

Development shaped by cue reliability in the barn owl's auditory midbrain

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Abstract: Sensory systems display capability to preferentially choose stimuli based on their reliability at conveying accurate information. While previous reports have shown the ability of the brain to reweigh cues based on ongoing or dynamic changes in reliability, how the brain may learn and maintain neural responses to sensory statistics expected to be stable over longer time periods remain significant open questions of potential mechanisms underlying naturalistic biased perception. This study provides evidence that the barn owl's midbrain is shaped by permanent statistics experienced during development. The barn owl's midbrain features a topographic map of auditory space where neurons compute horizontal sound location from the interaural time difference (ITD). Previous work has shown that frequency tuning of these midbrain map neurons is correlated with the pattern of most reliable frequencies for the neurons' preferred ITD. This pattern of ITD reliability is due to the filtering properties of the head, primarily determined by the facial ruff in the barn owl. In this study, we found that the absence of a facial ruff led to a decrease in the reliability of high frequencies originating from frontal space. To test if the owl's frequency tuning of midbrain map neurons is driven by permanent changes in the pattern of ITD reliability, these neurons were recorded from adult owls, who had the facial ruff removed as juveniles, and from juvenile owls, before the facial ruff developed. In both groups, we found that frontally-tuned neurons displayed tunings to frequencies lower than reported in normal adult owls, consistent with the difference in ITD reliability between the normal and ruff removed conditions. Juvenile owls also exhibited more heterogeneous frequency tuning, suggesting developmental processes that refine tuning to match the pattern of ITD reliability. Additional recordings immediately upstream of the midbrain map displayed ITD tuned neural responses for all frequencies across the owl's normal hearing range. Broader analysis of the effects of ruff-removal on the acoustical properties of spatial cues indicated a dominant role of ITD reliability in driving the adaptive changes in frequency tuning. These results support the hypothesis that frequency tuning in the midbrain map is developmentally adapted to permanent statistics of spatial cues, implementing probabilistic coding for sound localization.

Introduction

To accurately and efficiently perceive and react to the environmental scene, the brain must rely on the sensory cues that are naturally most reliable. The ability of the brain to quickly weigh ongoing reliability of sensory cues within different modalities has been well documented (Jacobs and Fine, 1999; Rosas et al., 2005; Fetsch et al., 2012; Dacke et al., 2019). However, in instances where sensory cue reliability is anticipated to be relatively stable and predictable, predetermined weights of sensory cues may be optimal. An example of this neural operation is particularly seen in human speech processing, where reliable phonetic properties are stable across speakers (Holt and Lotto, 2006; Iverson et al., 2003; Toscano and McMurray, 2010), and may only change over the course of decades (Toscano and Lansing, 2019). While extensive research has shown changes in neural responses induced by sensory statistics (David et al., 2004; Dean et al., 2005, Fetsch et al., 2012), properties and fundamental mechanisms of this adaptive coding is important for understanding the bases of optimal brain function. In this report, we used the barn owl as a model organism of sound localization to test whether and how the brain develops and adapts to changes in stimulus reliability by altering the tuning properties of sensory neurons in a manner predictive of these relevant natural statistics.

The barn owl is a highly specialized species, able to hunt in the dark solely using auditory stimuli (Payne, 1962). Barn owls use interaural time difference (ITD), the delay for a sound to reach one ear before the other, and interaural level difference (ILD), the difference in sound intensity between the two ears, to, respectively, compute sound location in azimuth and elevation (Moiseff and Konishi, 1981; Moiseff, 1989). ITD and ILD are represented in the barn owl's external nucleus of the inferior colliculus (ICx), creating a topographic midbrain map of sound location (Knudsen and Konishi, 1978). The barn owl shows specialization in its ability to compute ITD from frequencies as high as 10 kHz (Wagner et al., 1987; Carr and Konishi, 1990; Köppl, 1997). The reliability of ITD is described as how corruptible the ITD cue is to concurrent sounds, which is determined by the acoustical properties of the head, summarized in the head-related transfer function (HRTF) (Wightman and Kistler, 1989; Poon and Brugge, 1994; Brugge et al., 1994; Hartung and Sterbing, 1997; Keller et al., 1998), which describes the directional filtering that the external ears induce onto incoming sounds. These filtering properties vary across sound source location relative to the ears and the sound frequency. HRTF-based analysis has indicated that for sounds originating from frontal locations, ITD cues derived from the higher frequencies of the barn owl's hearing range are less susceptible to corruption from concurrent sounds; while for sounds from peripheral space, ITD cues derived from low frequencies are less susceptible to corruption (Cazettes et al., 2014). Consistent to the hypothesis of anticipated coding of sensory cue reliability, neurons in the ICx are tuned to the frequencies that are most reliable for their preferred ITD, even if the ongoing statistics are briefly changed (i.e. using earphones which bypass the head's filtering properties) (Cazettes et al., 2014). A relationship between frequency tuning and ITD tuning has been reported in the midbrain and brainstem of mammalian models as well, however this was proposed to be related to ITD neural coding and detection properties rather than anticipated ITD reliability (McAlpine et al., 2001; Hancock and Delgutte, 2004; Day and Semple, 2011; Bremen and Joris, 2013). In contrast, recent findings show that human spatial perception is driven by natural ITD statistics across frequencies, including ITD variability induced by concurrent sounds (Pavão et al., 2020), suggesting commonalities between humans and owls in the anticipation of ITD cue reliability based on acoustic properties of the head. Overall, these previous studies indicate that the predictive coding of natural ITD reliability is inherent in the brain of humans and owls, but directly testing development and causality of this statistical property on the frequency tuning of neurons representing auditory space and whether this coding is innately fixed or experience dependent remain open questions.

In the barn owl, the facial ruff, a disc of stiff feathers that surrounds the head, acts as an external ear, modulating the gain and phase of sounds reaching the eardrums (Coles and Guppy, 1988; Keller et al., 1998; Von Campenhausen and Wagner, 2006; Hausmann et al., 2009). Because the filtering effects of the facial ruff are direction and frequency dependent, we sought to assess whether the removal of the facial ruff would induce a

change in the pattern of ITD reliability, and whether the barn owl's auditory system adapts to these long-term changes. Previous reports studying the facial ruff removal in barn owls have focused on changes to the ILD (i.e. elevational) tuning, while noting few changes to the ITD tuning of neurons in the owl's midbrain map of auditory space (Knudsen et al., 1994). However, to our knowledge, there have been no studies that assessed whether ITD reliability and frequency tuning of midbrain neurons changed after facial ruff removal.

Based on these open questions, comparative analysis of ITD reliability was conducted using HRTFs from owls before and after facial ruff removal. Following this, the frequency tuning of neurons was measured in the ICx of barn owls where the facial ruff was removed during juvenile development. Additionally, the earliest-to-date recordings of the developing ICx were conducted in normal juvenile owls before the facial ruff develops but after hearing onset. We found frontally-tuned ICx neurons of normal and ruff-removed juvenile owls were predominately tuned to frequencies lower than the observed frequency tuning in normal adult owls. These changes in both ruff-removed and juvenile owls are consistent with estimated differences in ITD reliability between normal and ruff-absent conditions. These results indicate that tuning to high frequencies of frontally-tuned midbrain map neurons is developed and driven by experience during early life in the barn owl. In addition, recordings in the region immediately upstream of ICx confirmed that the ability to compute ITD from high frequencies (Carr and Konishi, 1990) was preserved in ruff-removed owls. Overall, this study demonstrates that the owl's sound localization pathway implements an experience-dependent representation of anticipated ITD statistics in the midbrain map of space, supporting the idea of the brain's adaptive anticipation of natural high-order sensory statistics.

Methods

HRTF Analysis

Pairs of HRTFs from five barn owls, with and without the facial ruff, were provided by Dr. Wagner (von Campenhausen and Wagner, 2006). The computation of estimated ITD reliability based on these HRTFs was conducted using a previously reported method (Cazettes et al., 2014). Briefly, two broadband signals, a target and masker, with flat spectrum across the owl's ITD detection frequency range (0.5 to 10 kHz; Köppl, 1997; Carr and Konishi, 1990), were convolved with head-related impulse-responses at each sampled sound source location of available HRTF datasets (azimuth: $\pm 160^\circ$ at 20° steps, elevation: 0°). The summed target and masker sounds were passed through a gammatone filter-bank (1-8 kHz, 0.2 kHz steps) as previously described (Fischer et al., 2009). Due to the sharp frequency selectivity of ITD detection units (Carr and Konishi, 1990; Fischer et al., 2011), interaural phase difference (IPD) of narrow frequency bands, which ITD is computed from, was used for this analysis. IPD was calculated for each frequency as the location of the maximum cross-correlation between the left and right inputs. To estimate reliability of ITD cues across frequency and locations, the circular standard deviation of IPD was computed for each target location, across all frequency ranges and masker locations. This procedure was repeated 10 times for each individual HRTF, and the circular standard deviation of IPD was averaged across repetitions. IPD reliability was calculated as the inverse standard deviation of the IPD (Landy et al., 2011).

For testing whether observed changes in neuronal tuning properties could be due to changes in spatial tuning, rather than ITD reliability, the same HRTFs from owls before and after ruff-removal were used to compute the ITD and ILD across frequency and spatial locations sampled in these HRTFs. This analysis was conducted for tones within the range of frequencies where changes in tuning were observed (3-7 kHz, at 1 kHz steps), to estimate changes in ITD/ILD mappings for each tone. Model neuronal responses tuned to frontal space were constructed using the following equations for ITD and ILD, respectively:

$$a_n(ITD) = a_{max} \frac{(e^{\cos(2\pi f(ITD-\mu_n))} - e^{-1})}{e^1 - e^{-1}}$$
$$a_n(ILD) = a_{max} e^{-\frac{(ILD-\delta_n)}{\sigma}}$$

where f is the tone frequency (in Hz), σ is the width parameter for the ILD tuning. The neuron's best ITD, μ_n , and best ILD, δ_n , were defined as 0 μ s and 0 dB, respectively. The maximum spike rate for both tuning curves was 10 spikes per second, set by a_{max} . The spatial responses for ITD and ILD were then multiplied, as consistent with previously reported mechanisms of ICx neurons (Peña and Konishi, 2001) and normalized. This resulted in a full spatial tuning map of a frontally-tuned neuron across frequencies.

Facial Ruff Removal

Two juvenile barn owls were hand-raised (one starting at 14 days old and one at hatching). Facial ruff was trimmed as it developed, starting at approximately one month old. As they were comfortable with humans, trimming occurred as owls rested, without the need of anesthesia or stress. Surgeries were not performed on these owls until 3 months of age, approximately one month after sexual maturity.

Surgery

Data were collected in two adult owls that had undergone facial ruff removal (see above) and 2 normal juvenile owls. Surgeries of adult owls were performed as previously described (Wang et al., 2012; Ferger and Shadron et al., 2021). Briefly, owls were first anesthetized with intramuscular injections of ketamine hydrochloride (Ketaset; 20 mg/kg) and xylazine (AnaSed, 4 mg/kg), then injected with lactated Ringer's solution (10 mL, s.c.). Supplemental injections of ketamine and xylazine were provided every 1-2 hours as needed to maintain sedation. In a preliminary surgery, a stainless-steel head-plate and reference post were attached to the skull using dental acrylic. Craniotomies were performed within dental acrylic wells above the coordinates for the auditory midbrain. During recordings, a small incision is made in the dura mater to insert electrodes. At the end of each recording, a sterile piece of plastic was fitted to cover the craniotomy, which was then covered in a fast-curing silicone elastomer (polyvinyl siloxane; Warner Tech Care). The owl was then administered carprofen (Rimadyl; 3 mg/kg, i.m.) to reduce pain. Recordings were repeated every 14 d or longer to allow proper recovery.

Because of the development of the skull precluding early surgeries in juvenile owls, the head-plate implantation surgery and electrophysiology recording were performed on the same day in these animals. Recording surgeries were performed at 42- and 44-days post hatching. At this time point, the juvenile barn owls are slightly above normal adult weight (Haresign and Moiseff, 1988), requiring administered anesthetics dosages similar to adults. Both owls recovered and were standing within one hour of surgery completion, and fully developed normally. Subsequent recordings were performed between 130 and 190 days old to verify normal frequency tuning in adulthood (observed but data not shown).

All procedures complied with the National Institute of Health guidelines and were approved by the institutional animal care and use committee of the Albert Einstein College of Medicine.

Acoustical stimuli

All experiments were performed in a sound-attenuating chamber (Industrial Acoustics). Stimuli were generated by System II hardware (Tucker-Davis Technologies), controlled by a computer with custom created software. Dichotic stimuli were presented through custom-built earphones containing a speaker (model 1914, Knowles) and microphone (model EK-23 024, Knowles). Earphones were calibrated to adjust for irregularities in phase and amplitude across the owl's hearing range, from 0.5 to 13 kHz.

Acoustic stimuli consisted of either broadband (0.5-11 kHz) or tonal signals with a 100 ms duration and 5 ms rise-fall time. For tonal stimuli, a step-size of 200 Hz was used, between 0.5 and 10 kHz. A 300 ms inter-stimulus interval was used to prevent response adaptation effects (Singheiser et al., 2012; Ferger et al., 2018).

Electrophysiological recordings

Single units were recorded extracellularly using 1 M Ω tungsten electrodes (A-M Systems) and amplified by a DP-301 differential amplifier (Warner Instruments). Electrical traces were recorded by System II hardware (Tucker-Davis Technologies) and custom-made software. The ICx and ICCLs midbrain regions were targeted stereotaxically (Knudsen and Knudsen, 1983). In addition, neurons were distinguished based on response properties. Single-units were isolated based on the spike amplitude and the uniformity of spike shape. Nevertheless, neurons close to each other in the map are known to have similar tuning properties (Cazettes et al., 2014). Specifically, ICx neurons display tuning to both ITD and ILD, with side-peaks in ITD tuning occurring at the reciprocal period of the unit's best frequency (Takahashi and Konishi, 1986; Fujita and Konishi, 1991; Wagner et al., 2007; Cazettes et al., 2016). The response rate of these side-peaks was usually suppressed as compared to the main peak (Takahashi and Konishi, 1986; Mazer, 1998; Pena and Konishi, 2000). Recordings in ICCLs were determined by their known change in the preferred frequency tuning of neurons: along the dorsal-ventral axis, tuning to frequency increases with depth (Knudsen and Konishi, 1978; Takahashi et al., 1989; Wagner et al., 2002). Additionally, ICCLs neurons display broad contralateral ILD tuning and side-peaks in ITD tuning that are indistinguishable in response rate to the main peak (Takahashi et al., 1989; Fujita and Konishi, 1991; Adolphs, 1993; Wagner et al., 2007). A minimum of 200 μ m between units was used to ensure isolation of subsequently recorded neurons.

Data Analysis

For each stimulus parameter, a response curve was computed by averaging the firing rate across stimulus repetitions. A Gaussian curve was fit onto the main peak of ITD tuning curve, with the best ITD determined by the maximum of the Gaussian. The main peak was defined as the peak in the ICx curve with the largest response, as the side peaks in ICx are usually much smaller relative to the main peak (**Fig. 2**). In ICCLs, as there is no side peak suppression due to the narrow frequency tuning (Wagner et al., 1987; Fujita and Konishi, 1991), the peak corresponding to the neurons' characteristic delay was determined during the recording by comparing neurons along the dorsal-ventral axis, which share a characteristic delay but show different frequency tuning, which manifests in neurons along this axis sharing one peak response at their characteristic delay, with other peaks misaligned (Wagner et al., 1987; Fujita and Konishi, 1991; Wagner et al., 2007). Thus, the peak corresponding to preferred ITD was defined ad hoc for each recording and ITDs not comprising the main peak were ignored for fitting the Gaussian.

As previously reported (Cazettes et al. 2014, 2016), the frequency tuning range was defined as the range of frequencies that elicited more than 50% of the maximum response. The lower and upper edges of this range correspond to the lowest and highest frequencies of the response range. Because ICx frequency tuning curves are generally broad and without a single peak, the best frequency was defined as the mean of the lowest and highest frequencies of the frequency range.

Pearson correlation coefficients were calculated for each experimental group, pooled across birds. Student's t-test was used to compare regression slope values. Mann-Whitney U-test was used to compare frequency tunings for frontal neurons between groups. Effect sizes were derived from the rank-biserial correlation, which uses the U statistic to compute the overlap between groups by calculating the correlation between the data and its rank in the Mann-Whitney U-test, on a scale of 0-1 (1 indicating no overlap).

Results

To first determine how ITD reliability changes after facial ruff removal, 5 HRTFs from barn owls before and after facial ruff removal were used, from the dataset originally published in von Campenhausen and Wagner (2006). The difference in phase for a sound reaching both ears was computed as the interaural phase difference (IPD), the cue underlying ITD computation. Thus, IPD reliability underlies ITD reliability. A signal's phase can be corrupted by concurrent sounds, altering the IPD in a frequency dependent manner (Cazettes et al., 2014). For a given sound source and frequency, the amount of corruption varies with the location of the concurrent sound. IPD reliability can be computed as the inverse of the standard deviation of this variability (Landy et al., 2011; Cazettes et al. 2014). To this end, we calculated the IPD for a given sound source across different locations of a second sound source using the HRTFs before and after facial ruff removal, on a frequency-by-frequency manner. Before ruff removal, the pattern of higher IPD reliability for high and lower frequencies in, respectively, frontal and peripheral locations (**Fig. 1a**) was largely the same as previously reported (Cazettes et al., 2014). After ruff removal, there was a sharp decrease in the reliability of high frequencies coming from frontal locations, with minimal changes elsewhere (**Fig. 1b**). Computing the difference in reliability between the two conditions highlights that after ruff removal, the changes in reliability were stronger for frequencies above 4 kHz coming from within $\pm 45^\circ$ of azimuth location (**Fig. 1c**). Previous reports show that there is a uniform decrease in gain of sound level across frequencies after facial ruff removal (von Campenhausen and Wagner, 2006), nullifying the interpretation that this is merely due to a loss of gain specifically at these higher frequencies. These acoustical simulations suggest that if ICx frequency tuning is driven by IPD reliability, and by extension ITD reliability, then we should expect lower frequency tuning in frontally-tuned ICx neurons in owls raised without the facial ruff.

To test if frequency tuning in the barn owl's ICx is shaped by ITD reliability, we modified ITD reliability by trimming the facial ruff from two barn owls as it grew in. While previous experiments have studied the effects of physical and virtual removal of the facial ruff on the spatial tuning of ICx neurons and sound localizing behavior (Knudsen et al. 1994; Hausmann et al. 2009), none of these reported an effect on neuronal frequency tuning in ruff-removed owls. Towards this goal, once these ruff-removed owls reached adulthood (6 months of age), we performed electrophysiological recordings across the ICx. We recorded 117 ICx neurons across the two owls. ITD and frequency tunings were then assessed for each neuron. An example ICx unit is shown in Figure 2. Typical ICx neurons display sharp tunings to ITD and ILD, with relatively broad frequency tuning width (>2 kHz) (Moiseff and Konishi 1983; Takahashi and Konishi 1986). Individual ICx neurons recorded from ruff-removed owls had typical ITD and ILD tunings. However, on a population wide scale, ILD tuning was correlated with ITD tuning (**Fig. 2d**), consistent with previous reports of facial ruff removal (Knudsen et al., 1994).

The correlation between ITD and frequency was markedly different in the ruff-removed owls compared to normal adult owls. In normal adult owls, neurons tuned to ITDs near $0 \mu\text{s}$, or frontal locations, are driven by high frequencies, while neurons tuned to large ITDs, or peripheral locations, are driven by low frequencies ($r^2 = 0.75$, $p = 5.6\text{e-}55$) (Cazettes et al., 2014). In the ruff-removed owls, there was a shallower slope of the linear correlation between ITD and frequency ($r^2 = 0.18$, $p = 1.6\text{e-}06$, **Fig. 3**). These two correlations were significantly different (t-test: $t = 8.97$, $p = 3.0\text{e-}19$). The y-intercepts of the regression lines, which can be used to compare the frequency tuning of frontal neurons, were also significantly different (normal owls = 5.6 kHz, ruff-removed owls = 4.6 kHz; $t = 7.56$, $p = 4.0\text{e-}14$). A Mann-Whitney U-test comparing the best frequency tuning of the frontally-tuned neurons, defined here as preferring ITDs $\leq 30 \mu\text{s}$ ($\sim 10^\circ$ eccentricity), produced consistent results ($u = 63$, $p = 7.3\text{e-}08$).

One potential cause of this change in frequency tuning could be due to disrupted ITD detection mechanisms induced by a change in gain of sound level, rather a change in ITD reliability. To test for this alternative, electrophysiological recordings of the lateral shell of the central nucleus of the inferior colliculus (ICCLs), the immediate upstream region of ICx, were performed. ICCLs neurons also display a topographic mapping of ITD, but, critically, are narrowly tuned to frequency, which increases along the dorsal-ventral axis, with tunings

spanning the barn owl's hearing range of 0.5-9 kHz (Knudsen and Konishi, 1978; Wagner et al., 2007). We recorded 43 ICx neurons from the same two ruff-removed owls in adulthood and found the normal frequency tuning range (1-8 kHz) across ITD selective neurons (**Fig. 4**). In particular, ICx neurons tuned to high frequencies and frontal ITDs in ruff-removed owls were observed (**Fig. 4**). This suggests that the auditory system is still able to use high frequencies to compute ITDs, but this is not passed onto the ICx.

Alternatively, the change in the frequency tuning of frontal neurons could be due to a remapping of ITD and ILD in a frequency-dependent manner following facial ruff removal. To test this possibility, we modeled the spatial tuning of frontally-tuned neurons across frequencies. Based on HRTFs from von Campenhausen and Wagner (2006), the ITD and ILD was computed for each spatial location sampled, across frequencies (described in Methods section). These ITDs and ILDs were passed through a model ICx neuron tuned to 0 μ s ITD and 0 dB ILD to simulate the neuron's response across space (**Fig. 5a**). This analysis was performed using the HRTFs of owls before (**Fig. 5b**) and after (**Fig. 5c**) facial ruff removal. In the ruff-removed condition, spatial tuning to elevation widened dramatically, as expected from previous reports (Knudsen et al., 1994; von Campenhausen and Wagner, 2006; Hausmann et al., 2009). However, we did not find any widening of azimuthal spatial tuning nor any loss in the ability to use high frequencies to compute ITD. In fact, after facial ruff removal, we noticed an increase in the ability to use high frequencies for frontal space, likely due to ILD being correlated with azimuth after facial ruff removal (Knudsen et al., 1994; **Fig. 2d**). These results further support the hypothesis that the barn owl's frequency tuning is driven by ITD reliability, rather than solely spatial tuning.

We next sought to determine the frequency tuning of juvenile owls before the facial ruff fully developed. Recordings were performed from two juvenile owls at 42- and 44-days post hatching. These time points corresponded to ongoing ruff development, as the ruff feathers were still within the sheathed stalks, with the ruff not fully developing until approximately 60 days post hatching (Haresign and Moiseff, 1988). To our knowledge, these recordings are the earliest performed during the development of the barn owl's midbrain. We were able to identify 39 ICx neurons, which showed typical topographic ITD tuning, as well as latencies and thresholds. However, we found that ILD tuning did not change with depth along the dorsal-ventral axis, as observed in normal adult ICx (Mogdans and Knudsen, 1993). Because the relationship between ILD and elevation is determined by the facial ruff (Knudsen et al., 1994; von Campenhausen and Wagner, 2006), this provided further evidence that the facial ruff was still underdeveloped in these juvenile owls. There was no correlation between ITD and best frequency in the juvenile owls ($r^2 = 0.18$, $p = .28$), although this may be attributed to the lack of recorded neurons tuned to ITDs $> 120 \mu$ s (**Fig. 6**). However, when we compared the best frequency tuning of frontal neurons (best ITDs $\leq 30 \mu$ s), there was a significant difference between the juvenile owls and both the normal ($u = 558$, $p = 5.9e-04$) and ruff-removed ($u = 281$, $p = 3.2e-03$) adult owls (**Fig. 7a**). The mean best frequency of the frontal neurons in juvenile owls was 4.9 kHz, which is between that of normal and ruff-removed adult owls. The size of these differences between juvenile owls and both normal and ruff-removed owls, measured by biserial rank correlation, further supported this result ($r = 0.55$ and $r = 0.43$, respectively). With a mean best frequency of 4.9 kHz for frontally-tuned neurons, this suggests that the neurons in the ICx of juvenile owls do not begin development tuned primarily to high frequencies, but that this develops as the facial ruff develops. Later recordings done in these same birds' ICx, performed in the 160-200 days old age range, display the typical high frequency tuning for frontally-tuned neurons (data not shown), supporting this hypothesis.

While there were clear differences in best frequency across juvenile, ruff-removed and normal adult owl groups, we found additional differences when comparing the high and low boundaries of each neuron's frequency tuning (see **Fig. 2b** for definitions). While there was a significant difference in the neurons' high frequency bounds between the juvenile and ruff-removed owls ($u = 206$, $p = 6.2e-05$), there was no significant difference between the juvenile and normal adult owls ($u = 409$, $p = .4$). In contrast, we saw the opposite for the low frequency bounds: there was a difference between the juvenile and normal adult owls ($u = 600$, $p = 3e-05$), but no significant difference between the juvenile and ruff-removed owls ($u = 466$, $p = .7$). These results are summarized in **Figure**

7b and suggest that the juvenile owls have ICx neurons that are more broadly frequency tuned than normal or ruff-removed adult owls, which then gets refined during development. In accordance with this, we found significant differences in the frequency-induced response range between the juvenile owls and both the normal adult owls ($u = 190$, $p = .003$) and ruff-removed adults ($u = 221$, $p = 1.6e-04$), but not between the normal and ruff-removed adults ($u = 418$, $p = .73$) (**Fig. 7c**). In addition, analysis of ITD tuning width of frontal neurons showed significantly broader tuning width in ruff-removed ($u = 72$, $p = 1.2e-07$) and juvenile owls ($u = 188$, $p = .0028$), consistent with their tuning to lower frequencies and the known relationship between frequency tuning and ITD tuning width of midbrain neurons (Takahashi and Konishi, 1986; Wagner et al., 2002) (**Fig. 7d**). These results indicate that the juvenile owls show larger heterogeneity and broadening of frequency tuning in the ICx, which adapts based on the pattern of ITD reliability that the bird experiences along early life.

Discussion

We report that in barn owls that developed without a facial ruff, there is an altered relationship between the tunings to ITD and frequency relative to previous reports from normal adult barn owls (Knudsen, 1984; Cazettes et al., 2014). These ruff-removed barn owls showed on average a decrease in frequency tuning for frontally-tuned ICx neurons, from 6 kHz to 4.5 kHz, consistent with the analysis of the effect of acoustical properties of the owl's head on ITD statistics. The changes in ITD reliability and correlated frequency tuning support the hypothesis of an adaptive predictive coding of this ITD statistic in the owl midbrain along normal developmental and experimentally-altered changes in the acoustical properties of the head.

The earliest recordings of the barn owl's midbrain, conducted in this study at 42 and 44 days after hatching, show tuning to ITD and ILD (**Fig. 6**). This is in line with previous reports on the auditory brainstem which indicate that the circuitry underlying ITD and ILD tuning are present (albeit immature) and that these binaural spatial cues are audible to the birds at this time point (Carr and Boudreau, 1996; Köppl and Nickel, 2007; Kraemer et al., 2017). However, consistent with reports of disrupted ILD tuning after facial ruff removal (Knudsen et al., 1994), ILD tuning was correlated with azimuthal tuning in the juvenile owls (**Fig. 4**). This ILD tuning pattern indicates that the facial ruff was underdeveloped at this time, thus not contributing to auditory processing. The best frequency tuning we found for frontally-tuned ICx neurons in juvenile owls were lower than what has been found in normal adults (Cazettes et al., 2014), but higher than what is found in ruff-removed owls (**Fig. 7**). This suggests that at this time point, the barn owl's ICx frequency tuning is already beginning to be shaped by ITD reliability, which may change rapidly in response to the facial ruff's development. Consistent with this hypothesis, we found that juvenile ICx neurons had slightly wider and heterogenous frequency tuning widths than either the normal adult or ruff removed adults, covering the ranges of both adult groups, but not a width that would indicate that each of these ICx neurons were sampling the entire frequency range available to the barn owl for ITD detection (0.5-9 kHz). This suggests high heterogeneity in the juvenile owl's ICx frequency tuning at the time that the facial ruff would begin to grow in. As the owl develops, these individual neurons may sharpen their frequency tuning to match the pattern of ITD reliability the owl experiences during development, or the neurons that respond to unreliable frequencies could be pruned during development. Future work dissecting developmental and experience-dependent changes to the ICx-ICx synapses may elucidate the fundamental mechanisms underlying this adaptive coding.

These results suggest a juvenile owl undergoes a process to refine the frequency tuning in the ICx based on the pattern of ITD reliability that the owl experiences during early-life development. Along normal development, the frequency tuning of frontally-tuned neurons changes in a manner consistent with an increase in high frequency reliability at frontal locations, determined by the acoustic properties of the facial ruff. It should be noted that the difference in frequency tuning of frontally-tuned neurons between normal adults and juveniles (rank-biserial correlation, $r = 0.55$) is smaller than the difference between normal adult and ruff-removed owls (rank-biserial

correlation, $r = 0.84$). This suggests that the ruff removed owls still underwent a refinement in ICx frequency tuning, but toward lower frequencies compared to normal adults. Although not directly tested in this study, the timing of ruff development aligns with previous reports of a critical period in the barn owl (Knudsen et al., 1984; Brainard and Knudsen, 1993; Brainard and Knudsen, 1998).

It is unlikely that the effect of ruff removal on ITD reliability is due solely to a change in gain of sound level, as previous reports found that ruff removal decreases the gain across frequencies, yet the gain remains higher for higher frequencies around 6-8 kHz (Coles and Guppy, 1987; von Campenhausen and Wagner, 2006), inconsistent with the estimated lower ITD reliability of high frequency sounds in frontal locations for these owls. Likewise, the rate of change of ITD ($\mu\text{s}/\text{deg}$), another significant statistic determining ITD discriminability (Feddersen et al., 1957; Gelfand, 2016; Pavão et al., 2020), is not reported to change significantly across frequencies after ruff removal (von Campenhausen and Wagner, 2006), reducing the possibility of it being an alternative mechanism driving change of frequency tuning. Additional testing of whether the observed change in frequency tuning of frontal neurons could be determined by the reported changes in the pattern of ITD and ILD across spatial locations after ruff removal (Knudsen et al. 1994; von Campenhausen and Wagner 2006) showed no systematic frequency dependent effects (**Fig. 5**). These conclusions support the premise that ITD reliability is a primary determinant of ICx frequency tuning.

Nevertheless, there may be limits to the extent that frequency tuning can be shifted due to ITD reliability. The majority of the barn owl's basilar papilla responds to 5-10 kHz (Köppl et al., 1993), which may induce a bias towards high frequencies into the downstream auditory centers. The eardrum itself may also have detection biases for frequencies above 3 kHz (Kettler et al., 2016). Consistently, the ICCs and midbrain maps contain few neurons tuned to frequencies below 1 kHz (Fig 4, Wagner et al., 2007; Cazettes et al., 2014). While these properties are not expected to be affected by the facial ruff, they likely evolved simultaneously with the evolution of the facial ruff to facilitate the use of ITD detection at high frequencies. This is akin to reports that the barn owl's sound localization cannot fully adapt to large displacements in the visual field (Knudsen and Knudsen, 1989; 1990).

There has been extensive research on how the brain encodes and adapts to changes of sensory statistics. Reports of early life exposure to low signal-to-noise ratios have suggested a delay in the maturation of sensory systems (Withington-Wray et al., 1990; Chang and Merzenich, 2003; Efrati and Gutfreund, 2011). In the auditory system, numerous reports showed that tonotopic maps can be adjusted in response to frequency specific noise (Zhang et al., 2001; Noreña et al., 2006; de Villers-Sidani et al., 2007) or notches (Gold and Knudsen, 2000). More recent findings suggest that certain noise contexts can alter tuning based on the stimulus statistics (Cruces-Solis, 2018; Homma et al., 2020). While these previous reports demonstrated changes in the auditory system induced by altering the statistics between signal and noise that mediate spectrotemporal discrimination, this study further finds evidence of adaptive plasticity to statistics of the ITD sensory cue, used for sound localization. Specifically, this study demonstrates that frequency tuning in the midbrain space map may also be driven by how well these frequencies convey a relevant spatial cue, ITD, which is initially computed in the brainstem (Carr and Konishi, 1990). This suggests that high-order statistics are detected across frequencies and locations and that adaptive coding is implemented in the barn owl's midbrain, where a map of auditory space emerges, suggesting that natural statistics are driving the implementation and development of a computational brain map (Knudsen et al., 1987). While the ongoing reliability of ITD cue is known to affect sound localization (Jeffress et al., 1962; Saberi et al., 1998), these findings support the theory of an essential role of anticipated ITD reliability, where its effect on neuronal tuning is acquired during development and maintained in spite of ongoing statistics, in the coding of sound location by population responses in the owl midbrain map (Fischer and Pena, 2011; Cazettes et al., 2014; Ferger and Shadron et al., 2021). In addition, the broader ITD tuning of frontal neurons in juvenile and ruff-removed owls (**Fig. 7d**) was predicted by their tuning to lower frequencies and potentially consistent with a proposed theory that the shape of tuning curves encodes reliability in the midbrain map (Cazettes et al., 2016). The changes in frequency tuning we found occurred in animals maintained in regular group aviaries with daily

feeding and absence of specific task training or survival needs such as hunting experience or auditory-driven tasks. Thus, the shaping of the owl's ICx frequency tuning based on anticipated ITD reliability may be a normal and robust step in owl's development. Because of this, the ruff-removed owl may be a useful model for future investigation of the molecular and synaptic mechanisms underlying experience-dependent coding of anticipated cue reliability.

In sum, this work provides evidence that the brain can assess the reliability of an auditory spatial cue along normal development and experience-dependent changes and use this information to drive neural tunings matching anticipated reliability across frequency and locations. To our knowledge, this is the first description of the natural learning of cue reliability, where the learning is implemented in a midbrain network, in contrast with previous work restricted to the forebrain (Keating et al., 2013). As anticipated ITD cue reliability has also been shown to drive spatial discriminability in humans (Pavão et al., 2020), it is possible that a similar learning process could occur as the human head and ears grow and develop. In addition, a previous report showing changes in human sound motion detection manipulated by cue reliability is also consistent with coding and detection of these statistics by brainstem regions (Saberri and Petrosyan, 2005). Overall, this study supports causality of anticipated sensory cue statistics of spatial cues on neuronal tuning properties in the auditory system and developmental and experience dependent plasticity driving this statistical inference.

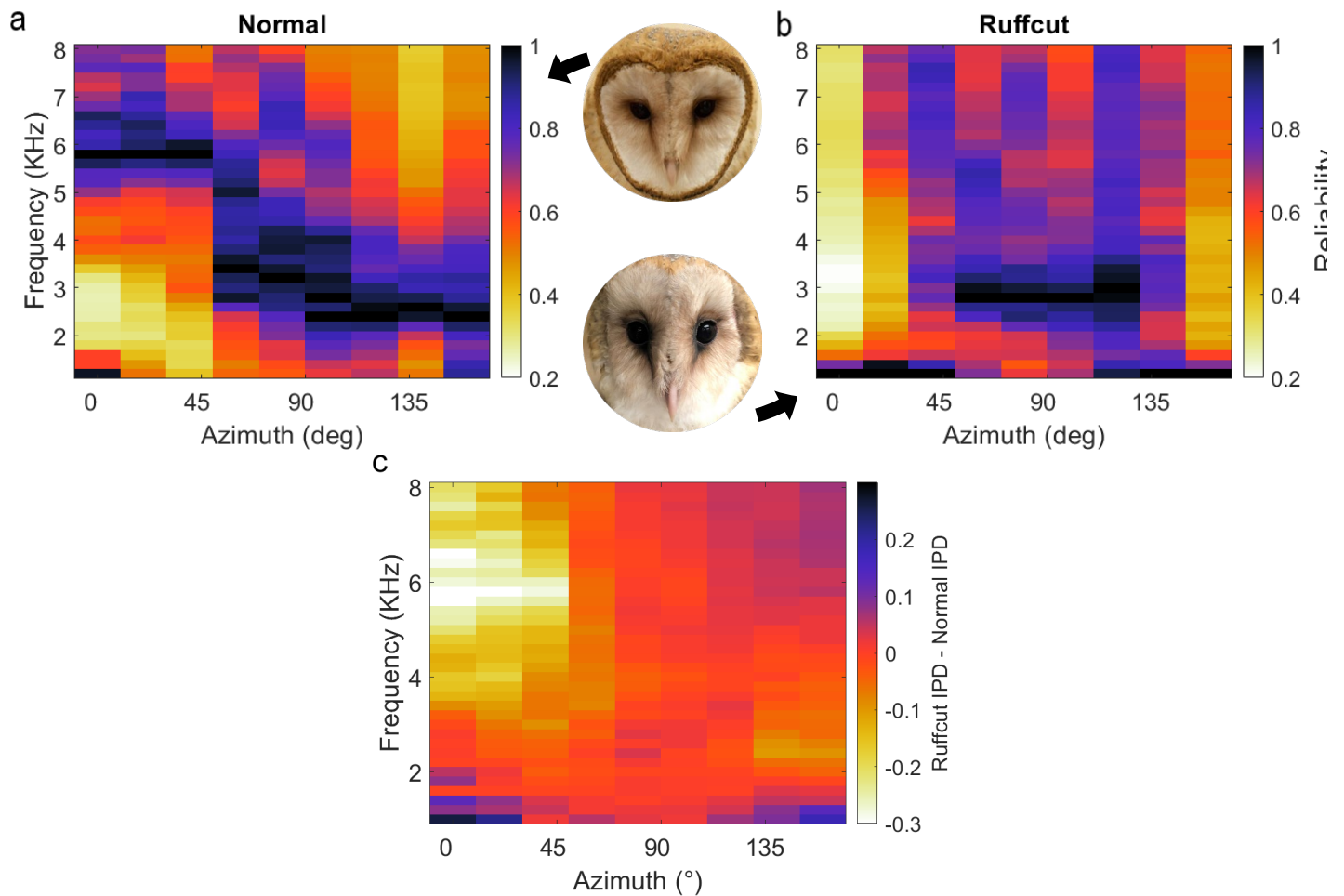


Figure 1. HRTF-based IPD reliability in owls with and without facial ruff. Target and masker broadband sounds across varying azimuth locations were convolved with HRTFs from owls before and after facial ruff removal, then summed. IPD reliability ($s.d.^{-1}$) was computed across frequencies and normalized for each location, then averaged across owls (see Methods) before (a) and after (b) the facial ruff removal. The difference between normal and ruff-removed IPDs indicates a substantial decrease in reliability for frequencies above 4 kHz at frontal locations (c). HRTF data from von Campenhausen and Wagner, 2006.

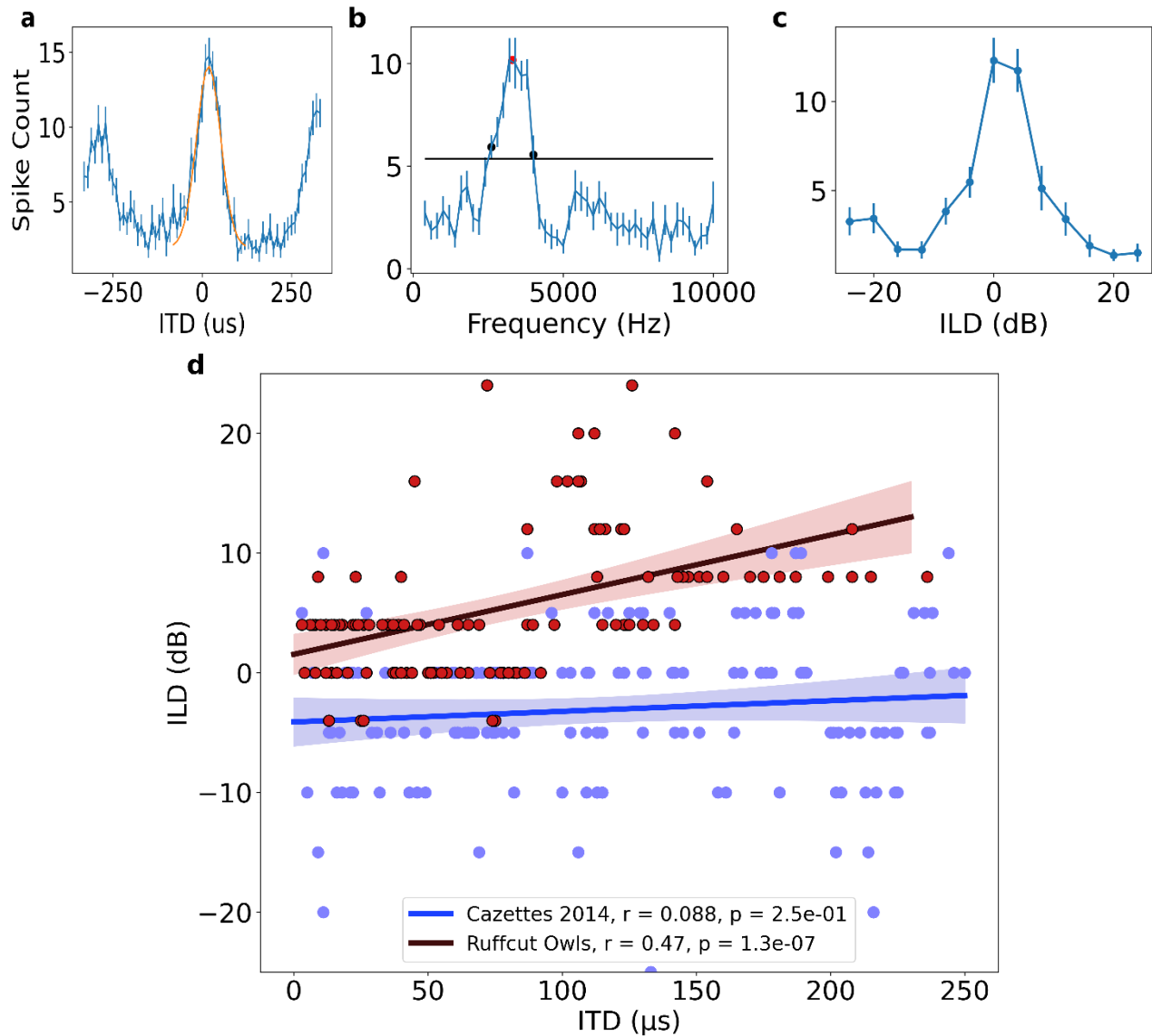


Figure 2. ICx neural responses in the ruff-removed barn owl. a) Example ITD tuning curve. Yellow curve represents Gaussian fit to main peak, with the maximum of this curve termed best ITD. **b)** Example frequency tuning curve. Black line indicates half-height used for determining half-width, low and high frequency bounds (black dots) and best frequency (red dot). **c)** Example ILD tuning curve. **d)** Best ILD plotted as a function of best ITD of neurons from ruff-removed (red dots) and normal owls (blue dots, from Cazettes et al., 2014). While there is no correlation between ITD and ILD tuning in normal owls (blue line), there is a correlation in ruff-removed owls (red line).

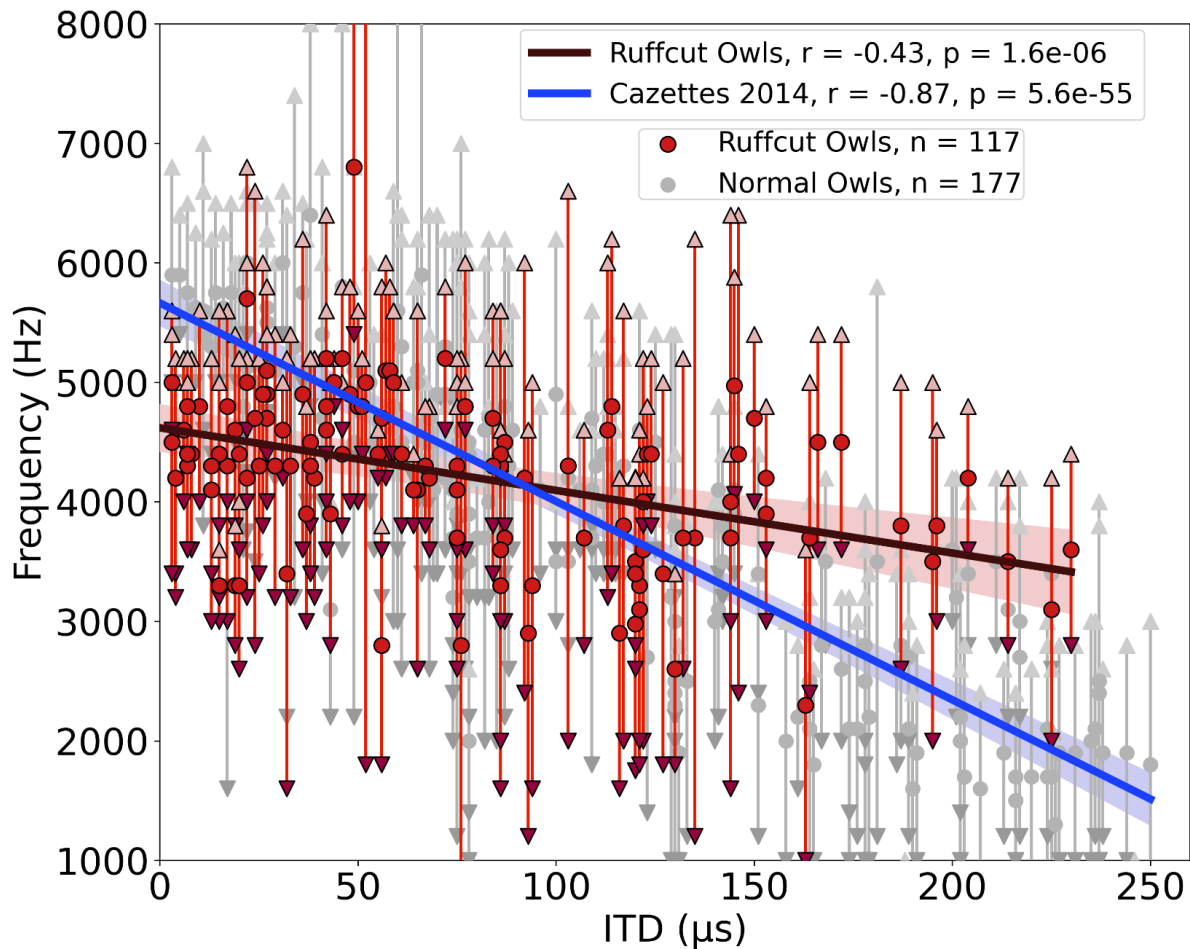


Figure 3. Different correlations between ITD and frequency tunings in ruff-removed and normal owls. Best frequency plotted as a function of best ITD of ICx neurons from ruff-removed owls (red dots) and normal owls (grey dots, from Cazettes et al., 2014). Up- and down-facing triangles indicate, respectively, high and low frequency bounds of each neuron. Linear regressions overlaid for ruff-removed (red line) and normal (blue line) owls, with 95% confidence intervals.

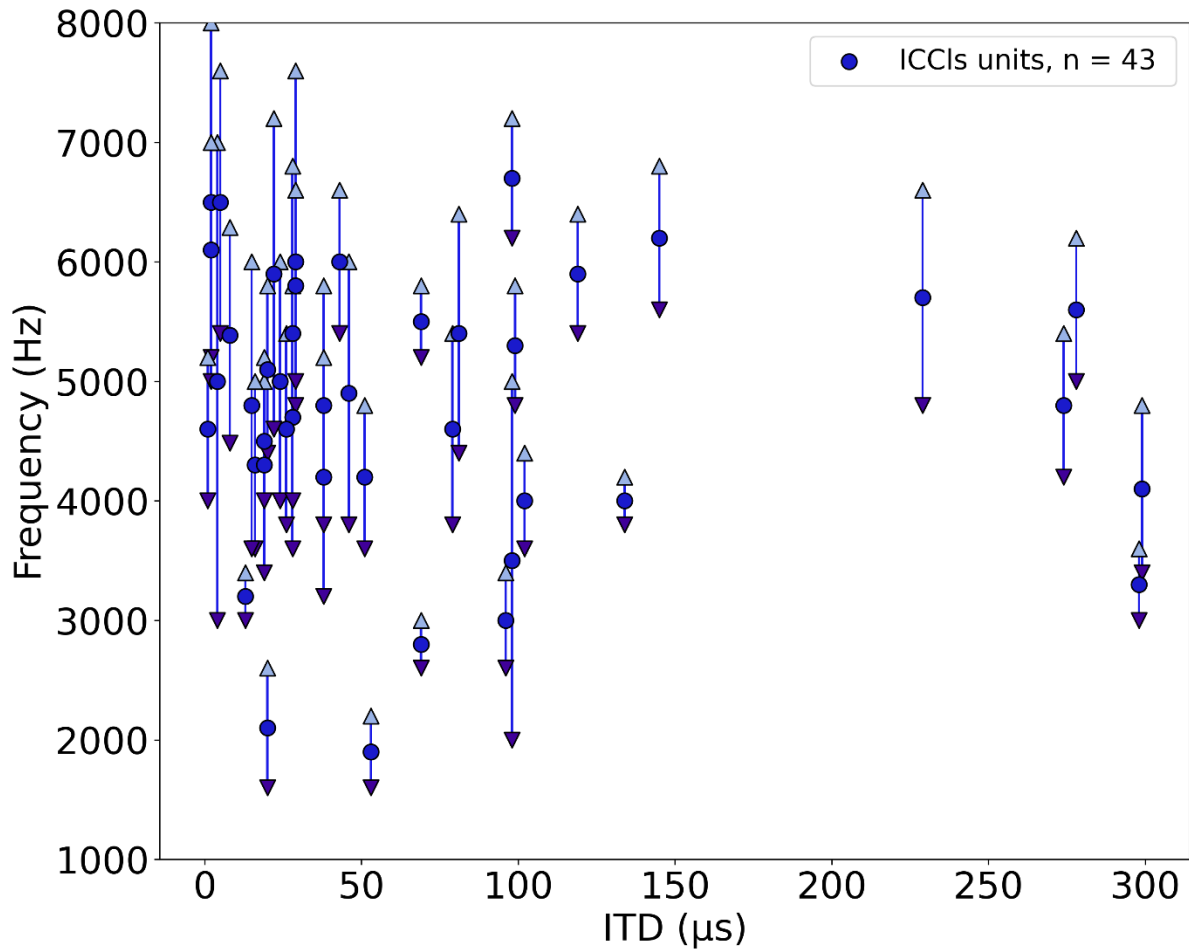


Figure 4. Frequency tunings in the ICC1s of ruff-removed owls span across the owl’s normal hearing range. Frequency tuning of ICC1s neurons of ruff-removed owls plotted as a function of their best ITD. Best frequency denoted by blue dots, frequency range denoted by arrows.

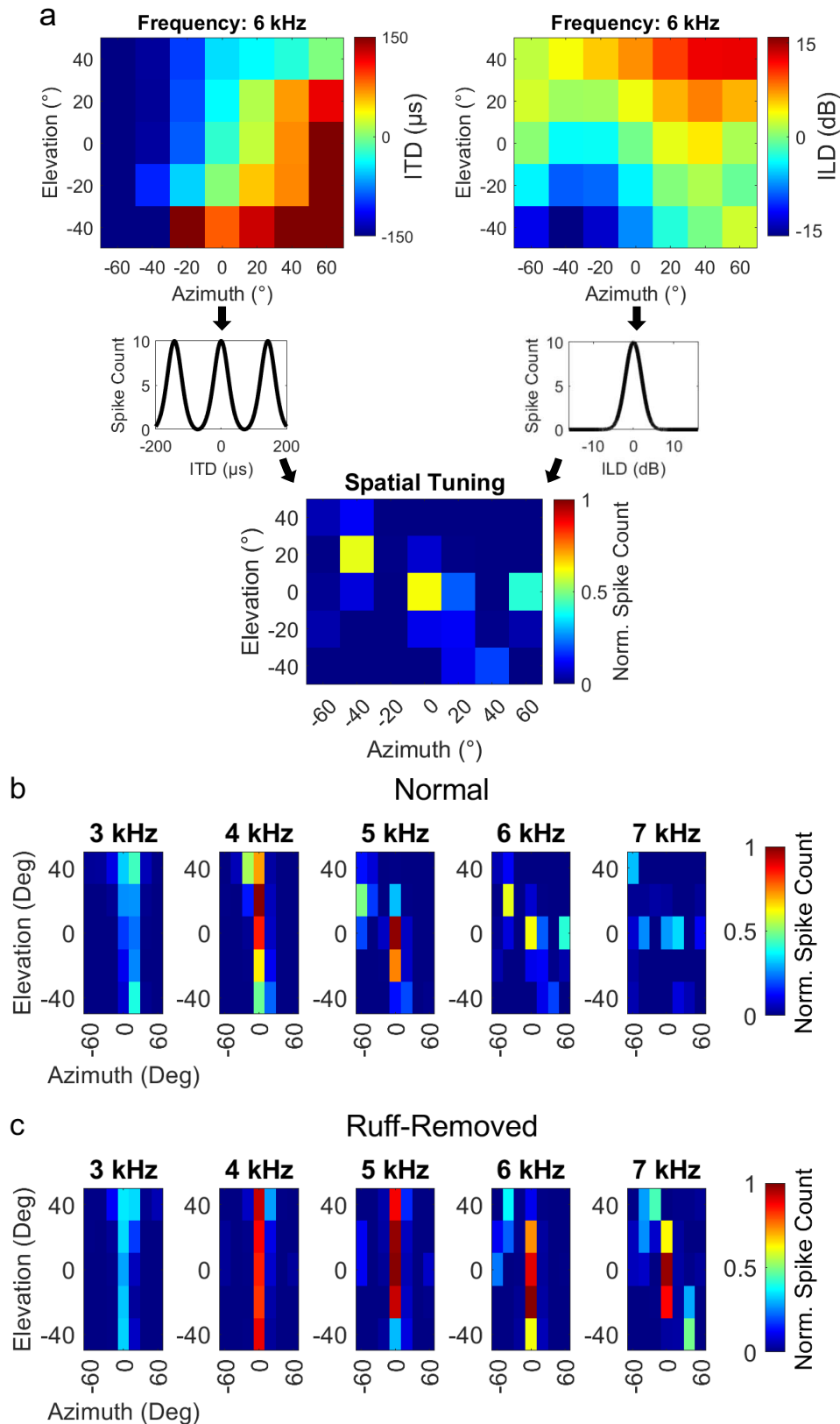


Figure 5. Spatial tuning for frontal space following ruff-removal does not show systematic alterations based on frequency. **a**) Schematic methodology to determine spatial tuning, using 6 kHz as an exemplary tone. ITD (upper left) and ILD (upper right) were estimated as a function of the spatial location of the sound source. Neural responses were predicted by entering the estimated ITD and ILD into modeled tuning curves for a simulated frontally-tuned neuron (middle plots). The overall spatial tuning was calculated by combinatorial multiplication then normalization of these modeled responses (lower plot). **b,c**) Spatial tuning maps for owls before (**b**) and after (**c**) ruff-removal, displayed for 5 example tones.

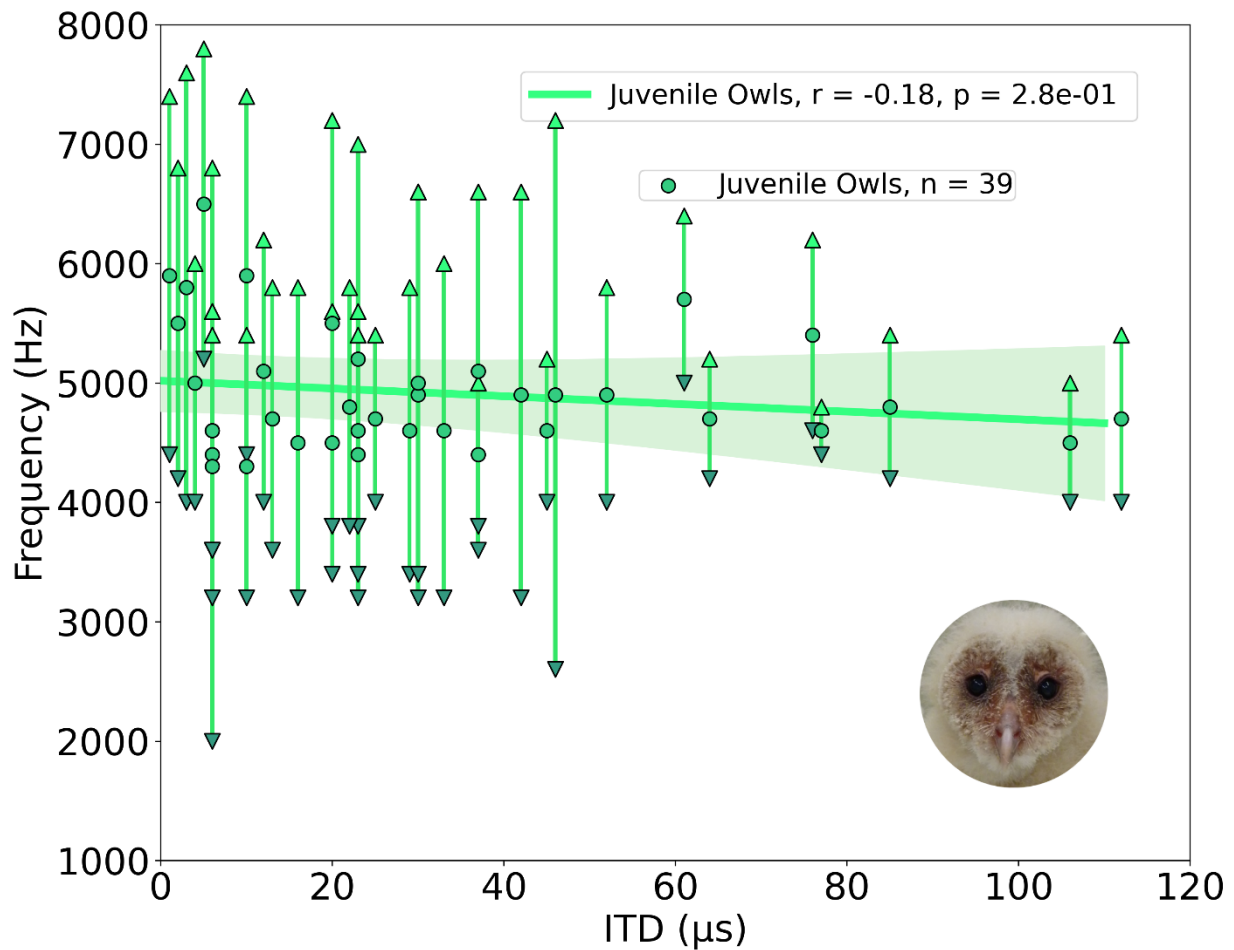


Figure 6. Tuning properties of the juvenile owl's ICx neurons. ICx neurons recorded from juvenile owls, before the facial ruff developed, plotted by their best ITD and frequency tuning range. Weak correlation between ITD and frequency (green line).

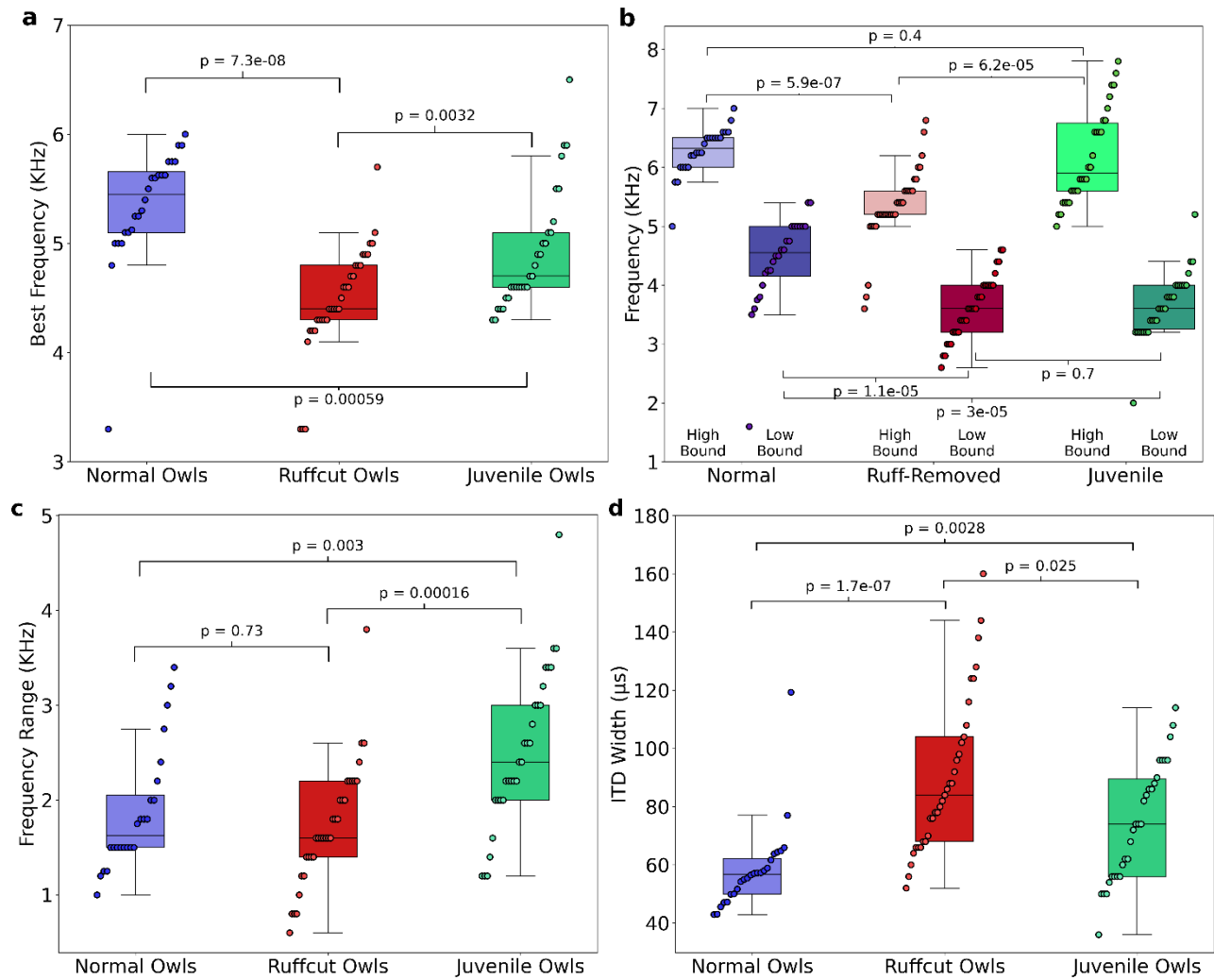


Figure 7. Comparisons of frequency and spatial tunings of frontally-tuned ICx neurons between normal, ruff-removed and juvenile owls. **a)** Box plots indicating the distribution of best frequencies for neurons tuned to frontal ITDs ($\pm 30 \mu$ s, equivalent to approximately $\pm 10^\circ$ azimuth). **b)** Box plots for each group, denoting the high and low bounds of frequency tuning curves. **c)** Box plots representing the responsive frequency range for neurons of each group. **d)** Box plots representing the width of ITD tuning curves of each group. Individual neurons and Mann-Whitney U-test p-values used to compare groups are shown over each box plot.

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