



Research Paper

Functional segregation of monaural and binaural selectivity in the pallid bat auditory cortex



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ARTICLE INFO

Article history:

Received 11 April 2016

Received in revised form

5 May 2016

Accepted 13 May 2016

Available online 24 May 2016

Keywords:

Auditory cortex

Sound localization

Binaural

Monaural

Echolocation

Level tolerance

ABSTRACT

Different fields of the auditory cortex can be distinguished by the extent and level tolerance of spatial selectivity. The mechanisms underlying the range of spatial tuning properties observed across cortical fields are unclear. Here, this issue was addressed in the pallid bat because its auditory cortex contains two segregated regions of response selectivity that serve two different behaviors: echolocation for obstacle avoidance and localization of prey-generated noise. This provides the unique opportunity to examine mechanisms of spatial properties in two functionally distinct regions. Previous studies have shown that spatial selectivity of neurons in the region selective for noise (noise-selective region, NSR) is level tolerant and shaped by interaural level difference (ILD) selectivity. In contrast, spatial selectivity of neurons in the echolocation region ('FM sweep-selective region' or FMSR) is strongly level dependent with many neurons responding to multiple distinct spatial locations for louder sounds. To determine the mechanisms underlying such level dependence, frequency, azimuth, rate-level responses and ILD selectivity were measured from the same FMSR neurons. The majority (~75%) of FMSR neurons were monaural (ILD insensitive). Azimuth tuning curves expanded or split into multiple peaks with increasing sound level in a manner that was predicted by the rate-level response of neurons. These data suggest that azimuth selectivity of FMSR neurons depends more on monaural ear directionality and rate-level responses. The pallid bat cortex utilizes segregated monaural and binaural regions to process echoes and prey-generated noise. Together the pallid bat FMSR/NSR data provide mechanistic explanations for a broad range of spatial tuning properties seen across species.

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1. Introduction

The auditory cortex, like other sensory cortices, consists of multiple fields distinguished by response selectivity that optimize representations of different attributes of sensory input. Spatial selectivity is one such property that distinguishes auditory cortical fields, leading to hypotheses about differential contributions of these fields to sound localization behavior (Harrington et al., 2008; Malhotra et al., 2004; Stecker et al., 2005; Woods et al., 2006). These differences include sharpness of spatial selectivity, sound level tolerance and presence of multi-peaked azimuth tuning curves. The mechanisms that differentiate spatial selectivity between cortical fields are unclear and thereby motivated the main aim of this study.

The subject of this study is the pallid bat (*Antrozous pallidus*), a species that listens to prey-generated noise (e.g., walking, rustling,

5–40 kHz band) to localize and hunt terrestrial prey (e.g., crickets, scorpions). Echolocation with downward frequency modulated (FM) sweeps (60 → 30 kHz, 2–5 msec) is used for orientation and obstacle avoidance (Bell, 1982; Barber et al., 2003). The midbrain-thalamus-cortex connections form parallel pathways selective for noise and downward FM sweeps (Fuzessery, 1994; Razak and Fuzessery, 2002; Razak et al., 2007). In the auditory cortex, there are two regions with functional properties that suggest involvement in prey localization (noise-selective region, NSR) and echolocation (FM sweep-selective region, FMSR), respectively (Razak and Fuzessery, 2002; Razak, 2011). The FMSR receives most of its input from the dorsal division of the medial geniculate body while the NSR receives its input primarily from the ventral division of the medial geniculate body (Razak et al., 2007). This organization provides the opportunity to compare sound localization mechanisms in two functionally distinct regions using behaviorally relevant sounds.

Previous studies have shown a number of differences in spatial tuning properties between the NSR and the FMSR. 2D spatial

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receptive fields (SRF) in the FMSR are significantly more level dependent than in the NSR (Razak et al., 2015). FMSR neurons are narrowly tuned to locations near the midline at low sound levels. FMSR SRFs expand considerably and many neurons respond to multiple non-contiguous locations with increasing sound level. NSR neurons are level tolerant and as a population, represent locations across the entire contralateral field. These data suggest that mechanisms of azimuth tuning in the FMSR are different than in the NSR. By recording interaural level difference (ILD) and azimuth selectivity from the same neurons, Razak (2011, 2012) showed that ILD response is the primary determinant of NSR azimuth selectivity. How azimuth selectivity is shaped in the FMSR is not known. Therefore, the main aim of this study was to test the relative contributions of monaural and binaural responses to azimuth selectivity in the FMSR, by recording frequency, ILD, azimuth selectivity and rate-level responses of the same FMSR neurons. FMSR data were compared with published NSR data (Razak, 2011, 2012) to determine mechanistic differences between the regions. The results show that most FMSR neurons, in sharp contrast to NSR, are monaural (ILD insensitive). FMSR neurons with monotonic rate-level functions show level dependent expansion of azimuth tuning. Neurons with non-monotonic rate-level functions show fragmentation of azimuth tuning into multiple peaks. These data indicate that the cortical region involved in obstacle avoidance with echolocation uses a different set of mechanisms to process spatial information than the region involved in localizing prey.

2. Materials and methods

Pallid bats were netted in Arizona, New Mexico and California and held in a 11 × 14 ft room at the University of California, Riverside. The bats were able to fly in this room and were provided crickets/mealworms and water *ad libitum*. The room was maintained on a reversed 12:12 light cycle. All procedures followed the animal welfare guidelines required by the National Institutes of Health and the Institutional Animal Care and Use Committee.

2.1. Surgical procedures

Recordings were obtained from adult pallid bats ($n = 5$) anesthetized with isoflurane inhalation, followed by an i.p. injection of pentobarbital sodium (30 µg/g body wt) and acepromazine (2 µg/g body wt). Both male and female bats were used. Up to four different recording sessions separated by 2–4 days were conducted in each bat. The skin was sutured and the bat was allowed to recover per approved protocol between each recording session. Each session lasted between 8 and 12 h. To expose the auditory cortex, the head was held in a bite bar, a midline incision was made in the scalp, and the muscles over the dorsal surface of the skull were reflected to the sides. The front of the skull was scraped clean and a layer of glass microbeads applied, followed by a layer of dental cement. The bat was then placed in a Plexiglas holder. A cylindrical aluminum head pin was inserted through a cross bar over the bat's head and cemented to the previously prepared region of the skull. This pin served to hold the bat's head secure during the recording session. The location of A1 was determined relative to the rostrocaudal extent of the midsagittal sinus, the distance laterally from the midsagittal sinus, and the location of a prominent lateral blood vessel that travels parallel to the midsagittal sinus (Razak and Fuzessery, 2002). The size of the exposure was ~2 mm². Exposed muscle was covered with petroleum jelly (Vaseline) and exposed brain surface was covered with paraffin oil to prevent desiccation.

2.2. Recording and stimulus protocols

Experiments were conducted in a warm (~80 °F), 8 × 8 square feet sound attenuation room lined with anechoic foam (Gretsch-Ken Industries, Oregon). All recordings were obtained from the right hemisphere simply due to ease of access within the sound booth. A previous study that examined ILD selectivity indicated qualitatively similar responses in both hemispheres of the pallid bat's cortex (Razak and Fuzessery, 2002). Bats were kept anesthetized throughout the course of the experiments with additional pentobarbital sodium (one-third of presurgical dose) injections. Acoustic stimulation and data acquisition were driven by custom written software (Batlab, written 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 (Yamaha AX430). Extracellular single-unit recordings were obtained using glass electrodes (1M NaCl, 2–10 MΩ impedance) at depths between 200 and 600 µm (layers III–V in pallid bat, Martin del Campo et al., 2014). Penetrations were made orthogonal to the surface of the cortex. Action potentials were amplified by a Dagan extracellular preamplifier (2400A) and a spike signal enhancer (FHC, Maine) and band-pass filtered (0.3–3 kHz, Krohn-Hite, MA). Waveforms and post-stimulus time histograms were stored using the Microstar DSP board and Batlab software. All data shown are from single-unit recordings identified by the consistency of action potential amplitude and waveform displayed on an oscilloscope. Responses were quantified as the total number of spikes elicited over 20 stimulus presentations at 1 Hz repetition rate. Spikes were counted over a 200 msec window from sound onset.

To record ILD, rate-level responses and azimuth selectivity from the same FMSR neurons, a sequential dichotic/free-field stimulation protocol was used as described previously (Razak, 2011, 2012). Dichotic stimulation to determine ILD selectivity was achieved using two LCY-K100 ribbon tweeters (Madisound, Wisconsin) fitted with funnels that were inserted into the external auditory canal. The amplifier-speaker-funnel frequency response curve measured with a ¼ inch microphone (Brüel and Kjaer, Denmark) was flat within ±3 dB for frequencies from 8 to 35 kHz. The roll-off from 35 to 80 kHz was gradual at a rate ~20 dB/octave. Distortion products were not present in the speaker output for the sound levels used in these studies.

After recording ILD selectivity (see below), the speaker funnels were removed from the external auditory canal and a free-field speaker was used to determine azimuth selectivity of the same neuron. Free-field stimulation was achieved with a third LCY-K100 speaker that was moved manually to different locations (75° contralateral to 75° ipsilateral in azimuth with a 15° resolution) on a semi-circular loop (40 cm radius with the bat's head as center). The loop was mounted on a vibration isolation table (TMC, Massachusetts). The bat was placed on the edge of the table such that its head was at the center of the loop. The bat's snout faced 0° azimuth/elevation. The cross-bar holding the head pin was secured behind the bat, leaving no interference between the free-field speaker and the bat's head.

2.3. Stimuli used

The FMSR was targeted for recordings in this study because this region contains neurons with response properties indicative of involvement in echolocation. The echolocation calls of adult pallid bats are typically 60 → 30 kHz downward FM sweeps with durations between 2 and 5 msec. The FMSR is located rostromedial to the NSR and contains neurons with characteristic frequencies (CF) between 30 and 70 kHz and strong selectivity for the downward FM

sweeps used by the pallid bat to echolocate (Razak and Fuzessery, 2002, 2006, 2008). These neurons rarely respond to noise of any bandwidth, providing a relatively easy way to distinguish the two regions. To isolate single neuron responses, search stimuli were presented from the free-field speaker positioned at 0° azimuth and elevation (to mimic echoes along the flight path). The search stimuli used were linear downward 60 → 30 kHz or 70 → 20 kHz FM sweeps (2–5 msec duration, intensities between 0 and 70 dB SPL, 1 Hz repetition rate, 1 msec rise/fall time). Upon isolation of a neuron, the CF was determined by presenting tones (5–10 msec duration, 1 msec rise/fall times, 1 Hz repetition rate) with frequencies between 25 and 70 kHz (1 or 5 kHz step) and levels between 0 and 70 dB SPL (5 dB step). The free-field speaker was at 0° azimuth/elevation for CF determination. The CF was defined as center of a range of tone frequencies that elicited action potentials to at least five successive stimulus repetitions at the lowest level tested. After identifying the CF, a downward FM sweep with the CF as the approximate center frequency, duration between 2 and 5 msec and bandwidths between 20 and 40 kHz was used as stimuli to record the following response properties:

2.3.1. FM sweep response threshold

The free-field speaker at 0° azimuth/elevation was used for this purpose. The level of the FM sweep was increased from 0 to 70 dB SPL (5 dB steps to start and 1 dB steps closer to threshold) to identify minimum threshold (MT) of the neuron. The MT was defined as the lowest level of the FM sweep presented from 0° azimuth/elevation to which the neuron responded to at least five successive presentations.

2.3.2. ILD selectivity

The ILD selectivity was determined using dichotic stimulation (speaker funnel inserted into the ears) with a fixed sound level at the contralateral (CL) ear (10–20 dB above MT). The intensity of the FM sweep at the ipsilateral (IL) ear was varied from 20 dB below to 20 dB above CL ear intensity, in 5 or 10 dB steps. This covers the behaviorally relevant range of ILDs for the pallid bat (Fuzessery, 1996). The speaker funnels were not sealed in the meatus to facilitate sequential dichotic/free-field stimulation of the same neurons. The attenuation of sound level at the opposite ear was at least 25 dB and permitted the presentation of ±20 dB ILDs. However, because the funnels were not sealed in the meatus, it was not possible to test very loud sounds in the CL ear due to possible crossover effects. The data presented in this study must therefore be considered with this caveat. In data presentation below, negative ILDs denote more intense IL ear sound than at the CL ear. Positive ILDs indicate CL > IL ear intensity.

Previous studies of the pallid bat cortex (both NSR and FMSR) have shown that almost all neurons are excited only by monaural CL ear stimuli or not at all by monaural stimuli. There is rarely any excitatory response to monaural stimulation of the IL ear (Razak and Fuzessery, 2002, 2010; Razak, 2011, 2012). Therefore, for monaural stimulation, pallid bat cortical neurons are either EO or OO. With binaural stimulation, neurons were considered binaurally inhibited (EO/I) if the response declined to at least 50% of the maximal monaural CL ear response with increasingly negative ILD. The neuron was considered peaked (P or OO/I) if the response to binaural stimulation was at least twice the response to monaural CL stimulation and the response subsequently decreased at least 25% of maximum with increasing IL intensity. A neuron was considered monaural (EO/O, ILD insensitive) if the ILD response was within 50% of maximum for ILDs between +20 and -20 dB. Because monaural IL response is rare, the 'EI' and 'EO' description is used in this paper to describe EO/I and EO/O responses in this study (Kitzes et al., 1980; Irvine et al., 1996). ILD sensitivity is stable across the range

of intensities tested in the pallid bat auditory cortex (Razak and Fuzessery, 2002). Therefore, ILD selectivity was determined only for a single CL intensity in this study. This allowed additional time to characterize azimuth and sound level tuning from many of the same neurons.

2.3.3. Azimuth selectivity

After ILD selectivity was determined with dichotic stimulation, the speaker funnels were removed from the ears and stimulation was switched to the free-field speaker to determine azimuth selectivity. Speaker positions between -75° (negative indicates IL loci) and +75° (positive indicates CL loci) in 15° steps were tested. Locations behind the animal were not studied. Azimuth selectivity for FM sweeps was determined at an intensity of 10 dB above MT in all neurons. In the majority of neurons, azimuth selectivity was also determined at one or more additional levels between 15 and 30 dB above MT to characterize the stability of azimuth selectivity across sound level in FMSR neurons. The range of sound levels tested is low to moderate because many of the neurons recorded were non-monotonic for sound levels and behaviorally, the pallid bat uses low amplitude echolocations calls resulting in a narrow range of behaviorally relevant echo levels (Griffin, 1958).

2.3.4. Rate-level responses

In a subset of neurons, the rate-level function was also obtained with the free-field speaker at 0° azimuth/elevation. The response of the neuron to the FM sweep presented between 0 and 70 dB SPL (5 or 10 dB resolution) was recorded. Rate-level functions were categorized as 'non-monotonic' if the response declined by at least 30% relative to the peak response with increasing level. If the response was within 30% of peak response at the highest level tested, the neuron was categorized as 'monotonic'.

3. Results

A previous study of the pallid bat FMSR reported on the effect of sound levels on 2D spatial receptive fields (Razak et al., 2015). However, the ILD selectivity or the rate-level responses of these neurons were not known to determine mechanisms of spatial selectivity. The current study reports novel data from FMSR in which ILD, azimuth selectivity and rate-level functions were recorded from the same neurons to determine the mechanisms of azimuth tuning. Comparison of these results with published data from the NSR collected using identical methods (Razak, 2011, 2012) will identify the azimuth tuning mechanisms used by different cortical fields involved in two different behaviors.

3.1. ILD and azimuth selectivity of FMSR neurons

Both ILD and azimuth selectivity data were obtained from 51 FMSR neurons. Two main types of ILD selectivity functions were recorded in the FMSR (Fig. 1A,C). In neurons classified as binaurally inhibited (EI), responses decreased below 50% of maximum as the sound level in the IL ear was increased (e.g., Fig. 1A). In neurons classified as monaural (EO or ILD insensitive), response was within 50% of maximum response at all ILDs tested (e.g., Fig. 1C). One major finding of this study was that the vast majority of neurons in the FMSR were monaural (Fig. 2). FMSR neurons typically have CFs >35 kHz (Razak and Fuzessery, 2002, 2006, 2008). In this frequency range, ~75% of neurons were monaural and only ~25% of neurons were EI. The preponderance of EO compared to EI neurons in the FMSR was seen across different CF ranges. All 51 neurons responded to monaural CL ear stimuli, but only two neurons responded to both monaural CL and IL ear stimuli. Therefore, neurons classified as 'EE' were very rare in the FMSR. The cortical locations of neurons

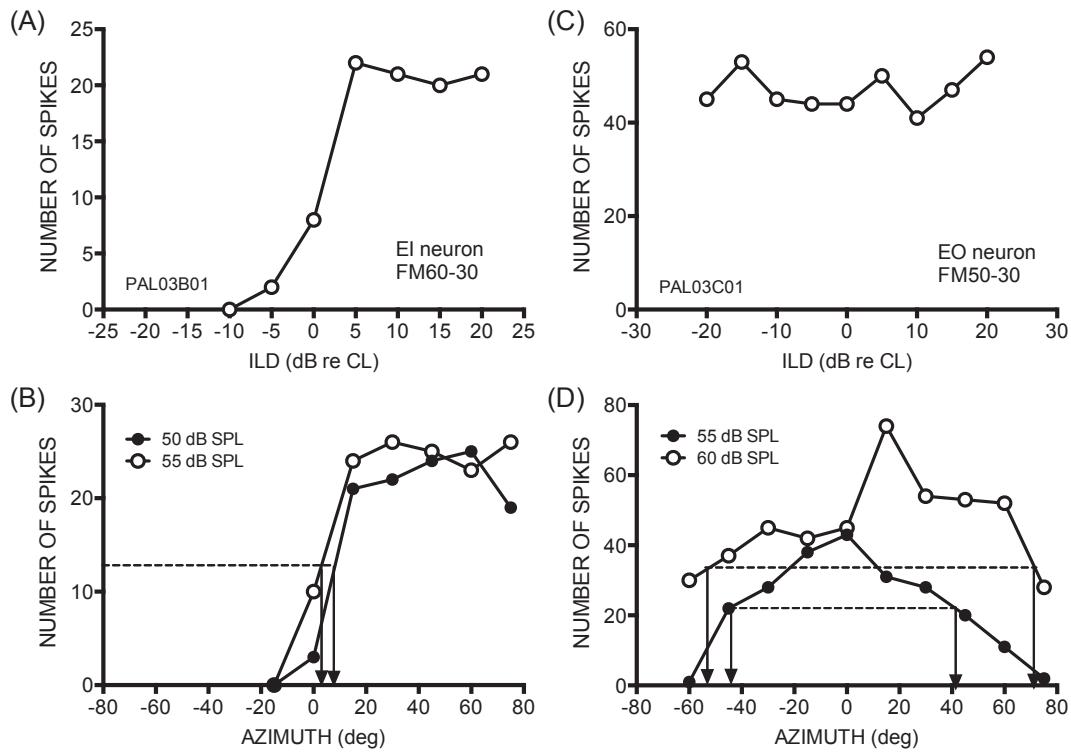


Fig. 1. Examples of IID and azimuth selectivity of FMSR neurons. (A) A neuron classified as binaurally inhibited (EI) based on its ILD response to a 60–30 kHz downward FM sweep (FM60-30). This neuron responded to monaural CL ear stimulation, but not to IL ear stimulation. ILD selectivity was recorded by presenting a constant intensity in the contralateral (CL) ear and by varying the ipsilateral (IL) ear intensity from 20 dB below to 20 dB above the CL ear intensity. Positive ILDs indicate sounds louder in the CL ear while negative ILDs indicate sounds that favor the IL ear. When tested binaurally, the response of this neuron declines below 50% of maximum response with increasing IL ear level. In this and other relevant graphs, the 'number of spikes' is the total spike count in response to 20 stimulus repetitions. (B) The azimuth selectivity of the same neuron shown in (A) recorded at two different sound levels with FM60-30 as stimulus. The dashed line indicates 50% of maximum response. The vertical arrows point to the 50% azimuth (azimuth at which response declines below 50% of maximum response). The ARFs show relatively little change at the two sound levels tested. (C) A neuron classified as EO (monaural or ILD insensitive) because its ILD response (to a 50–30 kHz downward FM sweep) was within 50% of maximum response. (D) The ARF of the same neuron as in (C) serves to illustrate the main contrast between EI and EO FMSR neurons. The ARF of this neuron in response to the FM50-30 stimulus expanded significantly even with a 5 dB SPL increase in sound level. The two left-most arrows measure the 50% azimuth at the two sound levels. The two inner arrows measure the 50% bandwidth (BW, range of azimuths producing >50% of maximum response) at the lower sound level. The two outer arrows measure the 50% BW for the louder sound. Both 50% azimuth and 50% BW of this monaural FMSR neuron are sound level dependent.

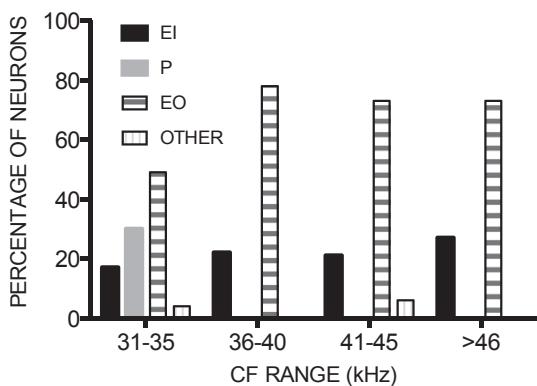


Fig. 2. Distribution of ILD tuning types within the FMSR ($n = 51$ neurons). The vast majority of FMSR neurons were ILD insensitive (monaural or EO). P-peaked (predominantly binaural or OO/PI); EI (binaurally inhibited); OTHER-neurons with ILD functions that were not classifiable according to the criteria used.

with different binaural/azimuth selectivity was not systematically mapped here, but it did not appear that EI neurons were more likely to be found in any restricted part of the FMSR. The dominant trend was simply that most FMSR neurons were EO.

A previous study showed that spatial selectivity in the FMSR was

strongly level dependent. However, the binaural or rate-selectivity of these neurons were not known and it was not clear if specific classes of FMSR neurons displayed different level dependences. To address the mechanisms of level dependence in FMSR neurons, azimuth selectivity was recorded at two or more sound levels from the 47/51 FMSR neurons with identified ILD responses. Fig. 1B, D serves to illustrate the differences in level tolerance of EI and EO FMSR neurons. The ARF of the EI neuron was relatively similar at the two sound levels tested (Fig. 1B). The ARF of the EO neuron (Fig. 1D) expanded considerably with an increase of 5 dB in stimulus level. Although only a 5 dB range of levels was tested in these two neurons, the contrast between these neurons serves to illustrate a major finding of this study. In general testing ARFs over a range of levels between 10 and 30 dB above threshold indicate that EO FMSR neurons are relatively narrowly tuned, with single peaked ARF, only near threshold. With increasing levels, the ARFs broadened (e.g., Fig. 3A–C) and/or began to show multiple peaks (e.g., Fig. 3D–F). Even a 10 dB increase in sound level rendered sharply tuned FMSR neurons non-selective for azimuth (e.g., Fig. 3B). Notably, in neurons that exhibited multiple peaks, the troughs at higher intensities appear near azimuth locations that produced peak responses at lower intensities.

Two measures of azimuth selectivity were used to quantify degree of level tolerance – 50% azimuth and 50% bandwidth (BW). The 50% azimuth is the azimuth location at which response

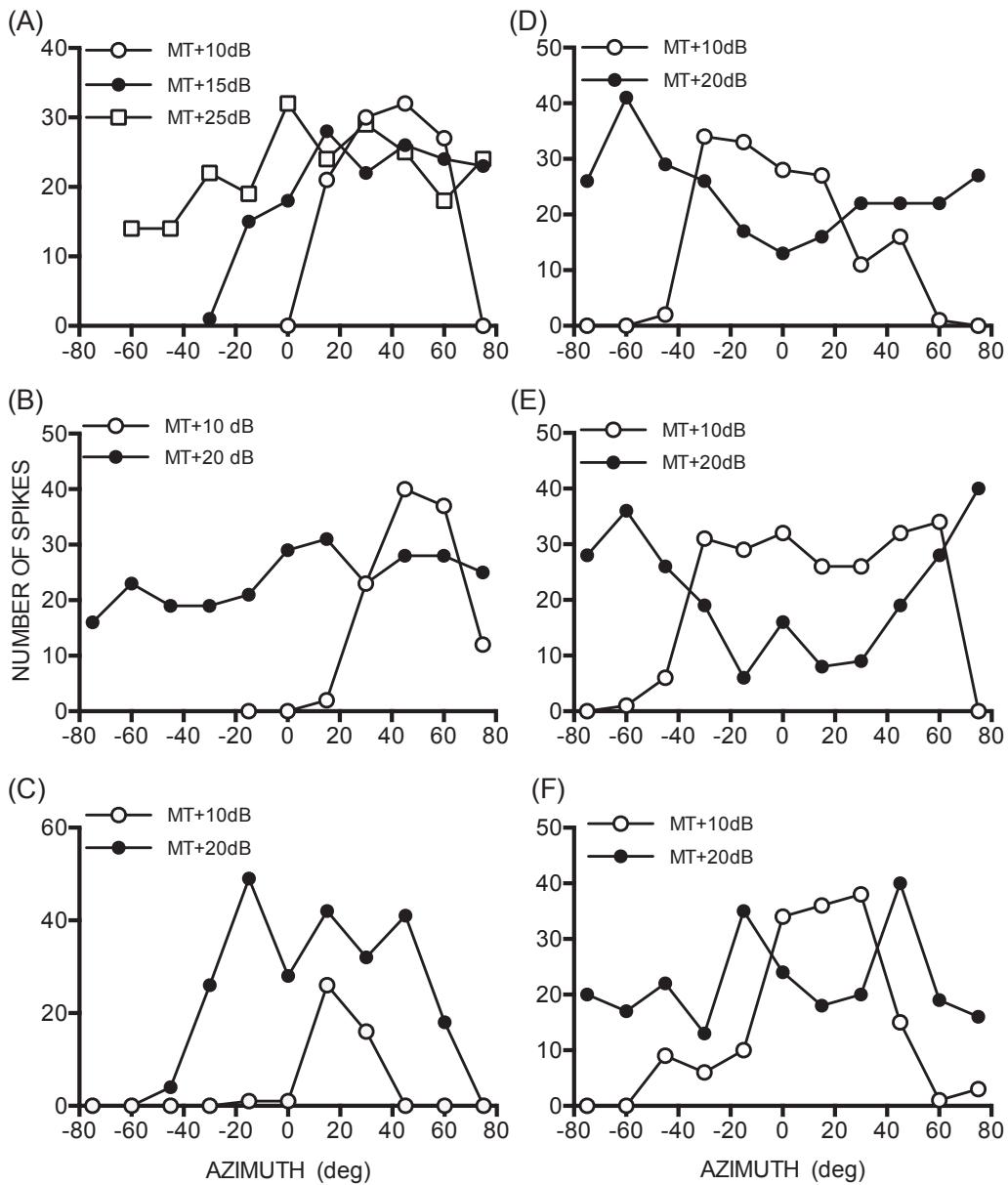


Fig. 3. Sound level dependence of FMSR neuron azimuth selectivity. (A–C) Azimuth selectivity expanded with increasing stimulus level in these three example FMSR neurons. MT: minimum threshold. Positive azimuth angles refer to contralateral azimuth and negative values refer to ipsilateral azimuth. (D–F) Three example FMSR neurons in which azimuth selectivity functions expanded with multiple peaks even with a 10 dB increase in stimulus level.

declines to 50% of maximum response as the sound is moved to increasingly IL locations. For example, the neuron shown in Fig. 1B has a 50% azimuth of 3° and 8° at the two levels tested (MT + 10 and MT + 15 dB), respectively. The 50% azimuth instability index (50% All) quantifies the change in 50% azimuth per dB change in intensity. The 50% All for the neuron in Fig. 1B for example is 1 deg/dB ((8–3)/5). For the neuron shown in Fig. 1D, the 50% All is 1.6 deg/dB ((−44 + 52)/5).

The 50% BW is the range of azimuth locations that produce 50% of maximum response. For example, the neuron shown in Fig. 1D exhibited 50% bandwidth of 83° (inner two arrows) and 124° (outer two arrows) at 10 and 15 dB above threshold, respectively. The 50% bandwidth instability index (50% BWII) is the degree change in 50% bandwidth per dB increase in sound intensity. The 50% BWII for the neuron shown in Fig. 1D is 8.2 deg/dB ((124–83)/5).

The mean (\pm s.e.) 50% All in EO FMSR neurons was 2.32 ± 0.33 deg/dB. In EI FMSR neurons, the 50% All was

0.83 ± 0.26 deg/dB. A one-way ANOVA (Tukey post-hoc pairwise comparison) was used to compare the 50% All values of EI and EO FMSR neurons along with previously published 50% All value for NSR neurons (0.69 ± 0.07 deg/dB, Razak, 2011, 2012). This analysis shows that the mean 50% All was significantly different between the groups ($p < 0.001$), with pairwise comparisons indicating that the EO FMSR neurons had a significantly higher mean 50% All than both of the other two groups ($p < 0.05$). There was no difference in 50% All between NSR and EI FMSR neurons ($p > 0.05$). This indicates that the level tolerance of the 50% azimuth of EI FMSR neurons was similar to those observed in the NSR. Thus, monaural FMSR neurons displayed greater level dependence than binaurally inhibited FMSR neurons.

In FMSR neurons in which the azimuth selectivity functions showed >50% decline in response on both sides of a peak, it was possible to calculate the 50% BW at the various sound levels tested (e.g., Fig. 1D). The mean (\pm s.e.) 50% BWII of EO FMSR neurons was

4.4 ± 0.54 deg/dB, which was significantly higher (*t*-test, $p < 0.0001$) than that found in the NSR (1.7 ± 0.32 deg/dB, Razak, 2011, 2012). This indicates that the change (typically expansion) in azimuth selectivity per dB change in SPL is ~2.6 times greater in the FMSR than in the NSR. Taken together, it is concluded that the vast majority of FMSR neurons are ILD insensitive and have level dependent azimuth selectivity. The relative ILD insensitivity in the FMSR is in stark contrast to the strong ILD selectivity observed in the NSR of the pallid bat auditory cortex in which >75% of the neurons show either EI or P type selectivity (Razak and Fuzessery, 2002; Razak, 2011, 2012).

3.2. Rate-level functions and azimuth selectivity

As shown in Fig. 3D–F, azimuth selectivity became multi-peaked with increasing sound level in some FMSR neurons. The appearance of a trough at azimuth locations that produced peak response at lower sound levels suggested that the sound level sensitivity of neurons shapes azimuth selectivity. To test this hypothesis, both rate-level functions and azimuth selectivity were recorded from 39 FMSR neurons. Rate-level functions were measured with FM sweeps as stimuli presented from a speaker at 0° in relation to the bat's snout.

Nineteen neurons were classified as non-monotonic and 20 were classified as monotonic. Fig. 4 shows two examples of non-monotonic FMSR neurons (Fig. 4A, D). These neurons were strongly tuned for sound level, with responses declining from maximum to zero within a 20 dB intensity change. Both neurons were typical of the vast majority of FMSR neurons in that they were monaural (Fig. 4B, E). The ARFs of these neurons showed multiple peaks with increasing sound level (Fig. 4C, F). The trough in the responses of both neurons around 0° occurs as the sound level increases into the non-monotonic realm of their respective rate-level sensitivity functions. An extension of this hypothesis is that neurons with monotonic rate-level sensitivity should simply show expanding azimuth functions (single peak expansion) with increasing sound level. Fig. 5 shows two examples of monotonic FMSR neurons (Fig. 5A, D). These neurons were monaural as well (Fig. 5B, E). ARFs of these neurons expanded with increasing sound level without fragmenting into multiple peaks.

Across the population of 39 neurons, a strong relationship was observed between rate-level and azimuth functions. A criterion of 30% trough magnitude (response between peaks declines by at least 30% of both peaks) was used to classify a neuron's azimuth selectivity as multi-peaked. 16 out of 19 (84.2%) neurons classified as non-monotonic were also multi-peaked at the higher sound levels. 17/20 (85%) of neurons classified as monotonic showed expanding azimuth functions with a single peak. These distributions are significantly different ($\chi^2 = 18.68$, $df = 1$, $p < 0.0001$). It must be noted that there was a much higher percentage of neurons with non-monotonic rate-level responses in the pallid bat auditory cortex than reflected by the distribution presented above (Measor and Razak, in preparation). Neurons with monotonic rate-level functions were specifically targeted here to test the proposed mechanism. Rate-level functions were measured by presenting the FM sweep stimuli at 0° azimuth. This will stimulate both ears. Therefore, this measure cannot be accurately termed as 'monaural rate-level function'. However, because only two of the neurons recorded responded to monaural IL ear input and because most neurons are ILD insensitive, it can be concluded that the rate-level sensitivity of FMSR neurons is driven primarily by the input at the CL ear.

Fig. 6 shows the distribution of the peak azimuth values of FMSR neurons recorded near threshold (MT + 10 dB). These are the sound levels at which the azimuth selectivity is narrow. The vast majority

of neurons have best azimuth of $<30^\circ$. This is appropriate for echolocation behavior because most relevant echoes are likely to arrive along the flight path centered near the azimuth (and elevation) midline. The pinna directionality shifts between $\sim 30^\circ$ and midline as frequency of the sound increased from 30 to 70 kHz (Fuzessery, 1996). The distribution of best azimuth near threshold overlaps with the azimuth locations for which the pinna is most sensitive adding support to the suggestion that monaural ear directionality shapes azimuth selectivity in the FMSR. Taken together these data suggest that level selectivity driven by monaural CL ear input, but not ILD selectivity, shapes azimuth selectivity of FMSR neurons.

4. Discussion

This study used a sequential dichotic/free-field stimulation paradigm to record frequency, ILD, and azimuth tuning and rate-level responses from the same neurons in the FMSR, a region putatively involved in echolocation behavior of the pallid bat. The main finding of this study is that the vast majority of FMSR neurons are monaural (EO) with azimuth tuning that expands with sound level in two different ways depending on rate-level responses. In neurons with monotonic rate-level functions, azimuth tuning expands about a single peak. In some cases, even a 10 dB increase in sound level causes a narrowly tuned neuron to respond to all locations tested. In neurons with non-monotonic rate-level functions azimuth tuning expands and fragments into multiple peaks. Approximately 25% of FMSR neurons are binaurally inhibited (EI). These neurons exhibit relatively more level tolerant azimuth tuning. Taken together with previous studies of the noise selective region (NSR), a region putatively involved in prey localization, these data indicate two parallel pathways in the pallid bat auditory system that utilize monaural and binaural systems for two different behaviors.

The data from this study provide novel insight into how various types of azimuth tuning, including multi-peaked neuron, are shaped. Multi-peaked spatial tuning has been reported in auditory cortex of many species (cat: Rajan et al., 1990a,b; Clarey et al., 1994; Stecker et al., 2005; ferret: Mrsic-Flogel et al., 2005; macaque monkey: Woods et al., 2006). By studying binaural, rate-level responses and azimuth selectivity of the same neurons, it can be seen that monaural (EO) FMSR neurons with monotonic rate-level functions show a single peaked azimuth receptive field that expands with sound level. Azimuth tuning of monaural FMSR neurons with non-monotonic rate-level functions also show expansion with sound level, but typically with fragmentation into multiple peaks. The pallid bat FMSR data show that a combination of ILD insensitivity and non-monotonic rate-level response will give rise to multi-peaked ARFs. Similar responses will arise for combinations of non-monotonic rate-level function and binaural types such as EE/O, EE/F and EO/F neurons found more commonly in other species' cortex. Thus, the nature of overlap between the binaural representation and monaural rate-level responses will determine if single or multi-peaked ARFs are present at any sound level tested (Nakamoto et al., 2004; Semple and Kitzes, 1993).

4.1. Mechanisms of azimuth tuning in FMSR versus NSR

FMSR neurons respond to CL ear input with minor or no influence from the IL ear either monaurally or binaurally. The ARF of these neurons is strongly dependent on the sound level. As has been previously suggested in IC (Semple et al., 1983) and cortical (Middlebrooks and Pettigrew, 1981; Mrsic-Flogel et al., 2005; Reale et al., 2003) neurons, the level dependent expansion of ARF is likely a reflection of the monaural ear directionality of the pallid bat for

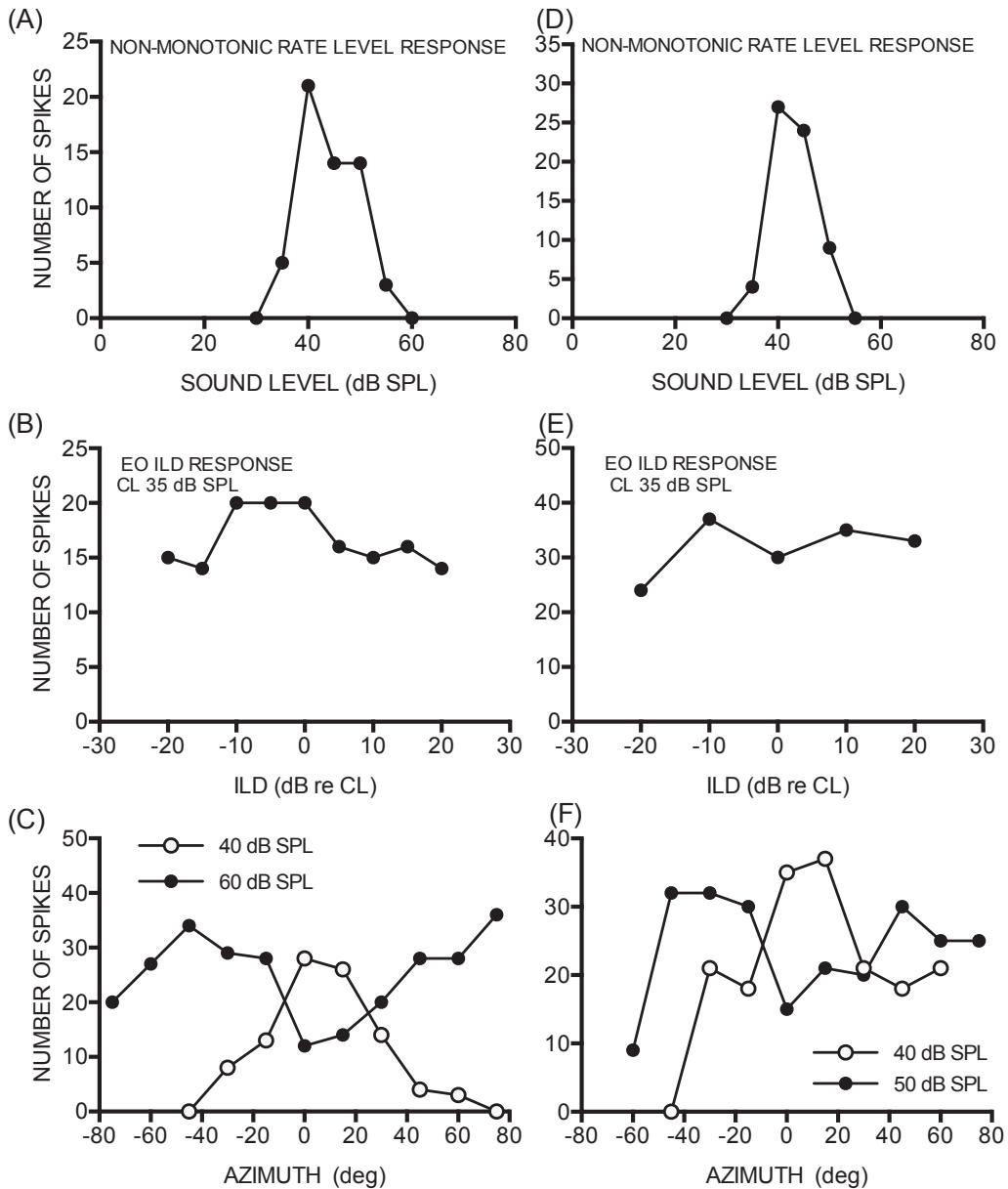


Fig. 4. Neurons with non-monotonic rate-level responses show multi-peaked azimuth receptive fields with increasing level. The left column shows rate-level responses (A), ILD selectivity (B) and azimuth selectivity (C) of an example FMSR neuron. The right column (D–F) shows the same properties for a second example neuron. Both neurons showed non-monotonic rate-level responses and were ILD insensitive (EO neurons). The ILD selectivity was recorded with CL ear intensity at 35 dB SPL for both neurons (note thresholds are different for responses obtained with speaker in ear canal versus speaker in free-field). The azimuth selectivity of both neurons was strongly sound level dependent such that the azimuth selectivity expanded and showed multiple peaks with increasing level.

frequencies >30 kHz. Spatially confined responses are seen along the acoustic axis at low levels. The sensitive area expands with increasing level. In the absence of any inhibition driven by the IL ear, the ARF expands with increasing sound level. Whether the ARF simple expands or becomes multi-peaked depends on the rate-level responses of the neuron. Taken together, these data suggest that ear directionality and CL ear driven rate-level response shape azimuth responses in most neurons in the cortical region selective for FM sweeps used in echolocation. Current studies are testing this hypothesis by recording from FMSR neurons before and during pinna/tragus manipulation. Approximately 25% of FMSR neurons that exhibit binaural selectivity (EI) are relatively more level-tolerant and may provide more stable information relevant to sound locations.

Azimuth is represented quite differently in the NSR. Previous studies of the pallid bat auditory cortex have shown that the majority (70–80%) of NSR neurons ($CF < 35$ kHz) are ILD selective (Razak and Fuzeeserry, 2002, 2010; Razak, 2011, 2012). Two binaural clusters distinguished by ILD selectivity dominate the NSR. The rostral part of the NSR contains neurons classified as peaked (OO/FI or EO/FI or predominantly binaural) because they respond poorly or not at all to monaural stimuli to either ear, but respond best to binaural stimuli with ILD ~0 dB. Predictably, these neurons respond best to azimuth angles ~0° and this cluster may serve as an acoustic fovea that enhances localization acuity near the midline (Dingle et al., 2010). The caudal part of the NSR contains EI neurons. Less than 10% of the neurons in the NSR are monaural. The azimuth selectivity of both peaked and EI neurons can be predicted by their

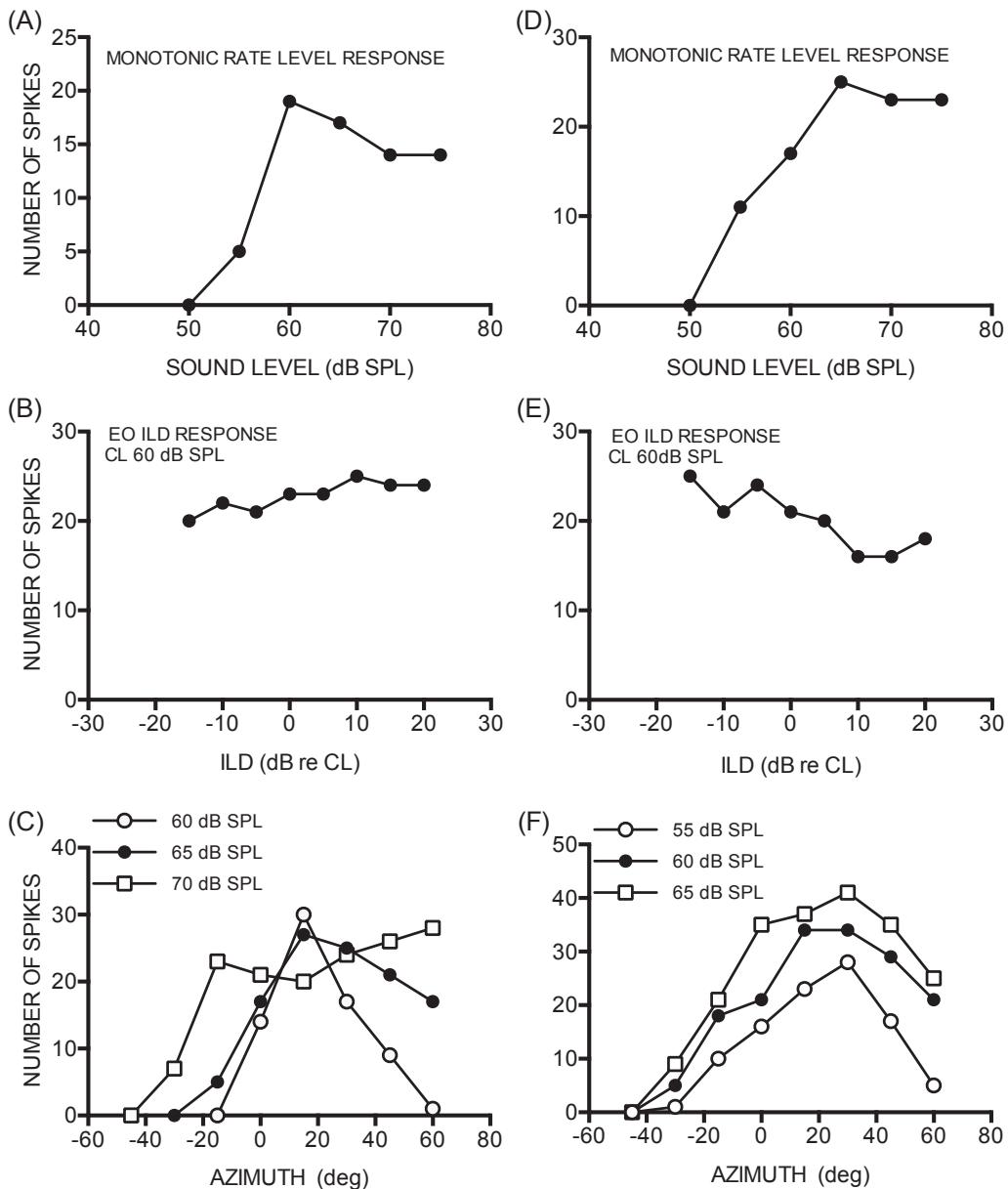


Fig. 5. Neurons with monotonic rate-level responses show single peak expansion of azimuth selectivity with sound level. The left column shows rate-level function (A), ILD selectivity (B) and azimuth selectivity (C) of an example FMSR neuron. The right column (D–F) shows the same properties for a second example neuron. Both neurons showed monotonic rate-level responses and were ILD insensitive (EO neurons). The ILD functions were recorded with CL clear level at 55 dB SPL and 60 dB SPL for the neurons shown in B and E, respectively. The azimuth selectivity of both neurons was level dependent such that the azimuth selectivity expanded with sound level, but without fragmenting into multiple peaks.

ILD sensitivity (Razak, 2012). 2D spatial representation in the NSR depends on overlapping ILD and frequency maps (Razak et al., 2015). Thus the NSR depends on ILD selectivity while the FMSR may depend on monaural ear directionality and rate-level response to shape azimuth selectivity.

Together, these data suggest that the monaural and binaural systems in the pallid bat are used for two different behaviors, echolocation and passive prey-localization, respectively. Fig. 7 provides a summary schematic of major trends in the overlapping representation of frequency, binaural properties and response selectivity. CFs increase in a caudolateral to rostromedial direction. The FMSR, tuned between 30 and 70 kHz and selective for the downward FM sweep direction and rates present in natural echolocation call, overlaps with monaural selectivity. The NSR, tuned

between 5 and 40 kHz and selective for noise bursts, overlaps with two major classes of binaural selectivity (peaked and EI). Approximately 10–20% of FMSR and NSR neurons show reversal of this major trend, but is not indicated in the schematic because no predictable arrangement of EI and EO neurons are seen in the FMSR and NSR, respectively.

In the cat inferior colliculus central nucleus (ICc), combined electrophysiology and retrograde labeling identified relatively distinct regions of monaural and binaural inputs (Loftus et al., 2010). The binaural inputs sculpted in the superior olivary complex and the monaural inputs from the cochlear nucleus and ventral nucleus of lateral lemniscus provide input to segregated functional zones of the ICc. Segregation of anatomical inputs from monaural and binaural brainstem nuclei into the IC is also seen in

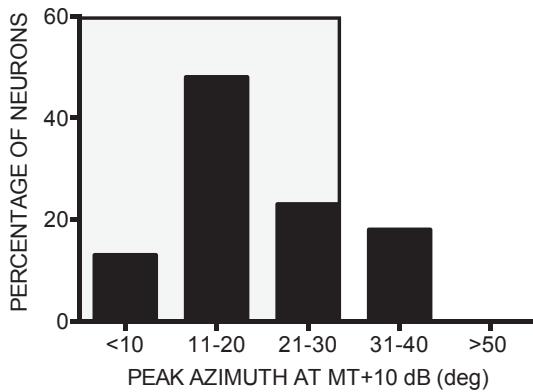


Fig. 6. Overlap of neural and pinna sensitivity in the echolocation frequency range. Distribution of peak azimuth values recorded at MT+10 dB in the FMSR of the pallid bat cortex. The shaded box represents the azimuth at which the bat's pinna is most sensitive in the 30–70 kHz range used in echolocation (adapted from Fuzessery, 1996).

gerbils (Cant and Benson, 2006). In the rat auditory thalamus, differences in level tolerant azimuth selectivity in parallel streams may correspond to these segregated inputs (Yao et al., 2015). The pallid bat auditory system may have utilized this, presumably common mammalian, arrangement to create response selectivity in the IC (Fuzessery, 1994) for sounds used in the two different behaviors in the segregated input-based functional zones. Future studies that determine ILD selectivity of IC neurons in relation to location in the IC and response selectivity, combined with retrograde tracer injections, will be necessary to test this hypothesis. The differential distribution of binaural selectivity in the cortical FMSR and NSR may be inherited from the IC along mostly parallel midbrain-thalamus-cortex pathways (Razak et al., 2007) that maintain the binaural/monaural functional segregation.

4.2. Functional significance of monaural FMSR neurons

Cortical binaural selectivity has been categorized across a number of species. The virtual absence of 'EE' type neurons and the preponderance of monaural cells in the pallid bat cortex (FMSR) appear to be a major difference with other species (cat: Imig and Adrian, 1977; Middlebrooks et al., 1980; Reale and Kettner, 1986;

Simple and Kitzes, 1993; ferret: Kelly and Judge, 1994; guinea pig: Rutkowski et al., 2000; rat: Kelly and Sally, 1988; big brown bat: Shen et al., 1997). This raises the question about why the FMSR is dominated by monaural cells with level dependent azimuth selectivity. These properties suggest that the FMSR, unlike the NSR, will provide poor location information. FMSR neurons are selective for space only for low sound levels. This is paradoxical given that the pallid bat depends on echolocation to localize and avoid obstacles along the flight path. For a large obstacle, or when the bat is close to an obstacle, returning echoes will be relatively loud. Because azimuth selectivity is broad and level dependent, a question arises as to how the bat accurately localizes and avoids the obstacle. It is possible that the EO neurons are involved primarily in detection of echoes, while the more level tolerant EI neurons play a role in localization. Alternately, timing codes (Furukawa and Middlebrooks, 2002) and/or population level representation (Zhou and Yang, 2012; Miller and Recanzone, 2009) may provide more level-tolerant spatial information even though individual cells' response rates do not. Another possibility is that the pallid bat may engage in low amplitude echolocation behavior and use the narrow azimuth receptive fields of EO neurons for sound localization. The pallid bat, being a gleaner that depends on passive hearing for prey localization (Bell, 1982), does not produce loud echolocation calls. Such a foraging strategy may have evolved in response to the ability of prey species to detect the loud echolocation calls of bats and produce defense behaviors (Holderied et al., 2011; Kawahara and Barber, 2015; Roeder, 1966). The pallid bat also performs 'intensity compensation' whereby the level of the outgoing call is reduced if the returning echoes were loud (Barber, personal communication). At low sound levels, the spatial tuning of high frequency neurons monaural neurons functioning near their thresholds is narrow. The spatial resolution afforded by small receptive fields at low sound levels may facilitate localization. For louder sounds, the same neurons have broader azimuth receptive fields, allowing the FMSR to respond to loud sounds from a broader region of space, thus aiding detection of nearby or large obstacles. Thus, the monaural FMSR system may be an adaptation for the bat to perform both detection and localization by actively controlling the sound level of the outgoing pulse.

4.3. Methodological issues

The functional organization of the pallid bat auditory cortex described above must be considered within the context of three methodological issues. First, the conclusion that most FMSR neurons are monaural is based on measuring ILDs with a single CL ear sound level with ILDs varied over ± 20 dB SPL. Additional CL ear sound levels were not tested because Razak and Fuzessery (2002) showed that the majority of FMSR neurons are monaural when tested at multiple CL ear sound levels. This was true even for a broader range of ILDs tested (± 30 dB SPL). Limited time allocated to testing ILDs allowed other response properties to be recorded from the same neurons here. However, it remains possible that some neurons in the current study may show different ILD responses at different sound levels. The conclusion that FMSR neuron azimuth selectivity is strongly level dependent is based on recordings obtained over a range of 30 dB above MT. This is a relatively narrow range, but the strong level dependence even within this range is supportive of the main conclusion that FMSR azimuth responses are level dependent. Moreover, the comparison with the NSR is also over similar range of levels and the contrast between the two regions in terms of level dependence is stark. Finally, recordings were obtained under sodium pentobarbital anesthesia. It might be possible that level tolerance may be higher in FMSR recordings from un-anesthetized animals (Mickey and Middlebrooks, 2003). It

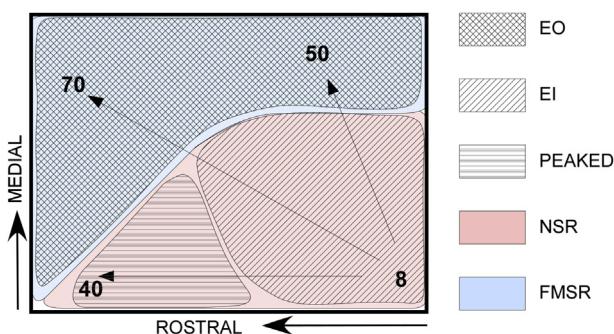


Fig. 7. Schematic of overlapping tonotopic, binaural and response selectivity maps in the pallid bat auditory cortex. The major trend in terms of functional organization in the pallid bat cortex is the close association between monaural selectivity and FMSR on the one hand and binaural selectivity and NSR on the other. This overlap causes distinct spatial tuning properties in the two regions involved in two different behaviors. Approximately 10–20% of neurons in NSR and FMSR reverse the trend (not shown in schematic). The numbers and arrows point to CF representation and direction of tonotopy. NSR: noise selective region, FMSR: FM sweep selective region, EO: monaural, EI: binaural inhibition.

is unlikely that the effects of the anesthetic is different between the NSR and FMSR and therefore does not dilute the conclusion that these two regions use different mechanisms to represent space.

5. Conclusions

The cortical regions putatively involved in prey localization and echolocation utilize different mechanisms of spatial representation with the NSR depending on overlapping binaural and frequency selectivity (Razak, 2011, 2012; Razak et al., 2015) and the FMSR depending on monaural ear directionality and rate-level response (this study). Parallel pathways and multiple cortical fields with differential response selectivity are common in sensory systems. In the auditory cortex, different regions can be distinguished based on spatial selectivity. For example in the macaque, caudal belt areas have sharper spatial tuning compared to more rostral areas (Tian et al., 2001; Woods et al., 2006). Likewise in the cat, the posterior auditory field neurons are more spatially sensitive and level tolerant than those in anterior auditory field and primary auditory cortex (Stecker et al., 2003; Harrington et al., 2008). Studies of NSR and FMSR of the pallid bat auditory cortex collectively explain how different cortical regions combine ear directionality, binaural selectivity, rate-level functions and frequency tuning to compute spatial information across multiple sound levels.

Conflicts of interest

I report no conflicts of interest.

Acknowledgements

I thank Dr. Zoltan Fuzessery and Dr. Len Kitzes for useful discussions of the data. This study was funded by the National Science Foundation (IOS 1252769).

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