Research Paper

Differences between auditory frequency-following responses and onset responses: Intracranial evidence from rat inferior colliculus

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a r t i c l e   i n f o

a b s t r a c t

A periodic sound, such as a pure tone, evokes both transient onset eld-potential responses and sustained frequency-following responses (FFRs) in the auditory midbrain, the inferior colliculus (IC). It is not clear whether the two types of responses are based on the same or different neural substrates. Although it has been assumed that FFRs are based on phase locking to the periodic sound, the evidence showing the direct relationship between the FFR amplitude and the phase-locking strength is still lacking. Using intracranial recordings from the rat central nucleus of inferior colliculus (ICC), this study was to examine whether FFRs and onset responses are different in sensitivity to pure-tone frequency and/or response-stimulus correlation, when a tone stimulus is presented either monaurally or binaurally. Particularly, this study was to examine whether the FFR amplitude is correlated with the strength of phase locking. The results showed that with the increase of tone-stimulus frequency from 1 to 2 kHz, the FFR amplitude decreased but the onset-response amplitude increased. Moreover, the FFR amplitude, but not the onset-response amplitude, was signi cantly correlated with the phase coherence between tone-evoked potentials and the tone stimulus. Finally, the FFR amplitude was negatively correlated with the onset-response amplitude. These results indicate that periodic-sound-evoked FFRs are based on phase-locking activities of sustained-response neurons, but onset responses are based on transient activities of onset-response neurons, suggesting that FFRs and onset responses are associated with different functions.

1. Introduction

The inferior colliculus (IC), which is considered to be the most essential hub in the auditory subcortical system, encodes spectral, spatial, and temporal features of sound stimuli (Schreiner and Winer, 2005). When a low/middle periodic sound-wave signal enters the auditory system, it evokes both transient onset responses (which occur some milliseconds after the sound onset) and sustained responses (which follow the spectral periodicity of the sound) in the IC (Ping et al., 2008; Du et al., 2009, 2011; for a review see Kraus and Nicol, 2005). The transient onset response re ect the early onset encoding, while the sustained responses, which are also named as the frequency-following responses (FFRs), re ect the instantaneous spectral information of the input acoustic signal. Behavioral dissociations between onset responses and FFRs have been reported (Johnson et al., 2005; Kraus and Nicol, 2005; Skoe and Kraus, 2010).

Accumulating evidence has con rmed that scalp-recorded onset and sustained brainstem responses to acoustic stimuli have different patterns (Galbraith and Brown, 1990; Krizman et al., 2010; Parthasarathy and Bartlett, 2012; Picton et al., 1978). There has been a long historical debate whether FFRs are a series of overlapping onset responses (e.g., Daly et al., 1976; Dau, 2003; Davis and Hirsh, 1974; Gerken et al., 1975; Picton et al., 1978; Goldstein and Kiang, 1958; Janssen et al., 1991; Bidelman, 2015). For example, Goldstein and Kiang (1958) have suggested that sustained potentials recorded in the auditory cortex would be based on convolution of unitary responses of elementary unit waveforms. Also, Dau

(2003) has built a computational FFR model based on the convolution of click evoked onset responses. However, more recently, Bidelman (2015) has suggested that the linear convolution of onset responses cannot be used for predicting sustained responses. Clearly, animal studies with intracranial recordings are needed to clarify the functional relationship between the onset and sustained portions of the brainstem responses.

The origin structure of human-scalp-recorded FFRs has been considered as the IC (e.g., Chandrasekaran and Kraus, 2010; Kraus et al., 2017; Marsh et al., 1974; Smith et al., 1975; Shinn-Cunningham et al., 2017; Sohmer et al., 1977; Weinberger et al., 1970; but also see Coffey et al., 2016, 2017). However, the directly electrophysiological evidence supporting the IC origin of FFRs is still not sufficient. In general, there is still a strong debate about the exact origins of FFRs. For example, Coffey and colleges (2016, 2017) have suggested a cortical contribution to FFRs. Thus, animal studies, which have the advantage of intracranial recordings directly from the IC, become important and necessary for addressing this issue. Particularly, using high-density, multi-channel electrode array, the recent Bidelman study (2015) has demonstrated not only that the FFR has functionally distinct response characteristics from the transient ABR, but also that the probable generators of FFRs are located within the IC of the upper brainstem. The onset-response properties and FFR properties of the IC can be revealed at the same time by direct intracranial recordings in laboratory animals (Ping et al., 2008; Du et al., 2009, 2011; Wang and Li, 2015). In the central nucleus of IC (ICC), which is the core component of the auditory midbrain, both neurons with the onset-firing pattern and those with the sustained firing pattern have been reported in animal studies (Wagner, 1994; Li and Kelly, 1992a,b, 1998; Reetz and Ehret, 1999; Peruzzi et al., 2000; Sivaramakrishnan and Oliver, 2001; Bal et al., 2002). These two types of neuron populations may contribute to evoked local-field potential onset responses and FFRs, respectively. Although it has been suggested that neurons with the sustained firing pattern can phase-lock the stimulus periodicity and provide the neural mechanisms underlying FFRs (Kuokkanen et al., 2010; for a review see Du et al., 2011), it is still not clear whether the strength of FFR phase-locking to sounds is correlated with the FFR amplitude.

The majority of auditory neurons in the IC are binaural (e.g., Kelly et al., 1991). Some of the binaural neurons are predominantly excited by stimuli at the contralateral ear and inhibited by stimuli at the ipsilateral ear, forming the so-called "EI" neurons, other binaural neurons are excited by stimuli at either ear, forming the so-called "EE" neurons, and the rest of neurons are only excited by contralateral stimuli, forming the so-called "EO" neurons (Kelly et al., 1991; Li and Kelly, 1992a,b). Previous studies have also shown that IC FFRs to binaural-chatter stimulation exhibit a feature of ipsilateral predominance, suggesting that EE neurons in the IC make the main contribution to binaural FFRs (Du et al., 2009). Thus, to estimate any binaural interaction effects on IC FFRs and/or onset responses, it is necessary to introduce both monaural (either ipsilateral or contralateral) and binaural stimulation conditions.

The primary aim of this study was to examine whether the tone-elicited FFR amplitude recorded in the ICC is correlated with the FFR phase-locking strength. The additional aim of this study was to examine whether FFRs and onset responses recorded in the ICC are based on the same or different neural substrates by comparing both the sensitivity to pure-tone frequency and the response-stimulus correlation between FFRs and onset responses when a tone stimulus is presented either monaurally or binaurally.

2. Materials and methods

2.1. Animal preparation

Eleven younger-adult male Sprague-Dawley rats (age: 10e12 weeks; weight: 280e350 g) were purchased from the Vital River Experimental Animal Company. They were anesthetized with 10% chloral hydrate (400 mg/kg, intraperitoneal) and the state of anesthesia was maintained steady throughout the experiment by supplemental injection of the same anesthetic (Kelly and Li, 1997; Du et al., 2009; Wang and Li, 2015). Stainless-steel recording electrodes (10e20 kΩ) insulated by a silicon tube (0.3 mm in diameter) except at the 0.25 mm diameter tip (Du et al., 2009; Ping et al., 2008; Wang and Li, 2015) were aimed at the ICC bilaterally. Based on the stereotaxic coordinates of Paxinos et al. (2009) and referenced to *Bregma*, the ICC coordinates were: AP, 8.8 to 9.2 mm; ML, 1.5 mm; DV, 4.5 to 5.0 mm. During electrical recordings in the experiment room with constant temperature, air pressure, and humidity, the rat was wrapped with blankets for maintaining body temperature.

Rats used in this study were treated in accordance with the Guidelines of the Beijing Laboratory Animal Center, and the Policies on the Use of Animal and Humans in Neuroscience Research approved by the Society for Neuroscience (2006). The experimental procedures were also approved by the Committee for Protecting Human and Animal Subjects in the Department of Psychology at Peking University.

2.2. Apparatus and stimuli

All the sound waves were processed by a TDT System II (Tucker-Davis Technologies, FL, USA) and presented through two ED1 earphones (Tucker-Davis Technologies, FL, USA). Two 12-cm TDT sound-delivery rubber tubes were connected to the ED1 earphones and inserted into each of the rat's ear canals for sound delivery. All the sounds were calibrated using a Larson Davis Audiometer Calibration and Electroacoustic Testing System (AUDitTM and System 824, Larson Davis, USA). The sound pressure level (SPL) of all signals was 72 dB for each earphone.

Pure tones with either 1 or 2 kHz frequency (10-kHz sampling rate, and 16-bit amplitude quantization) were generated using MATLAB (the MathWorks, Natick, MA, U.S.A.). All the tone duration was 700 ms with 10-ms linear onset/offset ramps and the (offset-onset) inter-stimulus interval was 300 ms.

Evoked neural potentials were recorded in a sound-attenuating chamber, amplified 1000 times by a TDT DB4 amplier, ltered through a 100e10000 Hz band-pass lter (with a 50-Hz notch), and averaged 100 times per stimulation condition. Online recordings were processed with TDT Biosig software, digitized at 16 kHz, and stored on a disk for off-line analyses. The same tone stimuli were used for each animal.

2.3. Data analyses

The onset latency of monaural and binaural evoked eld potentials were determined by measuring the time interval between the sound onset and the rst positive peak of the response waveform. The onset amplitude was dened as the amplitude of the rst positive peak. Fast-Fourier transform (FFT) was performed for each waveform and then the spectrum amplitudes were divided by the averaged spectrum amplitude ranged from 2 to 5000 Hz (consid-

As the measurement of the strength of phase-locking, the phase coherence between the tone stimulus and the evoked neural response was calculated. This measurement was based on the instantaneous phase difference (ΔF) between the tone stimulus and evoked potentials:

$$\Delta F\left(t_j\right) \frac{1}{4} F_{stim}\left(t_j\right) - F_{po}\left(t_j\right) \tag{1}$$

where F_{stim} and F_{po} are defined as phase series at time samples, t_j, from the stimulus and the evoked potential waveforms, respectively, computed using a Hilbert transform function. The phase coherence is defined based on the magnitude squared coherence spectral estimator (Hurtado et al., 2004):

$$g \frac{1}{4} \frac{1}{N} \sum_{j\frac{1}{4}1}^{N} e^{i\Delta F_j} \tag{2}$$

where N is the number of samples.

Phase coherence (g) has values between 0 and 1. Zero corresponds to a pair of independent signals, and 1 corresponds to the perfect phase-locking (Hurtado et al., 2004). To test the significance of the phase coherence, we introduced a null hypothesis of an independent phase relationship between the stimulus and response potentials. For a single response potential, a group (100 samples) of surrogate data were generated by a linear Gaussian distributed time series with the same mean and standard deviation (SD) as the original potential for analyses of the surrogate phase coherence values of the null hypothesis. One-sample t-tests between the data and surrogate values were conducted to test whether the phase coherence of the evoked potential were significantly different from random levels.

2.4. Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics 20 (SPSS Inc., Chicago, Illinois 60606). Repeated-measures analyses of variance (ANOVAs), post hoc tests (with Bonferroni adjustment), and Pearson correlation tests were conducted. The null-hypothesis rejection level was set at 0.05.

2.5. Histology

When all recordings were completed, rats were euthanized with an overdose of chloral hydrate. Lesion marks were made via the recording electrodes with an anodal DC current (500 mA for 10 s). The brains were stored in 10% formalin with 30% sucrose and then sectioned at 55 mm in the frontal plane in a cryostat (−20 °C). Sections were examined to determine locations of recording electrodes.

3. Results

3.1. Histology

According to the histological examination (Fig. 1), electrodes were precisely located within the ICC in 18 out of the 22 recording sites. The misplaced recording sites (n ¼ 4, open circles in Fig. 1) were removed from data analyses.

3.2. Response latency of pure-tone-evoked potentials

Evoked field potentials to the pure tone (which was presented either monaurally or binaurally) exhibited marked onset responses and FFRs (Fig. 2). For the onset response to the monaural stimulus

presented at the contralateral ear, the mean latency of the first positive peak potential was 7.96 ms (SD ¼ 0.78 ms) for the 1-kHz pure tone, and 7.42 ms (SD ¼ 0.62 ms) for the 2-kHz pure tone. For the onset response to the monaural stimulus presented at the ipsilateral ear, the mean latency of the first positive peak potential was 8.11 ms (SD ¼ 0.49 ms) for the 1-kHz pure tone, and 7.26 ms (SD ¼ 0.64 ms) for the 2-kHz pure tone. For the onset response to the stimulus presented binaurally, the mean latency of the first positive peak potentials was 8.22 ms (SD ¼ 0.42 ms) for the 1-kHz pure tone, and 7.57 ms (SD ¼ 0.46 ms) for the 2-kHz pure tone (Fig. 3A). These results of onset latencies were in agreement with the results reported by previous IC-recording studies (Du et al., 2009; Ping et al., 2008; Wang and Li, 2015).

To examine the tone-frequency effect and the stimulation-condition effect on the onset-response latency, 2 (frequency: 1 kHz and 2 kHz) by 3 (stimulation condition: contralateral, ipsilateral and bilateral) repeated-measured ANOVAs were conducted. The results showed that the main effect of frequency was significant ($F_{1, 16}$ ¼ 64.858, p < 0.001), but neither the main effect of stimulation condition ($F_{2, 32}$ ¼ 2.365, p ¼ 0.110) nor the interaction between the two factors ($F_{2, 32}$ ¼ 2.470, p ¼ 0.101) was significant (Fig. 3A). Post hoc tests showed that within each stimulation condition (contralateral, ipsilateral and bilateral), the mean latency to the 2-kHz tone was significantly shorter compared to the 1-kHz tone stimulation (all p < 0.05). Post hoc tests for each tone frequency showed no significant differences in latency across stimulation conditions (all p > 0.05) (Fig. 3A).

3.3. Tone-frequency effects on onset-response amplitude, FFR amplitude, and phase coherence

As shown in Fig. 3, with the increase of the tone frequency from 1 kHz to 2 kHz, it appears that the onset latency decreased, the onset amplitude increased, the FFR amplitude decreased, and the phase coherence decreased. Also, the onset amplitude, FFR amplitude, and phase coherence under the binaural stimulation condition appear to be larger than that under either the contralateral-stimulation condition or the ipsilateral-stimulation condition. A 2 (frequency: 1 kHz, 2 kHz) by 3 (stimulation condition: contralateral, ipsilateral and bilateral) repeated-measured ANOVA showed that both the main effect of frequency ($F_{1, 16}$ ¼ 21.922, p < 0.001) and the main effect of stimulation condition ($F_{2, 32}$ ¼ 6.149, p ¼ 0.005) were significant, and the interaction between the two factors was also significant ($F_{2, 32}$ ¼ 7.611, p ¼ 0.002).

The FFR amplitude under the binaural stimulation condition also appears to be larger than that under either the ipsilateral-stimulation condition or the contralateral-stimulation condition (Fig. 3C). A 2 (frequency) by 3 (stimulation condition) repeated-measured ANOVA showed that both the main effect of frequency ($F_{1, 16}$ ¼ 15.592, p ¼ 0.001) and the main effect of stimulation condition ($F_{2, 32}$ ¼ 30.285, p < 0.001) were significant, and the interaction between the two factors was also significant ($F_{2, 32}$ ¼ 9.324, p ¼ 0.001).

For phase coherence (Fig. 3D), a 2 (frequency) by 3 (stimulation condition) repeated-measured ANOVA showed that both the main effect of frequency ($F_{1, 16}$ ¼ 34.632, p < 0.001) and the main effect of stimulation condition ($F_{2, 32}$ ¼ 24.967, p < 0.001) were significant, and the interaction between the two factors was also significant ($F_{2, 32}$ ¼ 8.735, p ¼ 0.001).

To further estimate the frequency-preference pattern, post hoc tests within each of the 3 stimulation conditions were conducted for onset amplitude, FFR amplitude, and phase coherence, respectively. The results showed that the onset amplitude to the 2-kHz tone was significantly larger than that to the 1-kHz tone under each of the stimulation conditions (all p < 0.05) (Fig. 3B).
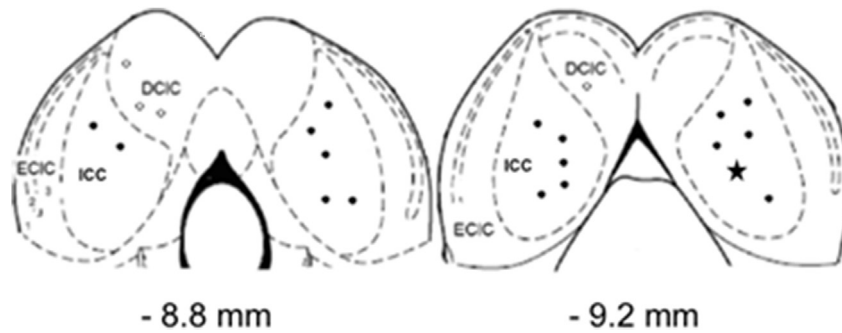
Fig. 1. Histological reconstruction of locations of recording electrodes aimed the bilateral central nucleus of the inferior colliculus (ICC) in 11 rats. Electrodes were precisely located within the ICC in 18 of the 22 penetrations (filled circles and the star). Four recording sites (open circles) were outside the ICC. Note that two electrodes were inserted per animal, one on each side of the ICC.
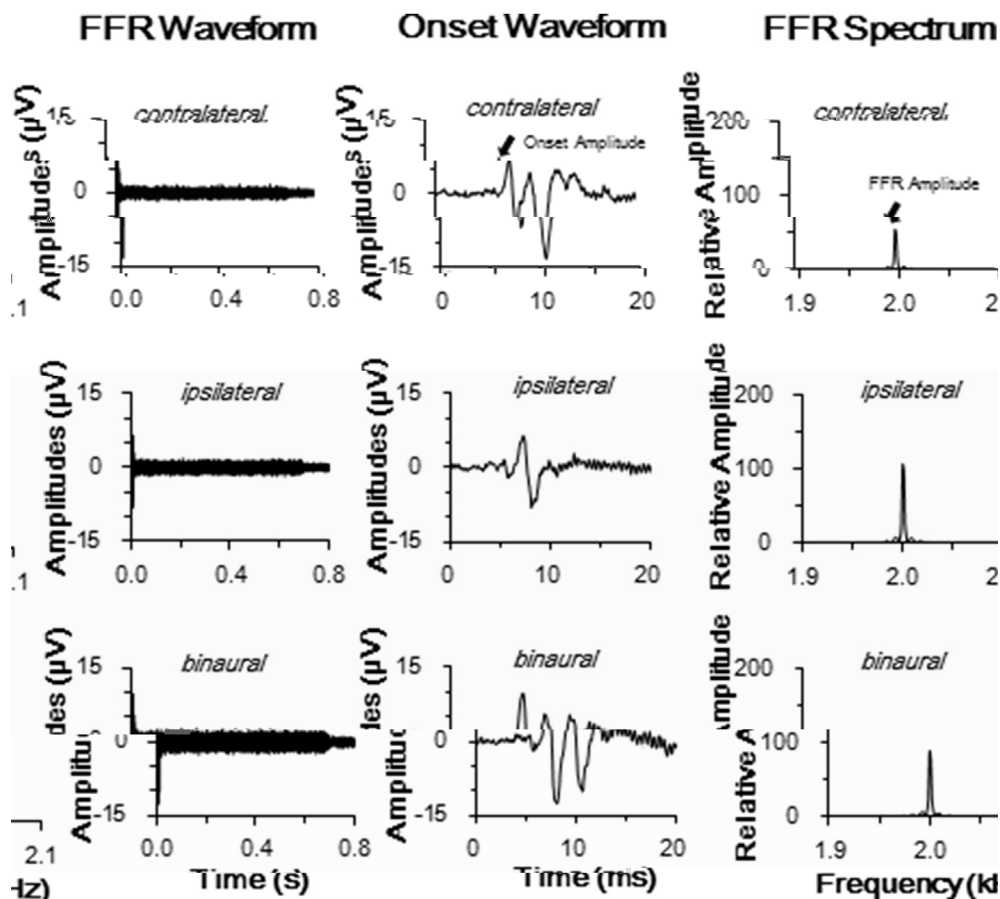

Fig. 2. Frequency-following responses (FFRs) and onset responses recorded from a randomly selected recording site (the star in Fig. 1) evoked by an either monaurally (contralateral, ipsilateral) or binaurally presented pure tone (frequency ¼ 2 kHz, duration ¼ 0.7 s). **Left panels:** Examples of raw waveforms of evoked potentials (time window: 0 to 800 ms). **Middle panels:** Examples of onset waveforms of evoked potentials. Black arrow indicates the curve point where the value of onset amplitude was taken. **Right panels:** Examples of long term spectra of FFRs conducted by fast-Fourier transform (FFT). Black arrow indicates the curve point where the value of FFR amplitude was taken.

In contrary, the FFR amplitude to the 2-kHz tone was significantly smaller than that to the 1-kHz tone when the pure tone was presented either ipsilaterally or bilaterally (both p 0.05), but not when the tone was presented contralaterally (p 0.189).

The phase coherence to the 2-kHz tone was significantly weaker than that to the 1-kHz tone when the tone stimulus was presented either ipsilaterally or bilaterally (both p 0.001), but not when the stimulus was presented contralaterally (p ¼ 0.242).

In summary, these results revealed the different frequency effects on onset amplitude, FFR amplitude, and phase coherence:

With the increase of tone-stimulus frequency from 1 to 2 kHz, the onset amplitude increased when either ear was stimulated, but both the FFR amplitude and the phase coherence decreased when the tone stimulus was presented either ipsilaterally or bilaterally.

3.4. Comparisons of the patterns of onset responses and FFRs

To further estimate the stimulation-evoked pattern, *post hoc* tests under each frequency condition were conducted for onset amplitude, FFR amplitude, and phase coherence, respectively. One
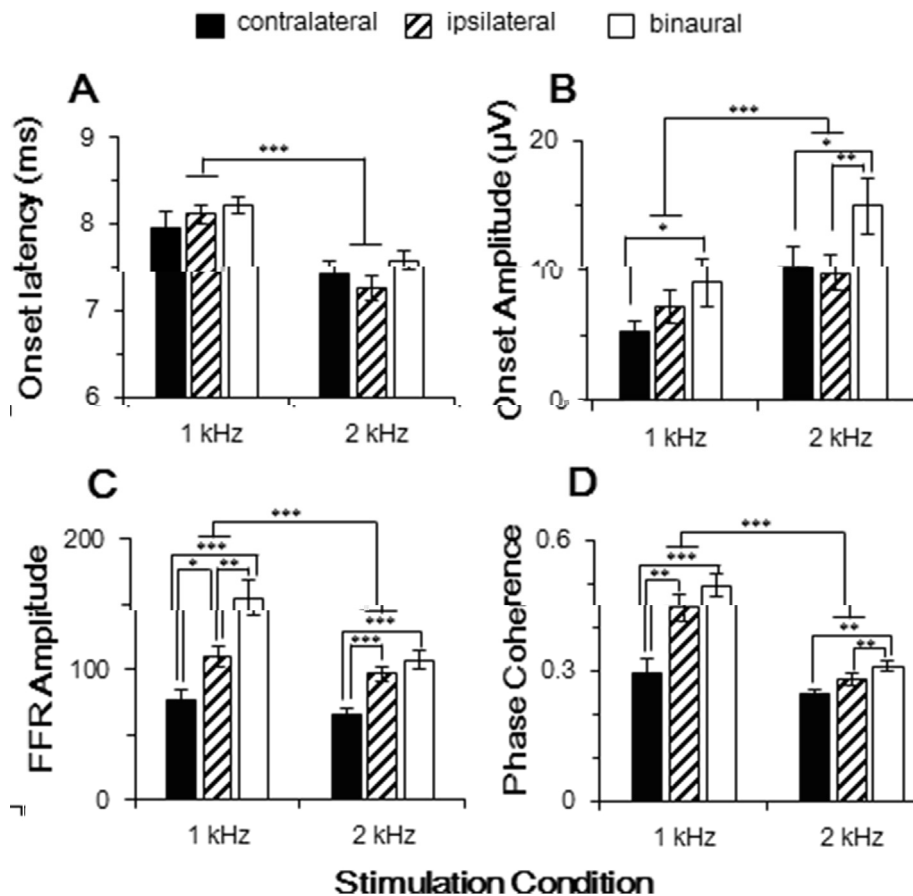
Fig. 3. Comparisons in (A) onset latency, (B) onset-response amplitude, (C) FFR amplitude, and (D) phase coherence of field potentials either between the tone-stimulus frequency (1 kHz, 2 kHz) or between the stimulation conditions (contralateral, ipsilateral and bilateral). *Black bars:* contralateral stimulation condition; *stripped bars:* ipsilateral stimulation condition; *white bars*: binaural stimulation condition. *Error bars:* standard errors of the mean. *, p < 0.05; **, p < 0.01; ***, p < 0.001.

of the consistent observations was that the onset amplitude, FFR amplitude, and phase coherence under the binaural-stimulation condition were significantly larger than those under the contralateral-stimulation condition (all *p* < 0.05) (Fig. 3).

Moreover, the FFR amplitude evoked contralaterally was significantly smaller than that evoked ipsilaterally when the tone frequency was either 1 or 2 kHz (both *p* < 0.05). However, this ipsilateral dominance was not found for the onset-response amplitude (both *p* > 0.05) (Fig. 3), suggesting a distinct difference in evoked pattern between onset responses and FFRs.

3.5. Correlation between FFR and phase coherence

To test whether FFRs and/or onset responses were correlated with phase coherence, Pearson correlation tests were conducted between the three indices (FFR amplitude, onset amplitude, and phase coherence). The results showed that significantly positive correlations were observed between the FFR amplitude and the phase coherence under all the stimulation conditions, except for the condition with bilateral 2-kHz pure-tone stimulation (all *p* < 0.004, with multiple comparison corrected, for details see in Fig. 4). However, no significantly positive correlation was observed between the phase coherence and the onset amplitude under each of the stimulation conditions (Fig. 4).

3.6. Correlation between FFR and onset response

To estimate the relationship between FFRs and onset responses, Pearson correlation tests were conducted under each of the stimulation conditions (Fig. 5) with the combination of results across the two frequency conditions. As shown in Fig. 5, significantly negative correlations were observed under the contralateral (*r* = 0.421, *p* = 0.012), ipsilateral (*r* = 0.479, *p* = 0.003), and bilateral (*r* = 0.537, *p* = 0.001) stimulation conditions. These results further demonstrated different mechanisms underlying FFRs and onset responses.

4. Discussion

The ICC is the endpoint integrating inputs from lower auditory brainstem structures (e.g., Li and Kelly, 1992a,b; Yin et al., 1987; Palmer et al., 1999; Shackleton et al., 2005; Shackleton and Palmer, 2006). The sustained discharge pattern is prevalent in ICC neurons (Li and Kelly, 1992a,b; Li et al., 1998; Reetz and Ehret, 1999; Bal et al., 2002). FFRs are generally defined as sustained neuro-electrical potentials that are assumed to be based on precisely phase-locked responses of neuron populations to instantaneous waveforms of low-to-middle-frequency acoustic stimuli (Chandrasekaran and Kraus, 2010; Du et al., 2009, 2011; Marsh and Worden, 1969; Moushegian et al., 1973; Ping et al., 2008; Weinberger et al., 1970; Worden and Marsh, 1968). In this study, using intracranial recordings in the rat ICC, the relationships between the FFR amplitude, FFR phase coherence, and onset response amplitude were examined. For the first time, the results of this study showed that the FFR amplitude was positively correlated with the phase coherence under each of the stimulation conditions

(contralateral, ipsilateral and bilateral stimulation). This study provides evidence that the tone-elicited FFRs recorded in the ICC are based on the phase locking responses of ICC neurons.

Although previous studies have suggested that subcortical FFR signatures of binaural processing are weak (for a review see Shinn-Cunningham et al., 2017), one of the consistent observations was that the onset amplitude, FFR amplitude, and phase coherence under the binaural-stimulation condition were significantly larger than those under the contralateral-stimulation condition. Also, in this study, the FFR amplitude evoked ipsilaterally was significantly large than that evoked contralaterally when the tone frequency was either 1 or 2 kHz. However, this ipsilateral dominance was not found for the onset-response amplitude. Also, both the FFR amplitude and the phase coherence to the 1-kHz tone were stronger than those to the 2-kHz tone when the pure tone was presented either ipsilaterally or bilaterally but not when the tone was presented contralaterally. These results are consistent with previous suggestion that EE neurons in the IC make the main contribution to binaural FFRs with an ipsilateral predominance (Du et al., 2009) and EE responses are most numerous at low frequencies (Kelly et al., 1991).

Single ICC neurons can phase lock to periodic sounds up to 1034 Hz (Liu et al., 2006) or even 1200 Hz (Langner, 1983). Although based on

phase-locked FFRs and onset responses in the IC are auditory brain responses with separated underlying neural mechanisms. Thus, the

pattern and those with the sustained ring pattern are two of the major neuron types in the ICC (Wagner, 1994; Li and Kelly, 1992a,b, 1998; Reetz and Ehret, 1999; Peruzzi et al., 2000; Sivaramakrishnan and Oliver, 2001; Bal et al., 2002). There has been a long debate regarding whether sustained FFRs are based on overlapping transient auditory brainstem evoked potentials (e.g., Daly et al., 1976; Dau, 2003; Davis and Hirsh, 1974; Gerken et al., 1975; Picton et al., 1978, Goldstein and Kiang, 1958; Janssen et al., 1991; Bidelman, 2015). Both the present studies with animal intracranial recordings and some previous studies with human scalp EEG recordings (e.g., Bidelman, 2015) have suggested that the sustained

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heares.2017.10.014.

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