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Hear Res. Author manuscript; available in PMC 2013 August 01.

Published in final edited form as:
Hear Res. 2012 August ; 290(1-2): 1–12. doi:10.1016/j.heares.2012.05.008.

Mechanisms underlying azimuth selectivity in the auditory cortex of the pallid bat

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Abstract

This study focused on mechanisms underlying azimuth selectivity in the primary auditory cortex (A1) of pallid bats. The pallid bat listens to prey-generated noise (5–35 kHz) to localize and hunt terrestrial prey. The region of A1 tuned between 5–35 kHz consists of two clusters of neurons distinguished by interaural intensity difference (IID) selectivity: binaurally inhibited (EI) and peaked. The first aim of this study was to use sequential dichotic/free-field stimulation to test the hypothesis that IID is the primary cue underlying azimuth selectivity in neurons tuned in the prey-generated noise frequency band. IID selectivity and ear directionality at the neuron's characteristic frequency (CF) were used to predict azimuth selectivity functions. The predicted azimuth selectivity was compared with the actual azimuth selectivity from the same neurons. Prediction accuracy was similarly high for EI neurons and peaked neurons with low CF, whereas predictions were increasingly inaccurate with increasing CF among the peaked neurons. The second aim of this study was to compare azimuth selectivity obtained with noise and CF tones to determine the extent to which stimulus bandwidth influences azimuth selectivity in neurons with different binaural properties. The azimuth selectivity functions were similar for the two stimuli in the majority of EI neurons. A greater percentage of peaked neurons showed differences in their azimuth selectivity for noise and tones. This included neurons with multiple peaks when tested with tones and a single peak when tested with noise. Taken together, data from the two aims suggest that azimuth tuning of EI neurons is primarily dictated by IID sensitivity at CF. Peaked neurons, particularly those with high CF, may integrate IID sensitivity across frequency to generate azimuth selectivity for broadband sound. The data are consistent with those found in cat and ferret A1 in that binaurally facilitated neurons depend to a greater extent (compared to EI neurons) on spectral integration of binaural properties to generate azimuth selectivity for broadband stimuli.

Keywords

sound localization; binaural properties; azimuth tuning; auditory cortex; pallid bat

1. Introduction

Information about the location of a sound is not directly represented in the cochlea, but is extracted by computations performed centrally through integration of binaural and monaural

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cues, frequency sensitivity and external ear directionality. Studies of mechanisms of sound localization, therefore, provide insights on how central and peripheral properties interact to shape neural computations. The primary auditory cortex (A1) is involved in sound localization behavior (Whitfield et al., 1972; Casseday and Diamond, 1977; Jenkins and Masterton, 1982; Jenkins and Merzenich, 1984; Kavanagh and Kelly, 1987; Heffner 1997; Malhotra et al., 2004), but how A1 represents sound locations remains debated (Rajan et al., 1990; Furukawa et al., 2000; Miller and Recanzone 2009, Razak, 2011).

The major objective of the present study was to determine the mechanisms underlying azimuth selectivity in A1 neurons in the pallid bat. The azimuth component of spatial selectivity of neurons can be quantified with the azimuth selectivity function (ASF) which plots neural response magnitudes against azimuth locations. Such ASFs can be categorized into hemifield-selective, midline-selective and omnidirectional (Middlebrooks and Pettigrew, 1981; Rajan et al., 1990). Predictions of ASF properties and shape based on binaural selectivity have been made based on independent studies of azimuth and binaural cue selectivity (Imig and Adrian 1977; Kitzes et al., 1980; Middlebrooks et al., 1980; Philips and Irvine, 1981; Reale and Kettner, 1986; Imig et al., 1990; Rajan et al., 1990; Semple and Kitzes 1993; Kelly and Judge 1994; Middlebrooks et al., 1994; Clarey et al., 1994; Brugge et al., 1996; Irvine et al., 1996; Rutkowski et al., 2000; Nakamoto et al., 2004; Stecker et al., 2005; Higgins et al., 2011). However, few studies have directly tested the predictions by studying ASF properties of neurons with known binaural selectivity. In the ferret A1, linear interactions between binaural spectrotemporal properties and external ear/head directionality predicted spatial tuning (Schnupp et al., 2001). The prediction accuracy was dependent on the binaural selectivity of neurons with better predictions for binaurally inhibited than binaurally facilitated neurons (Mrsic-Flogel et al., 2005). In the mustached bat inferior colliculus (IC), interactions between interaural intensity difference (IID) selectivity and ear directionality at the characteristic frequency (CF) of the neuron predicted azimuth tuning in both binaurally inhibited and facilitated neurons although it is not clear if prediction accuracy depended on binaural property (Fuzessery and Pollak 1985; Wenstrup et al., 1988). The first goal of the present study was to apply similar methods to predict azimuth tuning in A1 of the pallid bat, with the hypothesis that IID is the main cue underlying azimuth selectivity in the pallid bat A1. This aim also tested if prediction accuracy differed, as in the ferret, between binaurally inhibited and binaurally facilitated neurons.

The pallid bat listens to prey-generated noise (frequencies between 5–35 kHz) to localize and hunt terrestrial prey, while reserving echolocation (downward frequency modulated sweep 60→30 kHz, 1.5–6 msec duration) for obstacle avoidance (Bell, 1982; Barber et al., 2003). The connections between the IC, medial geniculate body and A1 are organized as parallel pathways that are selective for echolocation calls or noise (Fuzessery, 1994; Razak and Fuzessery, 2002; Razak et al., 2007). In A1, neurons tuned between 5–35 kHz show strong responses to noise and are likely involved in prey localization. This region of A1 is dominated by two clusters of neurons distinguished by IID selectivity (Razak and Fuzessery, 2002; 2010). One cluster contains binaurally inhibited (EI type) neurons. These neurons are excited by monaural contralateral ear stimulation and show no response to monaural ipsilateral ear stimulation. When stimulated binaurally, the IID response function exhibits a sigmoid shape with excitation for a range of IIDs favoring the contralateral ear, and inhibition as the ipsilateral ear intensity is increased. The majority of EI neurons exhibit hemifield-selective ASF (Razak, 2011). Rostral to the EI neurons is a cluster of neurons with peaked IID selectivity. These neurons produce weak or no response to monaural contralateral stimuli, monaural ipsilateral stimuli and binaural stimuli favoring either ear, but show strong binaural facilitation at IIDs near zero. These neurons encompass the EO/FI and OO/FI (predominantly binaural) categories (Kitzes et al., 1980; Phillips and Irvine, 1981; Fuzessery et al., 1990). All peaked neurons in the pallid bat A1 respond best to azimuths

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near the midline (Razak, 2011), and may underlie a separate midline channel as proposed in humans (Dingle et al., 2010).

In this study, the mechanisms underlying azimuth selectivity of EI and peaked neurons were evaluated. For this purpose, a sequential dichotic/free-field stimulation paradigm was employed (Moiseff and Konishi, 1981; Fuzessery and Pollak, 1985; Wenstrup et al., 1988). The dichotic stimulation allowed binaural and frequency selectivity to be measured. The free-field stimulation allowed measurement of ASF from the same neurons. A previous study using this method showed that ASF properties are correlated with IID properties (Razak, 2011). However, other cues such as interaural time differences generated by sound envelope may also contribute to ASFs (Lohuis and Fuzessery, 2000). The first aim of this study was to determine how well IID selectivity, taken together with the ear directionality at the neuron's CF predicted ASF. The dichotic measures were combined with published pallid bat external ear directionality (Fuzessery, 1996) to predict ASF. The actual and predicted ASF were then compared for each neuron.

The second aim of this study was to compare ASFs determined using noise and pure tones. Binaural cue-based azimuth localization and minimum audible angles in the horizontal plane improve with stimulus bandwidth (Brown et al., 1980; Butler, 1986; Martin and Webster, 1987; Terhune 1985). The few physiological studies that compared ASFs obtained with broadband noise and pure tones suggest that the neural correlate for improved localization with bandwidth may lie in narrower azimuth tuning to noise than tones (Aitkin and Martin 1987; Clarey et al., 1995). Clarey et al. (1995) found a shift in azimuth tuning for tone *versus* noise stimuli that was greater for neurons with midline *versus* hemifield azimuth selectivity. Based on monaural ear occlusion, Clarey et al. (1995) suggested that the midline- and hemifield-selective neurons were likely to exhibit binaural facilitation and binaural inhibition, respectively. Thus, as with the linear prediction data in ferrets, the tone/noise ASF comparison data point to differences in spectral integration depending on binaural sensitivity. Here, we recorded ASF with noise and tones to determine if there were differences in the peaked and EI neurons depending on stimulus bandwidth. This comparison will indicate the extent to which across-frequency interactions are necessary in generating spatial tuning in the EI and peaked neurons.

2. Methods

Adult pallid bats were netted in Arizona 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 were approved by the Institutional Animal Care and Use Committee.

2.1 Surgical procedures

Recordings were obtained from bats 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. 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

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the midsagittal sinus (Razak and Fuzessery, 2002). The size of the exposure was usually ~2 mm^2. Exposed muscle was covered with petroleum jelly, and exposed brain surface was covered with paraffin oil to prevent desiccation.

2.2 Recording procedures

The focus of electrophysiology in this study was the region of the pallid bat A1 tuned between 5–35 kHz and with robust responses to broadband noise. This region is tonotopically organized, has narrow frequency tuning and is a main target of input from the ventral division of the medial geniculate body indicting that it is part of A1 (Razak and Fuzessery, 2002; Razak et al., 2007). The peaked and EI neurons are found in distinct clusters within this region (Razak and Fuzessery, 2002, 2010).

Experiments were conducted in a warm (80°F), sound-proofed chamber lined with anechoic foam (Gretch-Ken Industries, Oregon). All recordings were obtained from the right hemisphere. 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 an integrated amplifier (Yamaha AX430) or a power amplifier (Parasound, HCA1100).

Extracellular single-unit recordings were obtained using glass electrodes (1M NaCl, 2–10 MΩ impedance) at depths between 200 and 600 μm. 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 peri-stimulus time histograms were stored using the Microstar DSP board and Batlab software. All data shown are from single-unit recordings identified based on window discrimination and 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. Spikes occurring within 200 msec of stimulus onset were counted. There is very little spontaneous activity in the pentobarbital anesthetized pallid bat cortex.

Overview of stimulation paradigm—For the first main objective of this study, IID selectivity, characteristic frequency (CF) and ASF were determined from the same neurons. To achieve this, a sequential dichotic/free-field stimulation paradigm was used for each neuron. Dichotic stimulation was used to record IID sensitivity and CF. The speakers were then removed from the ears, and stimulation was switched to a free-field speaker mounted on a loop to record ASF. All IID selectivity functions and ASFs for the first aim were determined with broadband noise (bandwidth 5–40 kHz, 5–10 ms duration, 1 msec rise/fall times) as the stimulus.

Dichotic stimulation details—IID selectivity functions were obtained using dichotic stimulation with two LCY-K100 ribbon tweeters (Madisound, Wisconsin) fitted with funnels that were inserted into the pinnae. The amplifier-speaker-funnel frequency response curve measured with a 1/4-in microphone (Bruel and Kjaer, Denmark) was flat within ±3 dB for frequencies from 8–35 kHz. The two speakers used for dichotic studies did not differ significantly in their frequency response. The speaker funnels were not sealed in the meatuses to facilitate sequential dichotic/free-field stimulation from the same neurons. The attenuation of speaker intensity at the opposite ear was at least 25 dB and permitted the

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presentation of ±20 dB IIDs. This covers the behaviorally relevant range of IIDs for the pallid bat (Fuzessery, 1996).

IID selectivity was determined with broadband noise as stimulus. The threshold of the neuron to noise was determined by stepping up intensity in 5 dB steps. Noise was presented in the contralateral ear at an intensity between 10 to 15 dB above noise threshold, while the intensity at the ipsilateral ear was varied from 20 dB below to 20 dB above contralateral intensity, in 5 dB steps. Negative IIDs denote more intense ipsilateral ear sound than at the contralateral ear. Positive IIDs favor the contralateral ear. Neurons were considered binaurally inhibited (EI) if the response declined at least 50% of the maximal response with increasingly negative IID (e.g., Fig. 1A). A neuron was considered peaked if the response decreased below 60% of maximum response for IIDs on both sides of an optimal IID (e.g., Fig. 1C). IID sensitivity is stable across intensities in the pallid bat A1 (Razak and Fuzessery, 2002, 2010). Therefore, IID curves were not determined at multiple contralateral intensities in this study.

Pure tones (5–40 kHz, 5–10 ms duration, 1 ms rise/fall times, 1 Hz repetition rate) presented through the speaker funnel inserted in the contralateral ear were used to determine CF. CF was defined as the tone frequency that elicited action potentials to at least five successive stimulus repetitions at the lowest intensity. This intensity was noted as the minimum threshold (MT) of the neuron. In a few neurons, the intensity was increased in 5 or 10 dB steps to record frequency tuning. However, this was not a major emphasis in this study. For neurons that did not respond to monaural tones, CF was determined by presenting binaural tones. The IID at which peak response occurred with noise (see below) was used to determine CF with binaural tones.

2.3 Free-field stimulation

Free-field stimulation was achieved with an LCY-K100 speaker that was moved manually to different locations on a semi-circular loop (40 cm radius with the bat's head as center). In the figures to follow, positive azimuth values denote contralateral space and negative azimuth values denote ipsilateral space. 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 and in the same horizontal plane allowing ASFs to be studied at an elevation of 0°. 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.

The speaker was positioned between −75° and +75° and moved with 15° resolution to determine ASF. Locations behind the animal were not studied. For the first aim, only broadband noise was used as the stimulus to determine ASF (termed 'noise-ASF'). Because the speaker is further away from the bat in the free-field condition, the threshold intensity can be higher compared to the dichotic condition. The intensity of stimulation was matched between dichotic and free-field studies to be at the same value above threshold (Wenstrup et al., 1988). For peaked neurons, free-field noise threshold was determined with the speaker at 0°. For EI neurons, the free-field noise threshold was determined with the speaker at 60°. Azimuth sensitivity functions were determined at intensities between 10–15 dB above noise threshold in all neurons.

To quantify the medial boundary of the ASF of EI neurons, the '50% azimuth' was determined. The 50% azimuth is defined as the azimuth at which response declines to 50% of maximum (vertical arrow in Fig. 1B). The 50% azimuth has been referred to as 'half-maximal azimuth' in the literature (Rajan et al., 1990). Three measures were quantified in peaked neuron ASF (Fig. 1D). To determine the 'peak azimuth', the range of azimuths that elicited >80% of maximum response was first marked on the ASF plot (upper dashed line in

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Fig. 1D). The peak azimuth was taken as the arithmetic mean of the two azimuths that framed this range. The '50% width' is the range of azimuths that elicited >50% of maximum response (azimuths between the two long arrows in Fig. 1D). The 50% width has been referred to as the 'half-maximal width' in the literature (Rajan et al., 1990). The 50% azimuth of peaked neurons was defined as done for EI neurons. Although peaked neurons exhibit two such values, only the 50% azimuth ipsilateral to the peak was quantified. The 50% width measure makes the 50% azimuth on the contralateral side redundant.

Ear directionality and ASF predictions—The IID-azimuth relationship in the pallid bat at different frequencies is known (Fuzessery, 1996). This paper reported on the IIDs generated at standardized locations in front of the bat for tones with frequencies between 10–80 kHz. Figure 2 shows an adaptation of data at 0° elevation from that paper. The IID-azimuth relationships for 10, 15, 20, 25 and 35 kHz tones from Fuzessery (1996) were adapted here to predict ASFs of neurons with CF in the 8–12, 13–17, 18–22 and 23–30 and 31–39 kHz range, respectively. The prediction method is described in detail in the Results section (associated with Figure 3). Briefly, the first step was to determine the CF, IID sensitivity and azimuth sensitivity functions of the neuron. This was followed by identifying the IIDs generated at different azimuth locations (using Figure 2) for the frequency corresponding to CF. Then the predicted ASF was plotted as azimuth locations against response magnitude elicited by IIDs generated at each azimuth (e.g., Figure 3). This predicted ASF was compared with the actual ASF measured with free-field stimulation by determining a cross-correlation coefficient for the match between the two functions.

Comparison of azimuth selectivity for CF tones and noise—For aim two, all procedures were as described in the 'free-field stimulation' section above, except ASFs were obtained for both CF tone and noise from each neuron. The majority of peaked and EI neurons in the pallid bat A1 show stability of both IID (Razak and Fuzessery, 2002, 2010) and ASF (Razak, 2011) properties over a moderate range of intensities (10–40 dB above threshold). Therefore, in most neurons only a single intensity was tested for each stimulus type. The intensity tested was between 10 – 25 dB above threshold for each stimulus type.

3. Results

Characteristic frequency, IID sensitivity and ASF were obtained using a sequential dichotic/free-field stimulation paradigm from 83 EI and 61 peaked neurons. The CF of these neurons was between 8–39 kHz. Previously a correlation was reported between azimuth selectivity and IID selectivity (Razak, 2011). The first aim of this study was to determine if IID was the primary localization cue in generating azimuth sensitivity by quantifying how well interactions between IID sensitivity and ear directionality at CF predicted ASF in EI and peaked neurons. The second aim was to compare ASFs recorded using CF tone ('tone-ASF') and noise ('noise-ASF') as stimulus. This comparison was made in 39 EI neurons and 37 peaked neurons.

3.1 Predicting azimuth sensitivity

Figure 3 illustrates the method for predicting ASF (based on Fuzessery and Pollak, 1985; Wenstrup et al., 1988; Fuzessery et al., 1990). It should be noted that ASF was predicted based on ear directionality for tones and IID functions for noise. The neuron in Figure 3 had a CF=21 kHz. Figure 3A shows the IID sensitivity of this EI neuron when tested with noise. The inset table in Figure 3A shows the predicted response magnitude for different azimuths based on the IID-azimuth relationship (from Figure 2 using the 20 kHz function) and IID sensitivity (Fig. 3A). For example, a 20 kHz tone at 60° azimuth generated an IID of +16 dB (Figure 2). The response of this neuron for an IID of 16 dB was 28 spikes (Figure 3A).

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Therefore, the predicted response for noise at 60° azimuth is 28 spikes. Likewise, the IID generated by a 20 kHz tone at 10° azimuth is 5 dB. The response of this neuron to an IID of 5 dB, and the predicted response to noise at 10° azimuth, is 9 spikes.

The 50% IID of this neuron (vertical arrow in Fig. 3A) was +7 dB. Figure 2 shows that this value of IID was generated at ~+14° azimuth. Therefore, the predicted 50% azimuth for this neuron was +14°. Figure 3B compares the actual ASF recorded from this neuron with the predicted response. They were quite similar (correlation coefficient, r = 0.96). The vertical arrows in Figure 3B show that the predicted and actual 50% azimuths were almost identical (~+14°). Despite the different stimuli used to determine ear directionality and IID selectivity, the overall similarity of predicted and actual ASF suggest that this neuron's ASF to broadband noise is largely determined by IID selectivity at CF.

Neurons with similar IID selectivity can exhibit different ASF properties depending on CF and ear directionality. This is illustrated by the example neurons in Figure 4. Both EI neurons exhibited similar IID selectivity, but exhibited different azimuth selectivity. The neuron in Fig. 4A had a CF=20 kHz. The IID-azimuth function at 20 kHz (Fig. 2) was used for predictions in this neuron. The 50% IID of this neuron (Fig. 4A) was −15 dB. This predicts a 50% azimuth of −32°. Figure 4B shows that the predicted and actual ASF were similar with a 50% azimuth of −32°. The neuron in Figure 4C had similar IID selectivity as the previous neuron, but a CF of 10 kHz. The IID-azimuth relationship for 10 kHz (Fig. 2) was used to make predictions in this neuron. The predicted ASF was omnidirectional for the azimuth range tested. The actual ASF was as predicted. Thus detailed ASF properties of these example EI neurons were accurately predicted by interactions between IID selectivity and ear directionality at CF, indicating that IID was the dominant binaural cue underlying their spatial tuning.

Across the population of EI neurons, the 50% azimuth was well predicted by interactions between IID, CF and ear directionality ($p<0.001$, Fig. 7A). The correlation between actual and predicted 50% azimuth ($r^2 = 0.92$) was better than the correlation between 50% IID and 50% azimuth ($r^2 = 0.73$, Razak, 2011) indicating improved predictability of azimuth selectivity from binaural properties when ear directionality at CF is taken into account. Correlation coefficients were obtained for the match between the predicted and actual ASFs for each neuron. In ~60% of EI neurons, the correlation coefficients were between 0.9–1 (Fig. 8A). The mean (± s.e) correlation coefficient for EI neurons was 0.87 ± 0.12. There was no relationship between correlation coefficients and CF (Fig. 8B). Taken together, these data indicate that the ASF of EI neurons to broadband noise was explained by IID sensitivity at the neuron's CF.

Figure 5A–D illustrates the comparison of predicted and actual ASF for two peaked neurons. The neurons had similar IID selectivity (Fig. 5A, C), but CF of 20 and 10 kHz, respectively. The predicted and actual ASF for the neuron with the higher CF were more selective (Fig. 5B) compared to the neuron with the lower CF (Fig. 5D). The predicted and actual ASF were closely matched in terms of 50% azimuth, peak azimuth and 50% azimuth bandwidth. As with the EI neurons, these peaked neurons illustrate how the CF/ear directionality interacts with IID selectivity to shape ASFs.

In contrast to EI neurons in which prediction accuracy was high across CF, the prediction method was inaccurate for 5/6 peaked neurons with CF between 23–30 kHz. The ASF of these neurons exhibited a single peak, although the predictions indicated they should have multiple peaks in their ASF (e.g., Fig. 6). The IID-azimuth relationship is non-monotonic at 25 kHz (Fig. 2). There are multiple azimuth locations at which similar IIDs are generated. Therefore, the predictions based on IID-azimuth functions obtained with tones give rise to

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multiple peaks in the ASF. The fact that ASF shows a single peak when tested with noise suggests that these neurons integrate binaural/monaural properties across multiple frequencies to generate broadband ASF.

In most peaked neurons, detailed properties of ASF such as 50% azimuth (Fig. 7B), peak azimuth (Fig. 7C) and 50% width (Fig. 7D) were predicted by interactions between IID, frequency selectivity and ear directionality at CF. The correlation between the predicted and actual peak azimuth ($r^2 = 0.84$) was better than the correlation between peak IID and peak azimuth ($r^2 = 0.6$, Razak, 2011) indicating the influence of CF and ear directionality in shaping azimuth selectivity. The prediction accuracy, however, was lower for peaked neurons compared to EI neurons (Fig. 8A). The mean (± s.e) correlation coefficient (0.7 ± 0.26) for peaked neurons was significantly lower than that of EI neurons (Mann-Whitney rank sum test, $p<0.001$). The decreased accuracy was mostly found for neurons with higher CF (Fig. 8C). Taken together, these data suggest that peaked neurons, particularly those with CF>23 kHz integrate binaural/monaural properties across multiple frequencies to generate their ASF to broadband noise. In these neurons, it is also possible that other localization cues such as envelope ITDs may play a role (Lohuis and Fuzessery, 2000).

3.2 Comparison of CF tone and noise azimuth selectivity

EI neurons—In the majority (29/39, 74%) of EI neurons, the ASF were similar for noise and CF tone (e.g., Fig. 9A). In the example neuron (Figure 9A), the 50% azimuth was similar for noise and CF tone (21 kHz). In the remaining 10 neurons, the response to tones was less than 60% of maximum response to noise (e.g., Figure 9B). Four of these neurons only responded to noise, and not to the tones tested. Across the population of EI neurons with both noise and tone response, (n=35), there was no difference in the 50% azimuth for noise and tones (50% azimuth for tones: −2.53 ± 3.9°, 50% azimuth for noise: −1.5 ± 4.5°, paired t-test, $p>0.05$). Consistent with the prediction data above, the noise-ASF of most EI neurons does not depend on across-frequency interactions of inputs with different binaural/monaural properties. In the minority of EI neurons, across-frequency interactions of inputs with similar binaural properties appear to summate to produce stronger responses to broadband noise than CF tone.

Peaked neurons—In 18/37 (49%) of peaked neurons, noise- and tone-ASFs were similar (e.g., Fig. 10A). Response to tones in 7/37 (19%) neurons was at least 60% lower than maximum response to noise (e.g., Fig. 10B, C). In these neurons as well, binaural facilitation was present for both tones and noise. Across the population of neurons (n=25) with peaked response to tones and noise, there was no difference in peak azimuth (tone: 10.5 ± 1.6°, noise: 11.1 ± 2.1°, $p>0.05$, Wilcoxon signed-rank test), 50% azimuth (tone: −9.3 ± 2.7°, noise: −6 ± 2.4°, $p>0.05$, paired t-test) or 50% width (tone: 46.6 ± 4.6°, noise: 45.4 ± 3.7°, $p>0.05$, paired t-test).

Twelve of the 37 peaked neurons showed differences in their CF tone- and noise-ASF. These neurons were of two types. The first type (5/12) showed a peaked noise-ASF and a sigmoid CF tone-ASF (e.g., Fig. 10D). The second type (7/12) exhibited a single peak noise-ASFs, but multiple peaks in their tone-ASFs (e.g., Fig. 10E, F). Concordant with the prediction data, all of these neurons had CF between 23–30 kHz. In each case, there was one peak at similar azimuths for tones and noise, and additional peaks for tones in flanking locations. The response magnitudes of the peaks were similar for noise and tones. These data show that stimulus bandwidth influenced azimuth tuning in more peaked than EI neurons.

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4. Discussion

4.1 Major findings of this study

The tone- and noise-ASFs of most (~75%) EI neurons were similar. The remaining 25% of EI neurons responded better to noise than to tones. Even in these neurons, when tone response was present, the 50% azimuth was similar for tones and noise. The ASF of EI neurons was well predicted (mean cross correlation of 0.87) by interactions of IID sensitivity and ear directionality near CF. These data indicate that in most EI neurons, the IID sensitivities across the excitatory frequency range must be similar (Mendelson and Grasse, 2000) and that azimuth sensitivity to broadband noise can be explained by binaural intensity sensitivity for CF tone. A greater percentage (51%) of peaked neurons showed differences in tone- and noise-ASFs. These neurons showed reduced responses to tones compared to noise, or broader (sigmoid *versus* peaked) or multi-peaked tone-ASF. The predicted ASFs were accurate relative to actual ASFs in most low-CF peaked neurons; predictability was lower for high-CF peaked neurons. This suggests that compared to EI neurons, more peaked neurons, particularly those with high CF, integrate different IID sensitivities at CF and off-CF to generate noise ASF (Mendelson and Grasse, 2000). Envelope ITD sensitivity may also be involved in the high-CF peaked neurons (Lohuis and Fuzessery, 2000). The prediction accuracy for almost all EI neurons and most low-CF peaked neurons indicate that IID is the main binaural cue used to shape azimuth selectivity in the pallid bat A1.

4.2 Comparison with previous studies

In ferret A1, a linear model of integration of frequency sensitivity to inputs from each ear and stimulus energy in virtual acoustic space stimuli predicted the shape and location of spatial receptive fields. The prediction accuracy was higher for binaurally inhibited neurons, compared to binaurally facilitated neurons. In the mustached bat IC, the integration of azimuth dependent changes in monaural intensity and IIDs, combined with IID selectivity and ear directionality predicted spatial selectivity in both binaurally inhibited and facilitated neurons. Whether prediction accuracy differed for the two types of neurons was not analyzed. In the pallid bat A1, spatial tuning was well predicted in the majority of neurons by interactions between IID selectivity and ear directionality. As in ferret A1, the predictions were better for EI neurons compared to neurons with binaural facilitation.

In terms of CF tone/noise ASF comparison, three observations in this study were similar to those reported previously in cat A1. First, at a gross level, ASF shapes indicative of selectivity for midline, contralateral and ipsilateral locations were similar for the two stimuli (Rajan et al., 1990). Second, nearly a quarter of neurons in both cat and pallid bat A1 were more sensitive to free-field noise than to tones (Clarey et al., 1995). Third, Clarey et al., (1995) showed that more high-CF neurons tuned to the midline (their 'BD-MID' cells are likely similar to the peaked cells here) compared to neurons with sigmoid ASF (their BD-HEMI cells are likely similar to the EI cells here) exhibited broader ASFs for tones than noise. In the pallid bat as well, a greater percentage of peaked cells (compared to EI cells), particularly those with CF>23 kHz, showed broader or ambiguous tuning to tones *versus* noise. Thus, in several species binaurally facilitated neurons integrate to a greater extent across sound frequency or spectral cues to indicate azimuth location.

4.3 Possible mechanisms of azimuth selectivity for broadband noise in peaked neurons

Seven peaked neurons responded better to noise than tones (e.g., Fig. 10B, C). In these neurons, a peak was still apparent in the tone-ASF at similar azimuths as the noise-ASF. This suggests that the CF input alone produces sub-optimal binaural facilitation. Across-frequency summation of inputs with facilitation at similar azimuths may produce the

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enhanced response to noise. Five neurons with peaked noise-ASF exhibited a sigmoid tone-ASF (e.g., Fig. 10D). This suggests that off-CF inputs stimulated by noise inhibit responses to contralateral azimuths. CF input is sufficient to suppress responses to ipsilateral azimuths. One model suggested for such integration posits input from two EI cells with different 50% azimuths (derived from Park and Pollak, 1993; the original model was for IID selectivity). One input, at CF, is excitatory. The second input, at an off-CF frequency and with 50% azimuth at a more contralateral location, provides inhibition. A neuron with such inputs will exhibit peak response at locations between the 50% azimuths of the two inputs. Iontophoresis data supports this model for peaked neurons in pallid bat A1 (Razak and Fuzessery, 2010). GABA-a receptor antagonists convert peaked IID sensitivity to EI sensitivity in A1, suggesting that the off-CF inhibition is driven locally through GABA-a receptors. The frequency tuning of this off-CF input is unclear from the present data. Future studies will address this by systematically increasing the bandwidth of noise below CF, above CF or centered at CF.

Seven neurons showed a single peaked noise-ASF and multi-peaked tone-ASF (e.g., Fig. 10E, F). In these neurons, one peak for tone coincided with the peak for noise. The multi-peaked tone-ASF is likely explained by the fact that similar IIDs may be generated at multiple azimuth locations. IID-azimuth relationships are frequency-dependent and for some frequencies, IIDs may saturate with increasing azimuth eccentricity or even show a non-monotonic relationship. For the pallid bat, IID-azimuth relationship is non-monotonic for a tone of 25 kHz (Figure 2). All the neurons with multi-peaked tone-ASFs had CF between 22–30 kHz suggesting that tone-ASF ambiguities arise because of the IID-azimuth relationship in this frequency range. The prediction data also indicated that neurons with CF between 23–30 kHz show multi-peaked ASFs.

Brainard et al., (1992) suggested a model for how responses to broadband stimuli may resolve such ambiguities in spatial tuning. In the barn owl optic tectum, noise elicits a space-specific response. Tones elicit responses from multiple discrete locations, one of which is the same location as seen with noise. The other locations (termed ‘accessory’ locations) include inhibitory surrounds. For broadband stimulus, the accessory responses for one frequency overlap with the inhibitory surround for another frequency, resulting in an unambiguous space-specific response. A similar mechanism may be in place in the peaked neurons of the pallid bat A1. Future studies will compare ASF for noise and multiple tones from the same neurons to address this mechanism in the pallid bat A1.

4.4 Methodological issues

IID sensitivity, CF and ear directionality for frequencies near CF were sufficient to predict azimuth tuning for noise in the majority of EI and peaked neurons. One caveat to note is that ear directionality functions were only available for tonal stimuli, whereas IID and azimuth functions in the present study were recorded in response to noise. Despite this, the predicted and actual ASFs of EI neurons matched closely, further strengthening the suggestion made above that binaural inhibition produced by CF tones was sufficient to explain noise ASF. In most peaked neurons, the predicted and actual ASFs were similar. The second caveat to note is that the predictions as well as noise/tone ASF comparisons were made only at a single intensity 10–40 dB above threshold. Both IID and azimuth sensitivity of A1 neurons in the pallid bat change relatively little in this intensity range (Razak and Fuzessery, 2002, 2010; Razak, 2011) suggesting that accuracy of predictions will be relatively invariant to absolute intensity within this range.

The third methodological issue is that azimuth-dependent changes in absolute monaural intensity were not included in the prediction model (Fuzessery and Pollak, 1985). This issue is related to the method used to determine IID selectivity and is therefore discussed together.

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To obtain IID selectivity function in this study, the intensity at the contralateral ear was fixed and the intensity at the ipsilateral ear was changed around the contralateral intensity. This procedure is called the excitatory monaural intensity (EMI) constant method. An alternate procedure is called the average binaural intensity (ABI) method (Irvine, 1987). In this method, the average intensity is kept constant by changing the intensity at both ears symmetrically around the constant value. The ABI method better captures azimuth-dependent changes in monaural intensities and IID, particularly at higher frequencies.

In the present study, a sufficient number of contralateral intensities was not studied to compare ABI- *versus* EMI-based IID plots. The EMI-based IID functions were, however, sufficient to predict ASF in almost all EI neurons and low-CF peaked neurons. Two properties of pallid bat A1 neurons explain why the EMI method worked well in predicting ASF. First, most EI and peaked neurons in the pallid bat A1 exhibit monotonic rate-intensity functions at least for intensities between 10–40 dB above threshold (Razak and Fuzessery, 2002). In the cat IC and A1, EMI and ABI methods produce similar IID sensitivity functions in neurons with monotonic monaural rate-intensity response (Irvine, 1987). Second, for intensities between 10–40 dB above threshold, the IID sensitivity function is not affected by absolute intensity in the pallid bat A1 (Razak and Fuzessery, 2002, 2010). All ASFs in the present study were obtained with intensities in this range. The ABI method may be better at predicting ASFs closer to threshold and in neurons with non-monotonic rate-intensity functions. Similarly, the azimuth-monaural intensity relationship may also be critical in predictions near threshold and in non-monotonic neurons.

4.5 Conclusions

The auditory cortex is involved in sound localization, but the nature of representation of sound location in A1 is only beginning to be understood (Miller and Recanzone, 2009, Razak, 2011). There is no systematic space map in A1 as seen in the midbrain (Middlebrooks and Pettigrew, 1981; Palmer and King, 1982; Rajan et al., 1990). However, there are systematic representations of azimuth properties within binaural clusters in the pallid bat A1 (Razak, 2011). The EI cluster contains a map in which the IID at which the neuron is inhibited (50% IID) varies systematically within the EI cluster. This gives rise to a representation in which the extent of active cortex varies systematically with azimuth within the EI cluster. The data from the present study indicate that this representation is unlikely to be affected by the bandwidth of noise. Neurons in the peaked cluster are sensitive to azimuths near the midline and may form an acoustic fovea for midline locations (Razak, 2011, Dingle et al., 2010). The data from this study indicate that stimulus bandwidth will alter the pattern of activity within this cluster.

As in the mustached bat IC (Fuzessery and Pollak, 1985; Wenstrup et al., 1988) and ferret A1 (Schnupp et al., 2001), linear models of interactions between frequency tuning, binaural selectivity and ear directionality were successful in predicting spatial tuning in the majority of A1 neurons in the pallid bat. High-CF peaked neurons appear to be an exception in that binaural facilitation may incorporate across-frequency integration of different binaural and/or monaural spectral cues. A higher percent of peaked neurons is seen in the cortex than inferior colliculus in cat and pallid bat (Irvine and Gago 1990; Irvine et al. 1996; Lohuis and Fuzessery 2000; Phillips and Irvine 1981; Semple and Kitzes 1993). In addition, iontophoresis of GABA-a receptor antagonists converts peaked selectivity to EI type selectivity (Razak and Fuzessery, 2010), suggesting that at least some of the spectral integration important for facilitation is generated at the cortical level. Thus, peaked azimuth selectivity may be an emergent A1 property. Future lesion studies will target peaked *versus* EI neurons to determine the contribution of different cortical binaural clusters to sound localization by the pallid bat.

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Acknowledgments

The study was funded by National Institute on Deafness and Other Communication Disorders Grant R03 DC009882-01A. I thank Dr. Zoltan Fuzessery for comments on an earlier version of the manuscript. I also thank Kevin Measor, Sarah Rotschafer and two anonymous reviewers for providing feedback on this manuscript.

List of Abbreviations

A1	Primary Auditory Cortex
ABI	Average Binaural Intensity
ASF	Azimuth Selectivity Function
CF	Characteristic Frequency
EI	Binaural Inhibition
EMI	Excitatory Monaural Intensity
IC	Inferior Colliculus
IID	Interaural Intensity Difference

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Highlights

- Dichotic/free-field stimulation was used to determine mechanisms of azimuth tuning.
- Binaural level cues explain azimuth tuning in most A1 neurons of the pallid bat.
- Midline-selective neurons exhibit different azimuth tuning to noise and tones.
- Data suggest neural correlates for sound bandwidth effect on localization.

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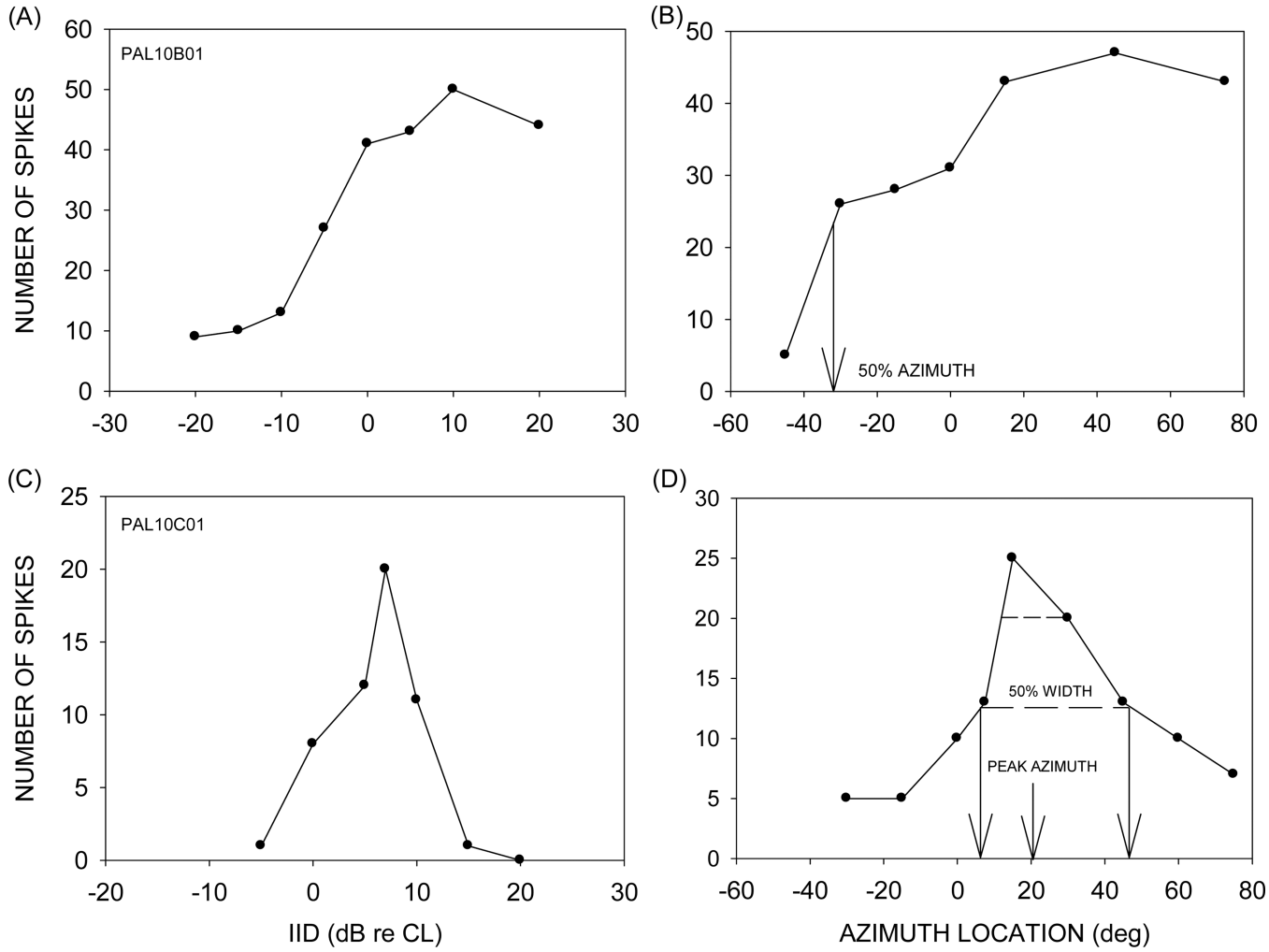

Figure 1.

(A) The IID selectivity of a binaurally inhibited (EI) neuron determined using broadband noise as stimulus. Positive IIDs denote a louder sound in the contralateral ear. Negative IIDs denote a louder sound in the ipsilateral ear. The response magnitude (ordinate) in this and subsequent figures is the number of spikes for 20 repetitions of each stimulus. **(B)** The azimuth sensitivity function (ASF) of the same EI neuron as in (A) obtained using broadband noise as stimulus. Positive azimuths denote contralateral locations. Negative azimuths denote ipsilateral locations. The vertical arrow points to the azimuth at which response declines to 50% of maximum. This is termed the '50% azimuth', and quantifies the medial boundary of the ASF. **(C)** The IID selectivity of a peaked neuron determined with noise as stimulus. **(D)** The ASF of the same peaked neuron determined with noise as stimulus. The short dashed line indicates the range of azimuth eliciting greater than 80% of maximum response. The arithmetic center of this range (short vertical arrow) is termed the 'peak azimuth'. The long dashed line marks the range of azimuth eliciting greater than 50% of maximum response. This range is termed '50% width'. In peaked neurons, the term '50% azimuth' is used to indicate azimuth at which response declines to 50% of maximum on the ipsilateral side of the peak.

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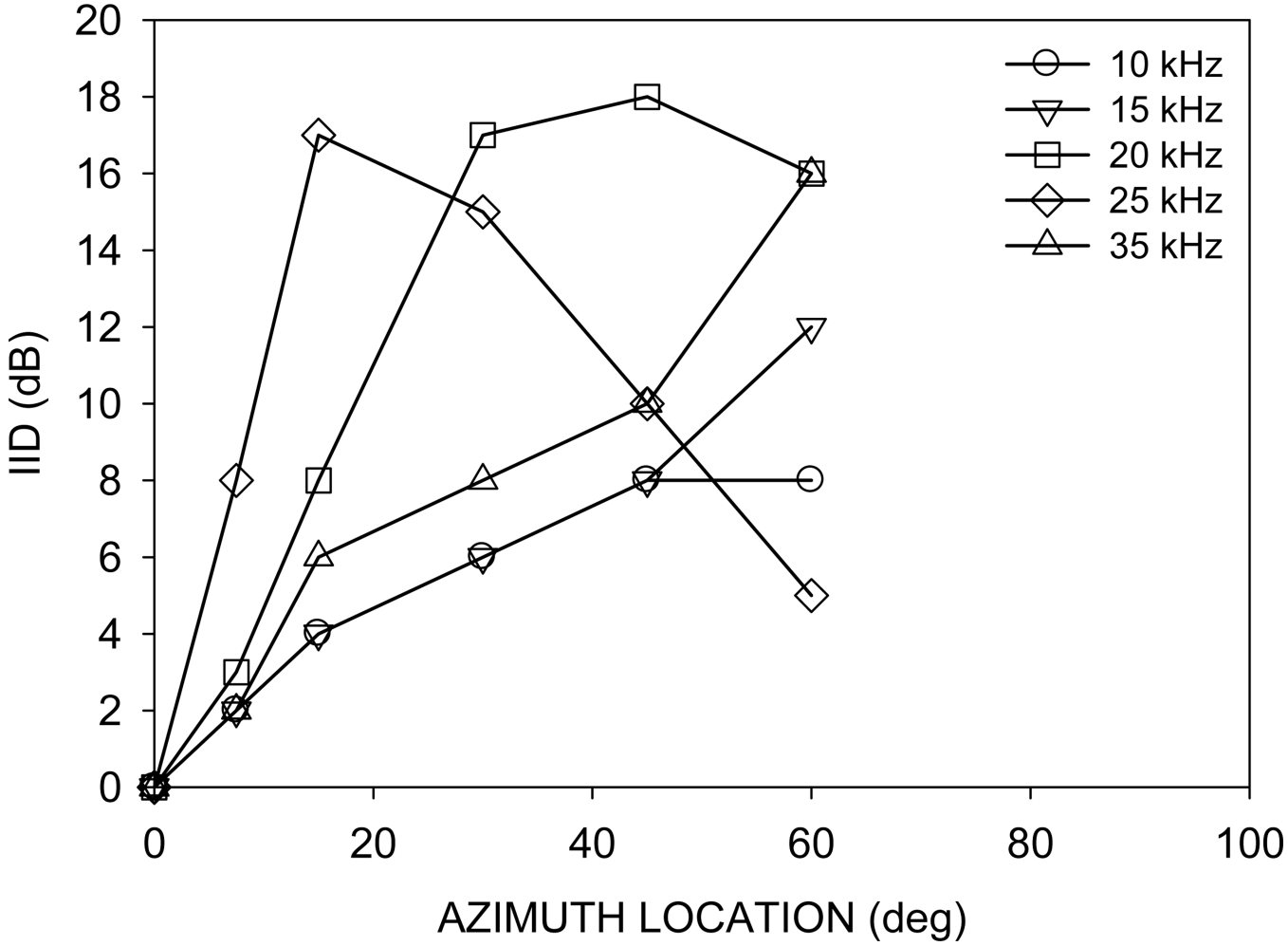

Figure 2. IID-Azimuth functions for five different frequencies

These data were adapted from Fuzessery (1996).

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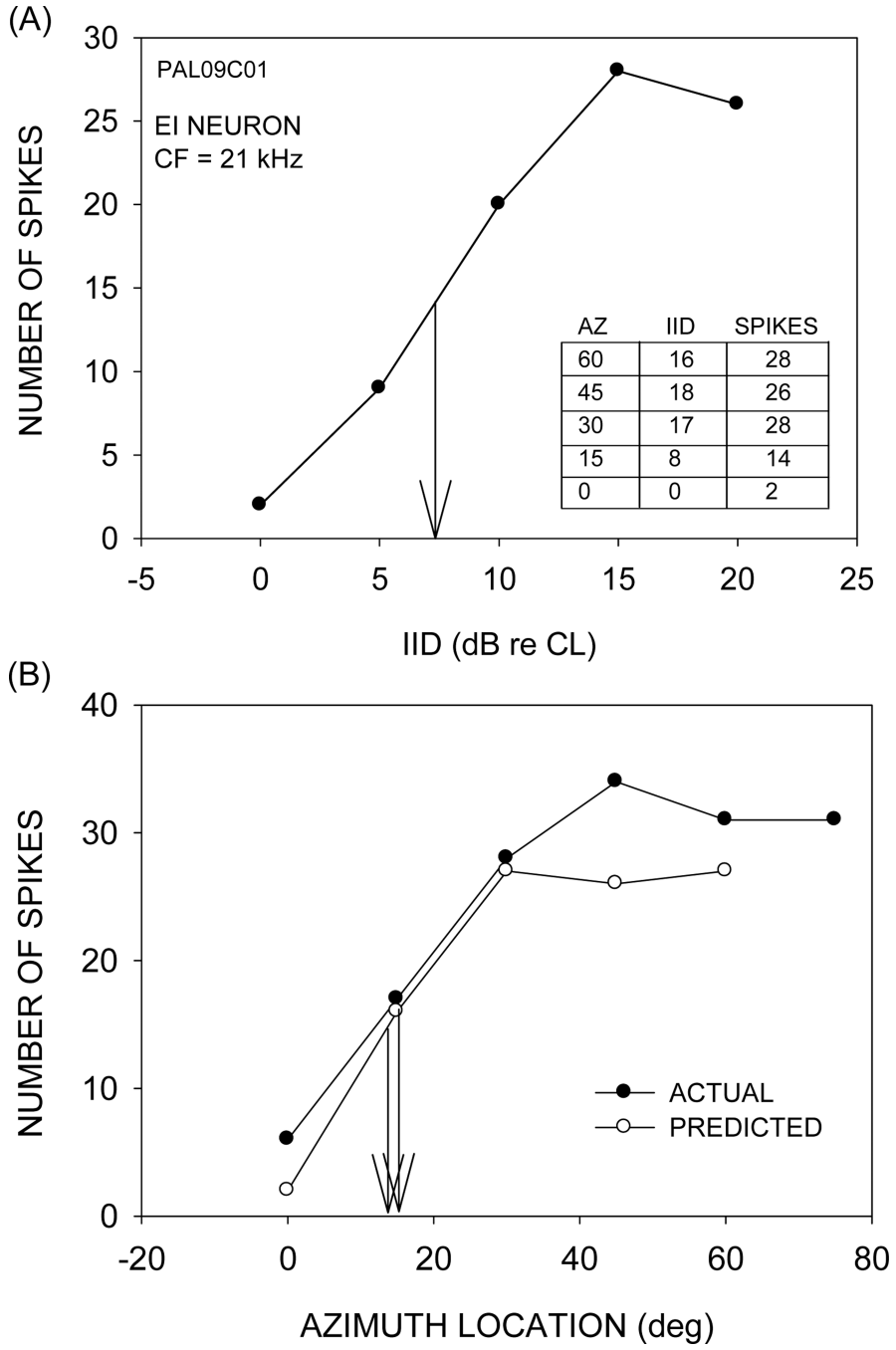

Figure 3. Predicting azimuth sensitivity of an EI neuron with a CF of 21 kHz using ear directionality, frequency tuning and IID sensitivity

(A) The IID sensitivity of the neuron was recorded using dichotic stimulation. The vertical arrow shows the IID at which response decreases to 50% of maximum. The table in the inset shows predicted number of spikes for each azimuth location based on the IID generated by a 20 kHz tone at that azimuth (using the IID-azimuth function for 20 kHz from Figure 2), and the IID sensitivity function of the neuron. The predicted azimuth function is plotted in **(B)** along with this neuron's actual azimuth function that was determined with free-field stimulation. The vertical arrows indicate the actual and predicted 50% azimuths, which were almost identical. IID and azimuth sensitivity functions were determined with broadband

noise. The predicted and actual ASF were similar (correlation coefficient, r = 0.96). Predicted ASFs in this and subsequent figures go up to only ±60° because the IID-azimuth relationship is only available for this range of azimuth.

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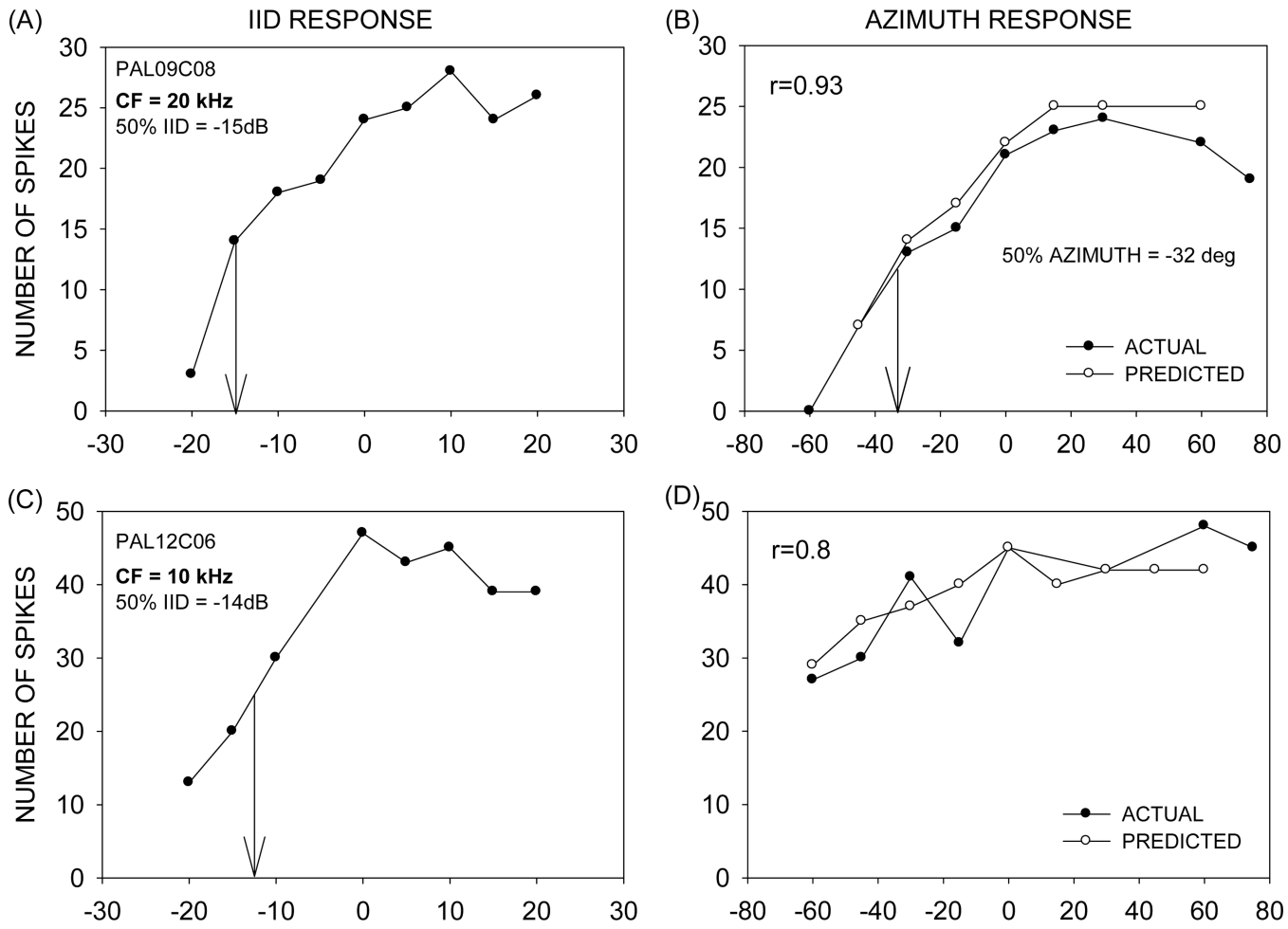

Figure 4. EI neurons can show different forms of azimuth selectivity depending on the CF and ear directionality at CF

(A) The CF of this EI neuron was 20 kHz and its 50% IID was - 15 dB (vertical arrow). **(B)** The predicted azimuth tuning indicated a sigmoid function with a 50% azimuth ~ −32° (vertical arrow). The actual azimuth function recorded was similar to the predicted curve (correlation coefficient, r = 0.93). **(C)** The CF of this EI neuron was 10 kHz, but the IID selectivity was similar to the EI neuron in 'A' (50% IID = −14 dB). **(D)** The predicted azimuth tuning was omnidirectional in that the response did not decline below 50% of maximum across the azimuths tested. The actual azimuth function was similar to the predicted function (r = 0.8).

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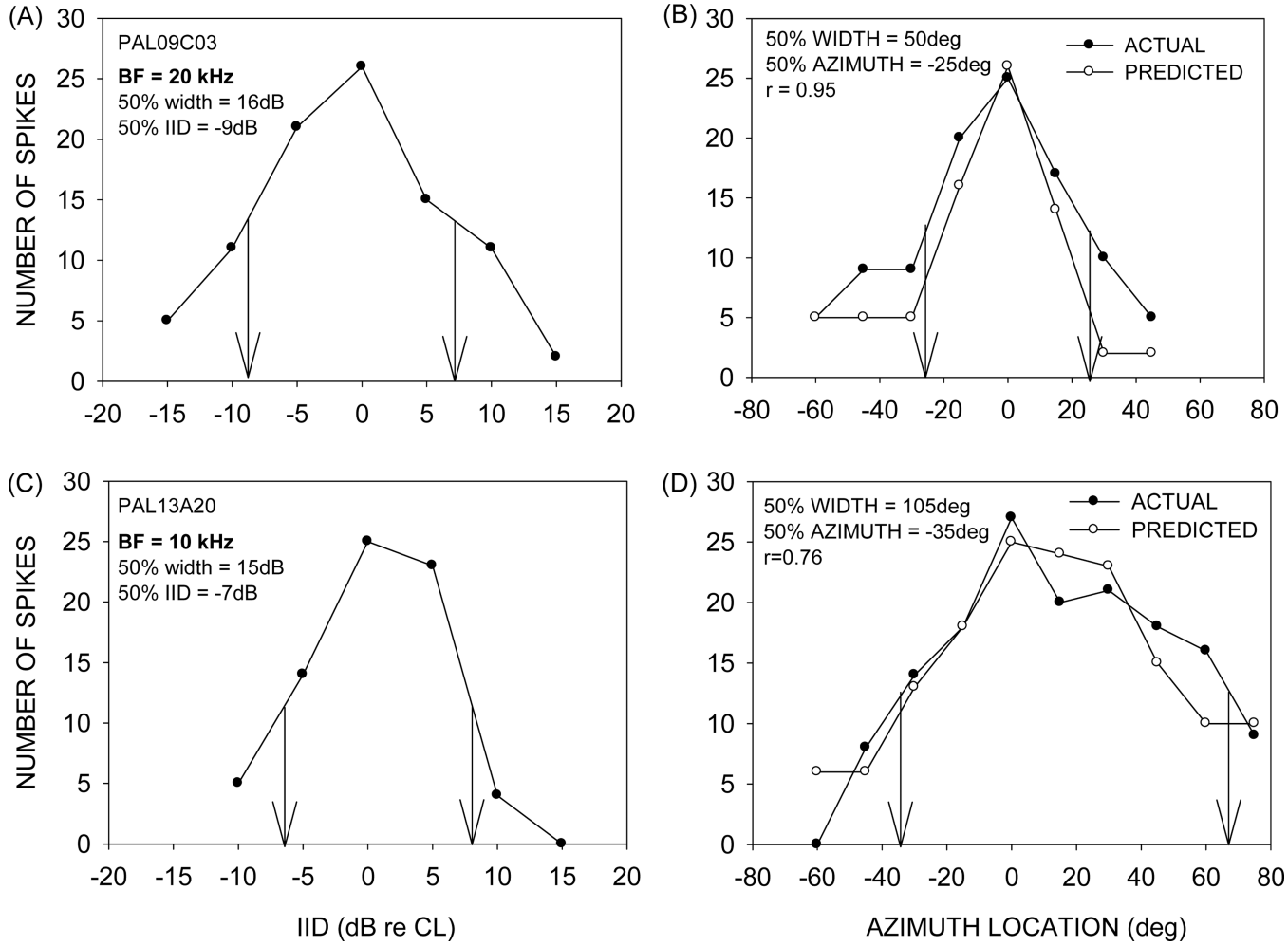

Figure 5. Predicting ASF of peaked neurons

(A) The peaked neuron shown here had a CF of 20 kHz. The 50% IID width (IID range between the two vertical arrows) and 50% IID are shown in the panel. **(B)** The predicted and actual azimuth functions show a peak at midline, 50% azimuth bandwidth (range of azimuths between the two vertical arrows) of ~50° and a 50% azimuth (left vertical arrow) ~ −25°. **(C)** This peaked neuron had similar IID selectivity as the neuron in (E), but a CF of 10 kHz. **(D)** The predicted azimuth function indicated a broader tuning compared to the previous neuron. The actual azimuth function matched these predictions.

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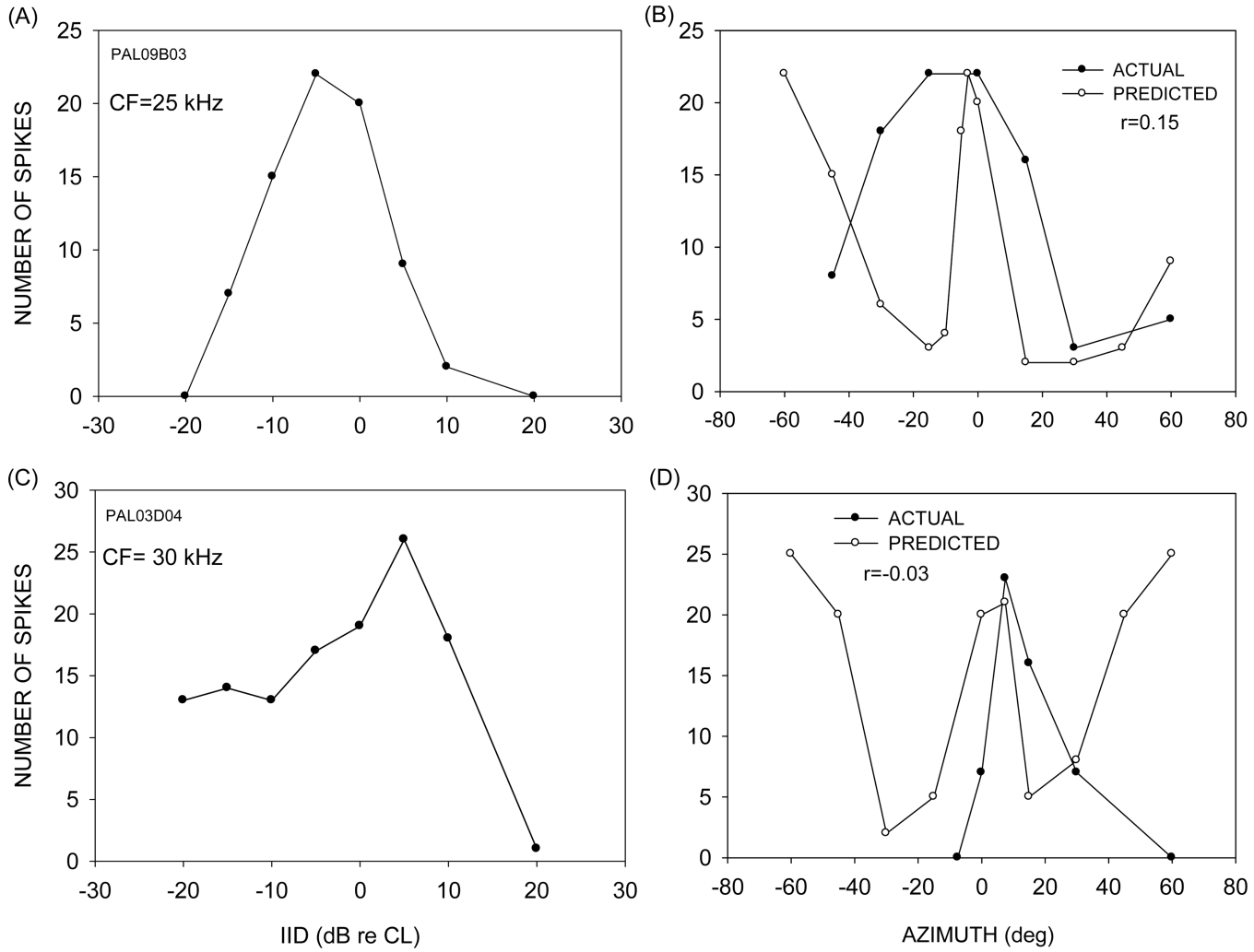

Figure 6. Peaked neurons with CF between 23–30 kHz were predicted to have multiple peaks

(A) IID selectivity of a neuron with CF=25 kHz. **(B)** The ASF is predicted to show two peaks, but the actual ASF tested with noise exhibited a single peak. **(C)** IID selectivity of a neuron with CF=30 kHz. **(D)** Using the ear directionality for 25 kHz predicts three peaks in the ASF. When tested with noise, only one peak was seen.

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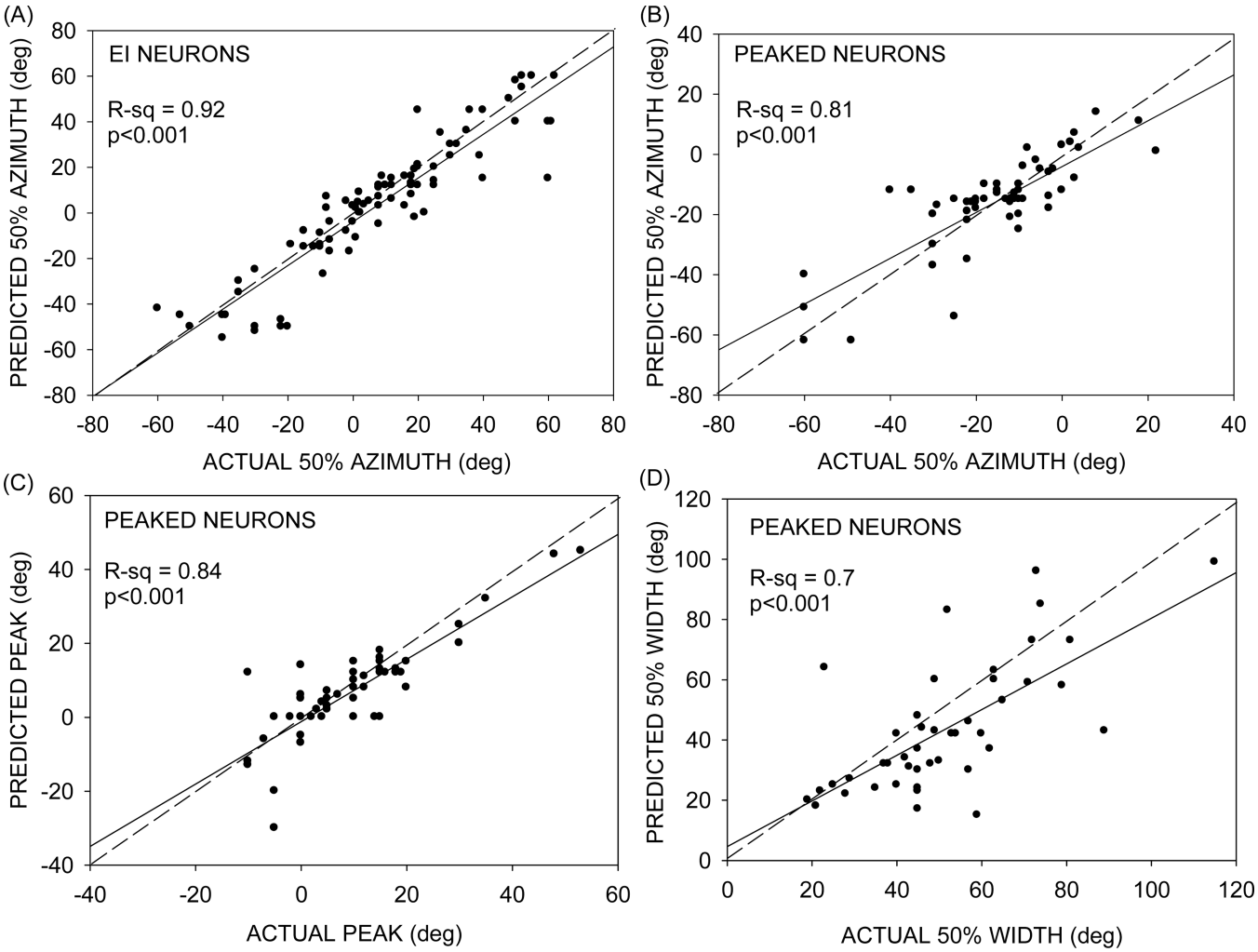

Figure 7. Azimuth tuning across the population of recorded neurons was predicted by interactions between IID, frequency tuning and ear directionality

(A) The predicted and actual 50% azimuth for EI neurons. The dashed lines in all panels indicate unity slope. **(B)** The predicted and actual 50% azimuth of peaked neurons. **(C)** The predicted and actual peak azimuth for peaked neurons. **(D)** The predicted and actual 50% azimuth bandwidth for peaked neurons.

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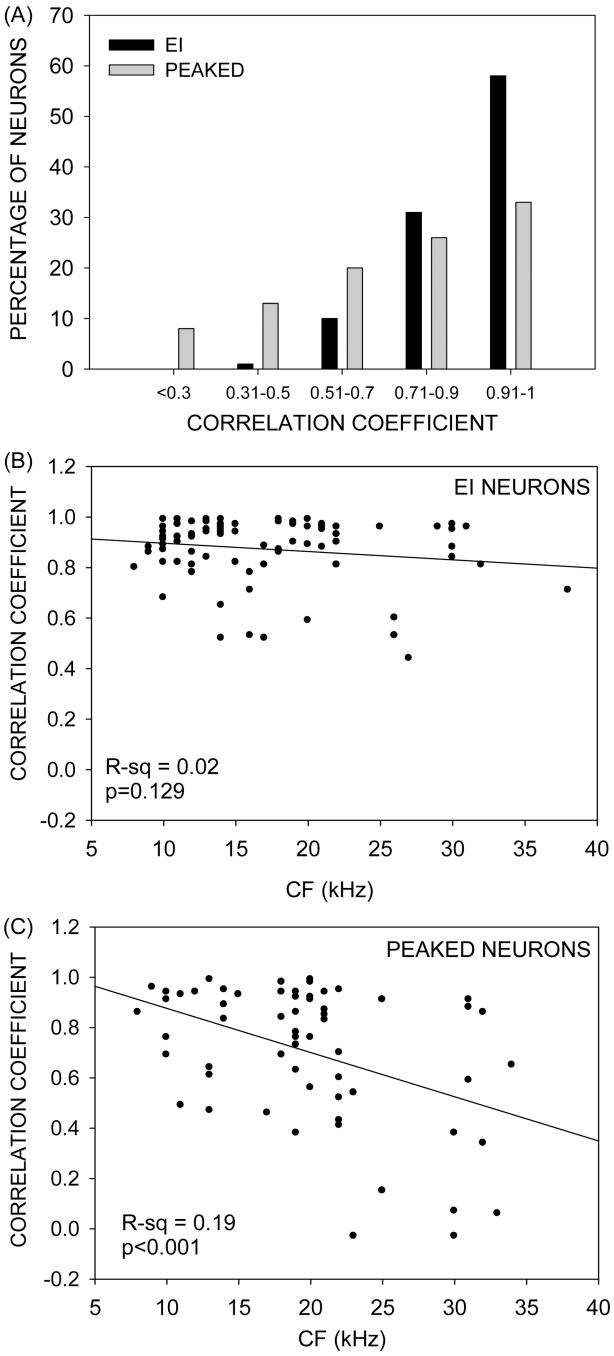

Figure 8. Predictability of noise-ASF in EI and peaked neurons

(A) Distributions of correlation coefficients in EI and peaked neurons. **(B)** There was no relationship between prediction accuracy in the EI neurons. **(C)** Correlation coefficients were high for most low-CF peaked neurons. There was a decline in prediction accuracy of high-CF peaked neurons.

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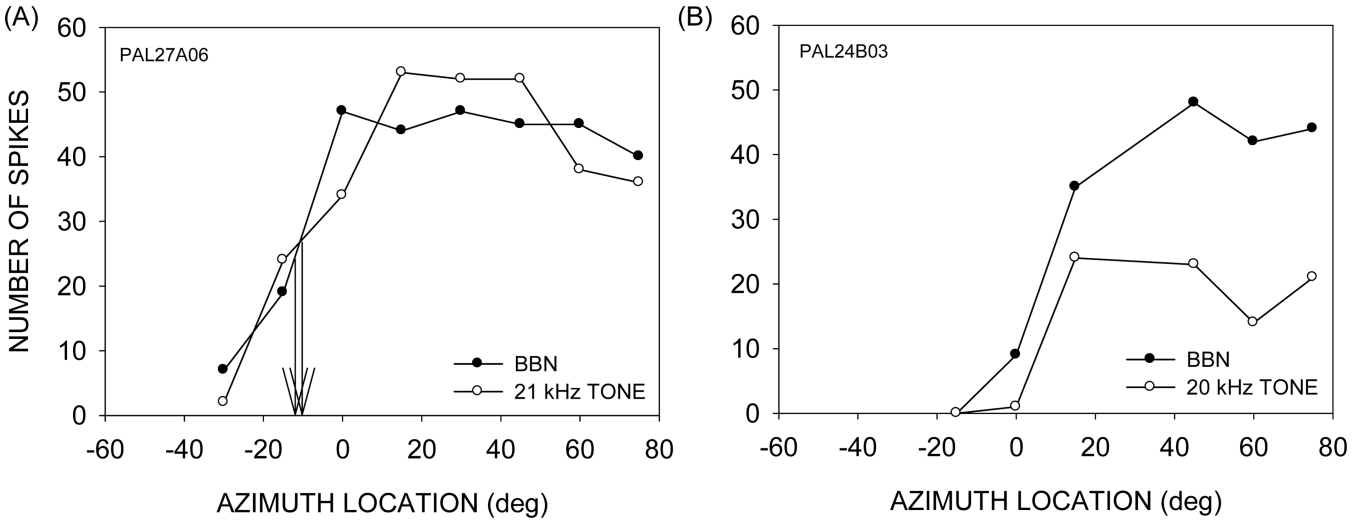

Figure 9. Azimuth sensitivity functions of EI neurons in response to broadband noise (BBN) and CF tone

(A) A neuron in which the ASFs were similar for noise and tones. The vertical arrows indicate the 50% azimuth, a measure of the medial boundary of ASF. The response magnitude shown in this and subsequent figures is for 20 repetitions of each stimulus. **(B)** A neuron which responded better to noise than to CF tone.

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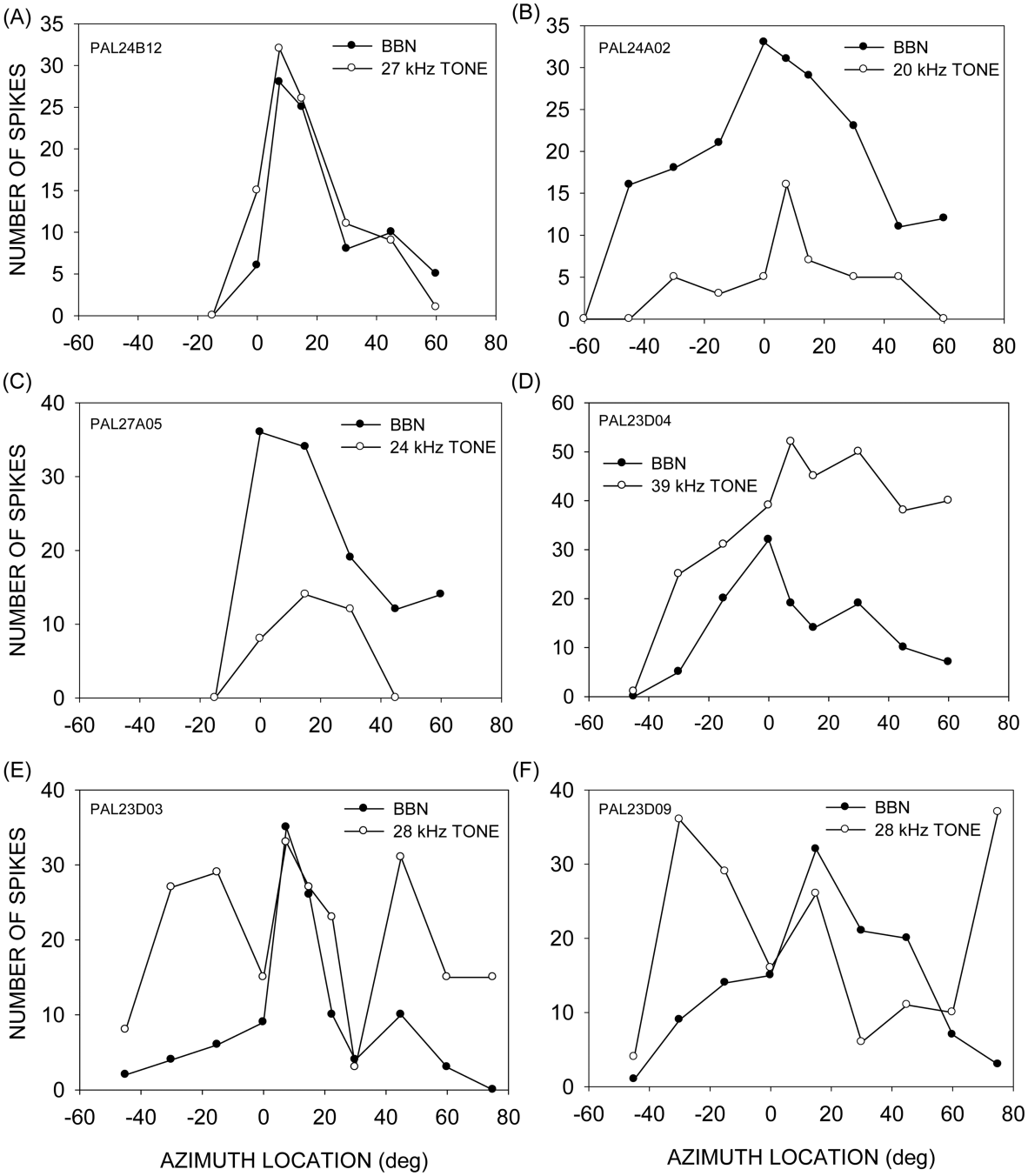

Figure 10. ASF of peaked neurons in response to noise and CF tones

(A) A neuron with almost identical ASF for the two stimuli. **(B, C)** Neurons with peaked response to both stimuli, but the response to CF tone was at least 60% below maximum responses to noise. **(D)** A neuron with peaked ASF to noise and sigmoid ASF to tone. **(E, F)** Neurons with single peaked ASF for noise and multi-peaked response to tones.