts toward slower

rates, indicating that these neurons integrate frequencies over longer time periods and provide maximal information at slower rates with development.

The developmental plasticity of FM sweep selectivity indicates that the underlying mechanisms are not fully established at least until P30 in mouse auditory cortex. Different mechanisms have been suggested to shape neuronal responses to FM sweeps (see Fuzessery et al., 2011 for review; Gittelman et al., 2009; Gordon and O'Neill, 1998; Razak and Fuzessery, 2006; Zhang et al., 2003). FM rate selectivity can be explained by properties of sideband inhibition and duration tuning (Fuzessery et al., 2006; Razak and Fuzessery, 2006). These two mechanisms shape FM rate selectivity in the core auditory cortex of mice as well (Trujillo et al., in preparation). Most auditory neurons exhibit an excitatory tuning

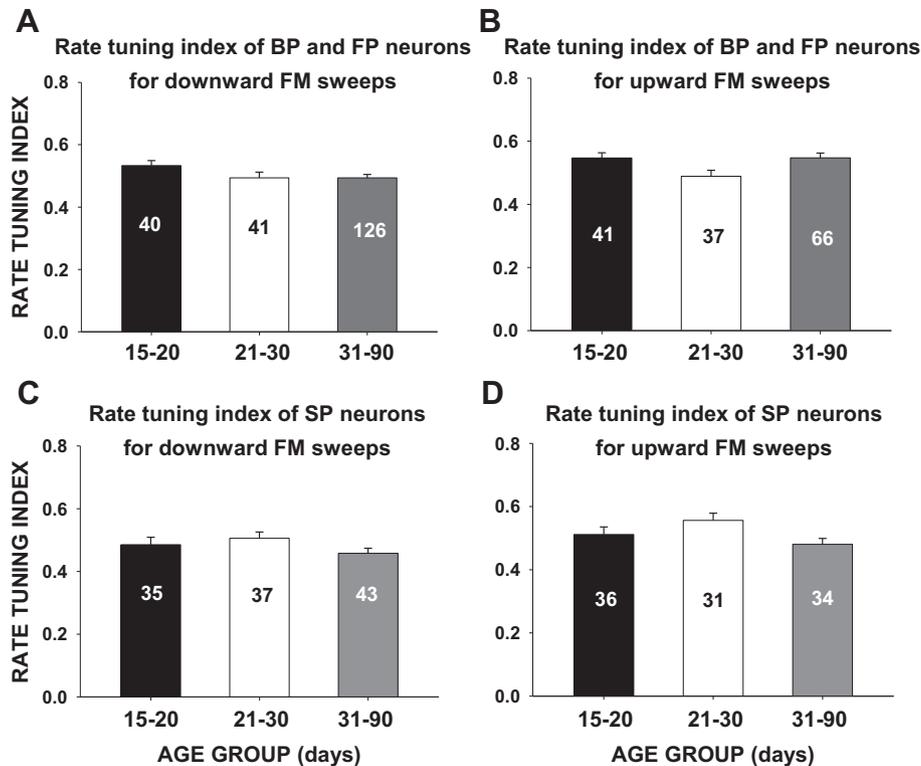


Fig. 8. Rate tuning index of BP, FP and SP neurons does not change with age. A) and B) RTI values of BP and FP neurons for downward and upward sweeps, respectively. No differences were found across the age groups (ANOVA on Ranks, $p > 0.05$). C) and D) RTI values of SP neurons for downward and upward sweeps, respectively. No differences were found among the three age groups (ANOVA on Ranks, $p > 0.05$). Data shown as mean \pm SEM. Numbers inside the bars represent the number of neurons tested.

curve and one or more inhibitory sidebands (Arthur et al., 1971; Suga et al., 1997; Sutter et al., 1999). The spectrotemporal interactions between the tuning curve and the sidebands shape FM rate selectivity. Fast-pass rate selectivity for downward sweeps can be explained as follows (Razak and Fuzessery, 2006). Consider a neuron with a delayed band of inhibition located outside the high-frequency edge of the tuning curve (termed ‘delayed high-frequency inhibition’). ‘Delayed’ indicates that if both excitatory and inhibitory tones were presented together, excitation will arrive at the neuron before inhibition. A downward sweep will traverse the high-frequency inhibition before reaching the excitatory frequencies. However, because the inhibition is delayed, sweeps with fast sweep rates can elicit excitation before the delayed inhibition arrives. For slow-sweeps, inhibition will squelch responses. This produces fast-pass sweep selectivity. The slowest sweep rate that elicits a response will depend on the delay and the bandwidth of the inhibitory sideband. The shorter the delay or broader the bandwidth of inhibition, the faster the sweep has to be to elicit responses. Therefore, the observed result in this study that neurons become selective for faster sweep rates indicates that the inhibitory sideband is arriving faster and/or the bandwidth of sideband is broadening during development (schematized in Fig. 10D). The differences in the developmental time course of upward and downward sweep selectivity observed in this study may also arise due to the differences in development of low and high frequency sidebands. This is observed during development of FM rate selectivity in A1 of pallid bats (Razak and Fuzessery, 2007a).

Prior studies on rodent auditory cortex suggest at least some of these changes may occur at the level of the cortex. Physiological changes in both excitatory neurons and inhibitory interneurons have been previously found to take place during the first postnatal month in rodents (Metherate and Aramakis, 1999; Oswald and Reyes, 2008).

Fast-spiking inhibitory interneurons shape sidebands in A1 (Wu et al., 2008). The suggestion that sideband inhibition becomes faster during development is consistent with *in vitro* studies of the mouse A1 showing that the intrinsic and circuit properties of fast-spiking inhibitory neurons of AI change between P10 and P29 (Oswald and Reyes, 2011). In particular, the latency and rise times of inhibitory post-synaptic potentials become shorter between P10 and P29 which would likely explain faster arrival of inhibition relative to excitation. Additionally, excitatory and inhibitory post-synaptic potentials of neurons of the auditory cortex of P19–29 mice decay faster and show decreased short term depression, which would allow them to respond with more temporal fidelity to the stimulus (Oswald and Reyes, 2008, 2011). This will also shorten integration times and account, at least in part, for the sharpening of the spectrotemporal selectivity observed in the present study.

The suggestion that relative extent of the inhibitory sideband broadens during development is supported by observed changes in tonal receptive fields of A1 neurons (Sun et al., 2010; Wu et al., 2008). In the adult rat auditory cortex, the broader inhibitory tuning curve compared to the excitatory curve may manifest as sideband inhibition. Around hearing onset, the excitatory tonal receptive fields match the inhibitory tonal receptive fields. As development progresses the excitatory tuning curve of neurons became narrower (as seen here in the mouse as well), meanwhile the inhibitory tuning curves remains broad. This causes a relative expansion of the sideband during development.

Short-pass and band-pass duration tuning for tones can also shape rate selectivity (Fuzessery et al., 2006). However, only ~10–20% of neurons were of this type in the mouse cortex across development. Duration tuning properties remain stable during development. Therefore, it is unlikely that the developmental changes in rate selectivity are explained by duration tuning.

4.4. Development of FM direction selectivity

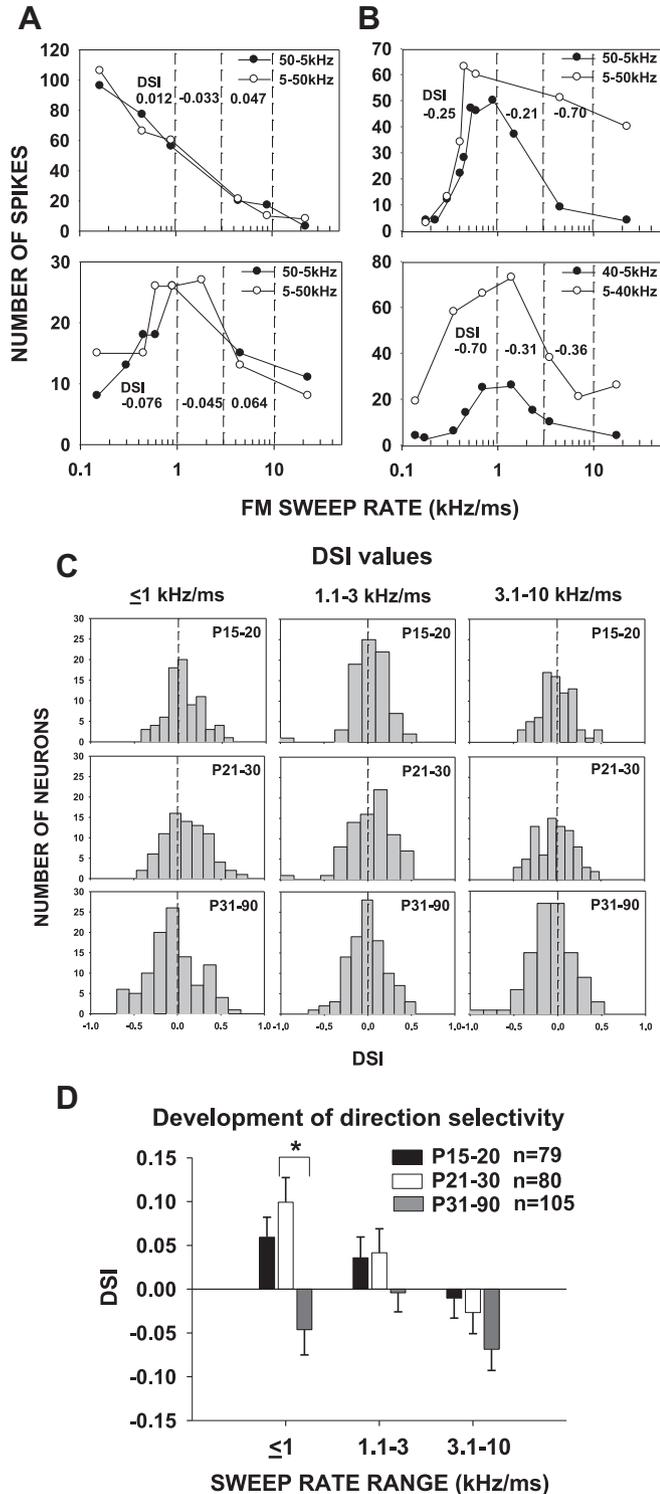


Fig. 9. Neurons of the auditory cortex become more selective for upward FM sweeps during development. A) Examples of neurons that respond similarly to downward and upward sweeps. The vertical dashed lines indicate the three rate-ranges over which DSI was calculated from each neuron. The numbers adjacent to the dashed lines show DSI values. B) Examples of neurons that preferred upward sweeps. C) Histograms of DSI values for each age group and rate range. D) Mean DSI values (\pm SEM) across ages for three ranges of rate (≤ 1 , 1.1–3 and 3.1–10 kHz/ms). There was a trend for neurons to become more selective for upward sweeps with age at all three FM rate ranges tested. The difference was significant at the slowest rates between P21–30 and P31–90 (ANOVA on Ranks, Dunn’s test, $p < 0.05$).

FM direction selectivity shows rate-dependent developmental change, with neurons becoming more selective for upward sweeps at the slowest rates tested. The two young age groups were similar to the adult group in that direction selectivity was poor on average (Trujillo et al., 2011). However, there was a tendency for young neurons to prefer downward sweeps on average. In the adult group, there was a significant change toward preferring upward sweeps at the slowest sweep rates tested.

Direction selectivity for FM sweeps has been previously found in A1 of bats, chinchillas, cats, ferrets, monkeys and rats (Atencio et al., 2007; Brown and Harrison, 2009; Mendelson et al., 1993; Nelken and Versnel, 2000; Razak and Fuzessery, 2006; Trujillo et al., 2011; Washington and Kanwal, 2008; Whitfield and Evans, 1965). Cortical FM direction selectivity appears to be developmentally regulated across species. Neurons of the auditory cortex of P3 and P28 chinchillas show a lower DSI compared to those of adults. Neurons become more selective to upward sweeps as chinchillas mature (Brown and Harrison, 2010). In the pallid bat’s auditory cortex, selectivity for downward sweeps (present in echolocation calls) increases during the first 12 weeks of postnatal development and requires normal experience with echolocation calls (Razak et al., 2008). Development of cortical DSI in mice was similar to chinchillas in that there was a trend for neurons to become selective for upward sweeps, with significant differences observed for the slowest rates tested. In rat A1, the DSI depends on the CF, with most low-CF neurons preferring upward sweeps and most high-CF neurons preferring downward sweeps (Zhang et al., 2003). In the present study, the CF range across all three groups was mostly in the relatively low-frequency range (7–30 kHz). Therefore, the increased selectivity for upward sweeps during development may reflect a low-CF bias in the core auditory cortex of the mouse. In mice, most high-CF neurons appear to be located outside the core auditory cortex (Stiebler et al., 1997) and central IC (Portfors et al., 2011).

The developmental increase in selectivity for upward sweeps at the slowest rates may be a consequence of decreased responses to downward sweeps at slow rates. As discussed previously, one of the main effects found in this study is the increase in percentage of fast-pass neurons and shift in selectivity toward faster sweep rates for downward sweeps. Such changes, while observed, were less significant for upward sweeps. The greater reduction in response to slow downward sweeps compared to slow upward sweeps may explain the observed developmental preference for upward sweeps. Alternately, the arrival time and/or bandwidth of high and low frequency inhibition may show asymmetries in maturation.

4.5. Methodological issues

The results reported in the current study were obtained from ketamine/xylazine anesthetized mice. Ketamine has been widely used in auditory cortex physiological studies (Calford and Semple, 1995; Campbell et al., 2010; Cohen et al., 2011; DeWeese et al., 2003; Eggermont and Smith, 1996; Garcia-Lazaro et al., 2006; Miller et al., 2001), although only a few studies have compared responses in awake animals to those obtained in ketamine anesthetized animals. The main differences observed in the auditory cortex of ketamine-anesthetized animals were a reduction of spontaneous activity and, in general, a reduced neuronal response to acoustic stimuli (Syka et al., 2005; Zurita et al., 1994). Walker et al. (2008) reported subtle differences between the responses obtained from the primary auditory cortex of awake ferrets compared to those obtained from ketamine/medetomidine anesthetized animals. Responses from awake ferrets were stronger to

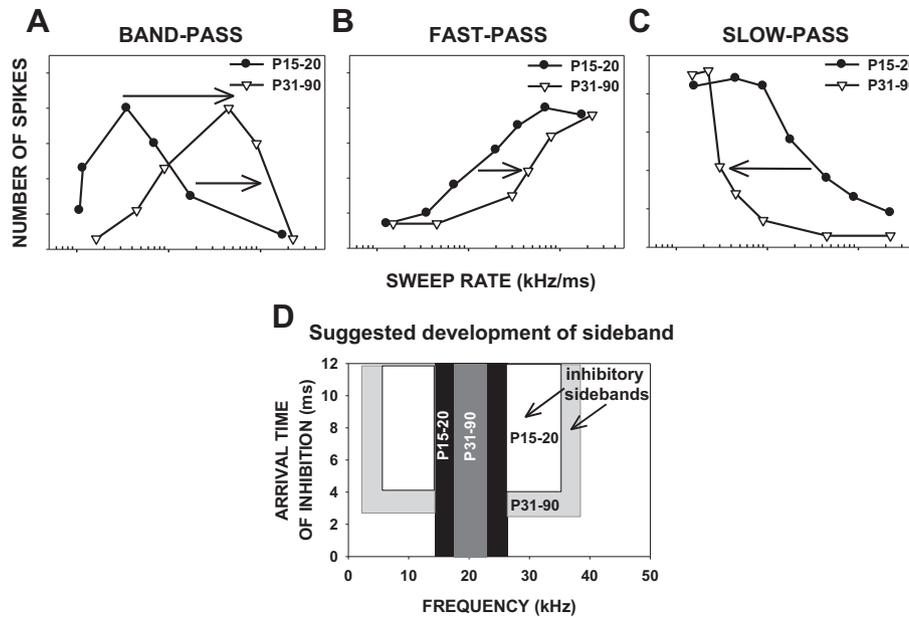


Fig. 10. Summary of results. A) Rate function of band-pass neurons shifts toward higher sweep rates during development, 50% cutoff values and best rates are higher in adults compared to young ones. B) Rate function of fast-pass neurons shifts toward higher sweep rates in adults, making 50% cutoff values higher than in young pups. C) Rate function of slow-pass neurons shifts toward lower sweep rates with development. D) Proposed developmental changes of inhibitory sidebands. The schematic depicts the arrival time of inhibition relative to excitation and the excitatory and inhibitory frequencies. The sideband inhibition of the P15–20 animals (white) becomes faster and/or wider (light gray) in P31–90 animals. Faster and wider inhibitory sideband would explain the results obtained in this study and summarized in A, B and C. Notice that the excitatory tuning curve becomes narrower as animals get older (black: P15–20; dark gray: P31–90).

the onset and offset of the sound than in anesthetized ferrets, but no fundamental differences were found between the two data sets. Therefore, it is possible the overall response magnitudes recorded in this study were lower, but observed developmental change in response selectivity is unlikely an artifact of the anesthetic. The lack of offset responding neurons may be an effect of the anesthetic in this study.

5. Conclusions

Our data show that the C57 mouse auditory cortex is not mature in terms of response selectivity to tones or FM sweeps until \sim P30. Responses are similar between P30–P60 and P60–P90 indicating adult-like responses are mostly obtained \sim P30 (Trujillo et al., 2011). Different response properties in the core auditory cortex have different maturational time courses and this may underlie observed differences in the time periods during which different response properties are affected by experience (Insanally et al., 2010). The changes in FM sweep rate and direction selectivity are likely explained by changes in properties of sideband inhibition (Razak and Fuzessery, 2007a). Sideband inhibition incorporates cross-frequency interactions of excitation and inhibition. Duration tuning is stable during development and therefore cannot explain changes in FM rate selectivity. Duration tuning involves within-CF interactions of excitation and inhibition. Taken together, these data suggest that cross-frequency interactions develop slowly compared to within-frequency interactions in core auditory cortex (Happel et al., 2010).

The behavioral relevance of the strong selectivity for a narrow range of FM sweep rates in the core auditory cortex is unclear. While rats and Mongolian gerbils can discriminate FM sweep direction, rodents' abilities to discriminate FM sweep rates are not known. The electrophysiology data presented here suggest sweep rates that mice may detect and discriminate best. The mean 50% cut-off rate of SP, BP and FP neurons shift toward 1 kHz/ms during

development. Neurons are likely to provide maximum information about sweep rates near the 50% cut-off rate (Harper and McAlpine, 2004). The developmental change in rate selectivity may therefore enable mice to better discriminate rates near 1 kHz/ms. Studies that follow development of FM sweep rate discrimination are required to test this hypothesis. It is also pertinent to note that ultrasonic vocalizations of mice contain FM sweeps with rates between 0.5 and 2 kHz/ms (Panksepp et al., 2007). However, a number of these vocalizations are produced at very high-frequencies (>70 kHz), while the vast majority of neurons in the auditory system (including the 'ultrasonic field') respond to frequencies <70 kHz. Holmstrom et al. (2010) suggested that the low-frequency neurons respond to very high-frequency vocalizations based on the distortion products falling near neuronal CFs. Therefore, the low-CF neurons may provide information about vocalizations across a broad frequency range. Whether the developmental changes observed in FM sweep selectivity are driven by early experience with such calls or simply reflect experience-independent maturation of synaptic and intrinsic properties remain unclear from the present data. Future studies that augment developmental acoustic environment with FM sweeps of fixed parameters will address this issue.

Acknowledgments

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