Auditory midbrain representation of a break in interaural correlation

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Wang Q, Li L. Auditory midbrain representation of a break in interaural correlation. *J Neurophysiol* 114: 2258–2264, 2015. First published August 12, 2015; doi:10.1152/jn.00645.2015.—The auditory peripheral system filters broadband sounds into narrowband waves and decomposes narrowband waves into quickly varying temporal fine structures (TFSs) and slowly varying envelopes. When a noise is presented binaurally (with the interaural correlation being 1), human listeners can detect a transient break in interaural correlation (BIC), which does not alter monaural inputs substantially. The central correlates of BIC are unknown. This study examined whether phase locking-based frequency-following responses (FFRs) of neuron populations in the rat auditory midbrain [inferior colliculus (IC)] to interaurally correlated steady-state narrowband noises are modulated by introduction of a BIC. The results showed that the noise-induced FFR exhibited both a TFS component (FFR_{TFS}) and an envelope component (FFR_{Env}), signaling the center frequency and bandwidth, respectively. Introduction of either a BIC or an interaurally correlated amplitude gap (which had the summated amplitude matched to the BIC) significantly reduced both FFR_{TFS} and FFR_{Env}. However, the BIC-induced FFR_{TFS} reduction and FFR_{Env} reduction were not correlated with the amplitude gap-induced FFR_{TFS} reduction and FFR_{Env} reduction, respectively. Thus, although introduction of a BIC does not affect monaural inputs, it causes a temporary reduction in sustained responses of IC neuron populations to the noise. This BIC-induced FFR reduction is not based on a simple linear summation of noise signals.

envelope; frequency-following responses; inferior colliculus; interaural correlation; temporal fine structure

INTERAURAL CORRELATION (IAC) is defined as the similarity of sound waves presented at the two ears (Jeffress et al. 1962). IAC-based binaural processing plays a critical role in both sound localization (Coffey et al. 2006; Franken et al. 2014; Soeta and Nakagawa 2006) and target-object detection in noisy environments (Durlach et al. 1986; Palmer et al. 1999). The IAC also affects the auditory perception. For example, when the IAC drops from 1 to 0, without affecting the spectra of monaural inputs, the auditory image of the simultaneously arriving binaural sounds changes vividly from a single image located at the head center into two separated images at each ear (Blauert and Lindemann 1986; Culling et al. 2001). Accordingly, human listeners with normal hearing can easily detect an interaurally uncorrelated fragment embedded in the interaurally correlated noises (Akeroyd and Summerfield 1999; Boehnke et al. 2002; Huang et al. 2008, 2009a, 2009b; Kong et

al. 2012, 2015; Li et al. 2009, 2013), i.e., a transient change of IAC from 1 to 0, then back to 1 [so-called "break in interaural correlation" (BIC)]. Note that introduction of a BIC does not significantly alter monaural inputs. Until now, the neural correlates of the BIC in the central auditory system have not been reported in the literature.

The peripheral auditory system not only band-pass filters broadband sounds into a series of narrowband waves orderly distributing along the basilar membrane but also decomposes narrowband waves into both quickly varying temporal fine structures (TFSs) and slowly varying envelopes (Moore 2008; Rosen 1992). These two temporal components are subsequently represented by temporal firing patterns of the auditory nerves (Johnson 1980; Joris and Yin 1992; Young and Sachs 1979). Although the neural representation of a BIC in the central auditory system may contain TFS and envelope components, listeners in fact do not perceive the BIC as separated TFS and envelope percepts.

Both scalp-recorded and intracranially recorded frequency-following responses (FFRs) are sustained neuroelectrical potentials 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. 2009a, 2009b, 2011, 2012; Marsh and Worden 1969; Moushegian et al. 1973; Ping et al. 2008; Weinberger et al. 1970; Worden and Marsh 1968). FFRs can efficiently convey both TFS information (e.g., Chandrasekaran and Kraus 2010; Du et al. 2011; Galbraith 1994; Krishnan 2002; Krishnan and Gandour 2009; Russo et al. 2004) and envelope information (also called envelope-following response) (e.g., Aiken and Picton 2006, 2008; Dolphin and Mountain 1992, 1993; Hall 1979; Shinn-Cunningham et al. 2013; Supin and Popov 1995; Zhu et al. 2013). FFRs start to occur in the auditory nerve (Dau 2003) and can be intracranially recorded in both the lower auditory brain stem structures (Kuokkanen et al. 2010; Wagner et al. 2005, 2009) and the auditory midbrain, the inferior colliculus (IC) (Du et al. 2009b; Ping et al. 2008). In humans, the origin of human scalp-recorded FFRs has been widely considered to be the IC (e.g., Chandrasekaran and Kraus 2010; Marsh 1974; Smith et al. 1975; Sohmer et al. 1977; Weinberger et al. 1970).

The IC is the end point that both converges inputs from lower auditory brain stem structures and processes IAC signals (Palmer et al. 1999; Shackleton et al. 2005; Shackleton and Palmer 2006; Yin et al. 1987). It is also considered the critical generator for human scalp-recorded FFRs (Chandrasekaran and Kraus 2010; Marsh 1974; Smith et al. 1975; Sohmer et

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1977; Weinberger et al. 1970). This study investigated the following four issues with rats as the mammal modeling subjects: *1*) in the IC, whether a narrowband noise can evoke local-field FFRs that contain the TFS component (FFR_{TFS}) and the envelope component (FFR_{Env}); *2*) whether the FFR_{TFS} and/or FFR_{Env} to interaurally correlated noises are affected by introduction of a BIC; *3*) whether the BIC-evoked change in FFR_{TFS} contributes to the neural BIC detection differently from that in FFR_{Env}; and *4*) whether the binaural integration of IC neuron populations for neural detection of a BIC is based on a simple linear summation (i.e., cross-correlation) of noise signals from the two ears.

MATERIALS AND METHODS

Animal preparation. Eight young adult male Sprague-Dawley rats (age 10–12 wk, weight 280–350 g) were purchased from the Vital River Experimental Animal Company. They were anesthetized with 10% chloral hydrate (400 mg/kg ip), and the state of anesthesia was maintained throughout the experiment by supplemental injection of the same anesthetic. Stainless steel recording electrodes (10–20 kΩ) insulated by a silicon tube (0.3 mm in diameter) except at the 0.25-mm-diameter tip (Du et al. 2009b; Ping et al. 2008) were aimed at the central nucleus of the IC bilaterally. Based on the stereotaxic coordinates of Paxinos and Watson (1997) and referenced to bregma, the coordinates of the aimed IC site were AP, −8.8 mm; ML, ±1.5 mm; DV, −4.5 to −5.0 mm. Two electrodes were inserted per animal, one on each side of the IC.

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 Animals and Humans in 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.

Apparatus and stimuli. All sound waves were processed by a TDT System II (Tucker-Davis Technologies) and presented through two ED1 earphones. 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 narrowband noises were calibrated with a Larson Davis Audiometer Calibration and Electroacoustic Testing System (AUDit and System 824, Larson Davis). The sound pressure level (SPL) of all signals was 72 dB for each earphone.

Gaussian wideband noises (10-kHz sampling rate and 16-bit amplitude quantization) were generated and filtered by a 512-point digital filter with a center frequency of 2,000 Hz and a bandwidth of 0.466 octaves with MATLAB (MathWorks, Natick, MA). The stimulus duration was 900 ms with 10-ms linear onset/offset ramps, and the (offset-onset) interstimulus interval was 100 ms.

Under the baseline-stimulation condition that occurred before and after the occurrence of either the BIC or the interaurally correlated amplitude gap (Corgap), the interaurally correlated noises (IAC = 1) were presented for the total duration of 900 ms. Under the BIC-stimulation condition, a 200-ms uncorrelated noise fragment (IAC = −0.046) was substituted into the temporal middle of the noise (i.e., from 350 to 550 ms from the noise onset) with no interaural delays. Note that mathematically the amplitude of the linear summation of two uncorrelated noises is smaller than that of two correlated noises (Fig. 1). Thus if the central binaural integration follows the simple theoretical summation, the magnitude of neural signals under the BIC-stimulation condition should be smaller than that under the baseline-stimulation condition (Fig. 1*B*, *left*).

Since the linear summation of binaural signals under the BIC-stimulation condition leads to an amplitude reduction (Fig. 1*A*), the Corgap-stimulation condition was introduced as the stimulation control condition. Under the Corgap-stimulation condition, the two monaurally presented noises were identical (correlated), but their ampli-

tudes were equal to 50% of the left-right summated signal amplitude under the BIC-stimulation condition. In other words, the linearly summated left ear and right ear signals under the BIC-stimulation condition and those under the Corgap-stimulation condition are identical (Fig. 1). The BIC and Corgap were distinguished in the value of the IAC coefficient (during the fragment period from 350 to 550 ms after the sound onset). Note that monaurally the intensity of the Corgap-stimulation condition was reduced during the fragment period compared with the pre- and postfragment periods but the monaural intensity under the BIC-stimulation condition was not reduced.

Evoked neural potentials were recorded in a sound-attenuating chamber, amplified 1,000 times by a TDT DB4 amplifier, filtered through a 100- to 10,000-Hz band-pass filter (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 stimuli were used for each animal under a certain stimulation condition. Also, both the prefragment and the postfragment were not changed across stimulation conditions.

Data analyses. Theoretically, a steady-state Gaussian narrowband noise with a center frequency of *c* Hz and a bandwidth of *b* Hz has a TFS energy around *c* Hz and an envelope energy within the frequency range between 0 and *b* Hz (Longtin et al. 2008). Thus for a narrowband noise with bandwidth *b*, the TFS energy distributes from the low-cut (f_{lc}) to the high-cut (f_{hc}) frequencies, and the f_{hc} is below the frequency *b*. The normalized amplitude of FFR_{TFS} can be calculated by the following function:

$$FFR_{TFS} \_ normalized \_ amplitude = \sum_{l=f_{lc}}^{f_{hc}} Amp_l \Big/ \sum_{n=2}^{5,000} Amp_n \quad (1)$$

The normalized amplitude of FFR_{Env} can be calculated by the following function:

$$FFR_{Env} \_ normalized \_ amplitude = \sum_{l=2}^{b} Amp_l \Big/ \sum_{n=2}^{5,000} Amp_n \quad (2)$$

where the denominator represents the level of noise floor ranging from 2 to 5,000 Hz while the numerator represents the spectral region of interest. The FFR_{TFS} and FFR_{Env} components were extracted to calculated normalized amplitude with *functions 1* and *2*.

To estimate the neural detection of the BIC fragment and that of the Corgap fragment, responses in each of the three 200-ms periods were separately processed: prefragment (100–300 ms after noise onset), fragment (350–550 ms), and postfragment (600–800 ms). Furthermore, the (neural) fragment detection index (FDI) was defined as the relative difference between the amplitude of the fragment (BIC or Corgap) and the average of prefragment amplitude and postfragment amplitude (normalized against the average of pre- and postfragment amplitudes).

Statistical analyses. Statistical analyses were performed with IBM SPSS Statistics 20 (SPSS, Chicago, IL). Within-subjects, repeated-measures analyses of variance (ANOVAs), *t*-tests, and Pearson correlation were conducted to examine differences between stimulation conditions or correlation between responses. The null hypothesis rejection level was set at 0.05.

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 μA for 10 s). The brains were stored in 10% formalin with 30% sucrose and then sectioned at 55 μm in the frontal plane in a cryostat (−20°C). Sections were examined to determine locations of recording electrodes.
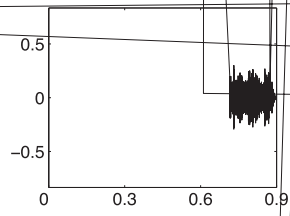
RESULTS

His
the
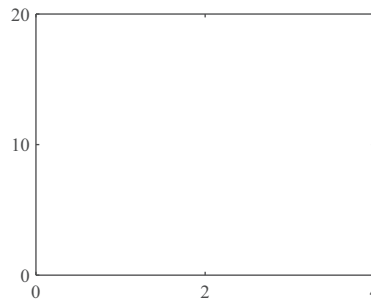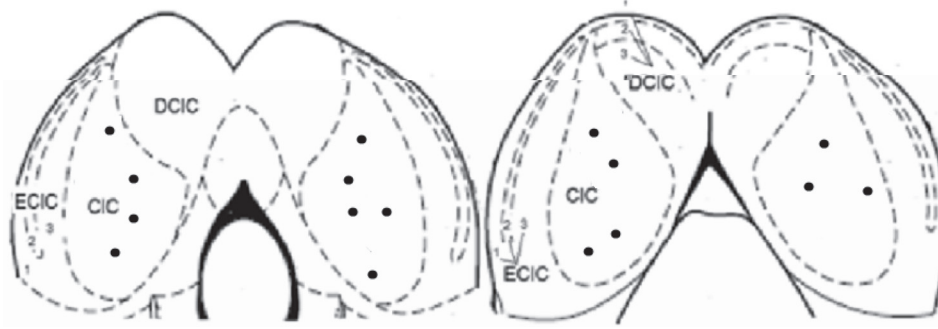
recording sites, $P < 0.05$); the S-R correlation between the noise envelope and the IC FFR_{Env} was also significant (for all recording sites, $P < 0.001$).

To examine whether the BIC and Corgap fragments affected IC FFRs, normalized amplitudes of FFR_{TFS} and FFR_{Env} in the three periods (prefragment, fragment, and postfragment) were calculated separately. Figure 3A shows that both FFR_{TFS} and FFR_{Env} decreased as either the BIC or the Corgap occurred. For the FFR_{TFS}, a 2 × 3 (stimulation condition: BIC, Corgap; response period: prefragment, fragment, and postfragment) two-way repeated-measures ANOVA showed that the both the main effect of stimulation condition ($F_{1,15} = 8.889$, $P = 0.009$, partial $\eta^2 = 0.372$) and the main effect of response period ($F_{1,15} = 22.249$, $P < 0.001$, partial $\eta^2 = 0.597$) were significant but the interaction effect was not significant ($F_{2,30} = 0.606$, $P = 0.552$, partial $\eta^2 = 0.039$). Post hoc tests confirmed that the amplitude of FFR_{TFS} during the BIC was significantly lower than that during the Corgap ($P = 0.031$, with Bonferroni adjustment).

For FFR_{Env}, a two-way repeated-measures ANOVA showed that both the main effect of stimulation condition ($F_{1,15} = 5.563$, $P = 0.032$, partial $\eta^2 = 0.271$) and the main effect of response period ($F_{1,15} = 17.629$, $P < 0.001$, partial $\eta^2 = 0.540$) were significant but the interaction between the two factors was not significant ($F_{2,30} = 2.122$, $P = 0.137$, partial $\eta^2 = 0.124$). Post hoc tests confirmed that the amplitude of FFR_{Env} during the BIC was significantly lower than that during the Corgap ($P = 0.040$, with Bonferroni adjustment).

Post hoc tests also showed that no significant differences occurred between the pre- and postfragments under each of the stimulation conditions (for all $P > 0.05$, with Bonferroni adjustment). Thus the normalized amplitudes of pre- and postfragments were averaged in the following analyses of the fragment effects.

Correlations between fragment detection indexes. The FDI was introduced as the relative amplitude difference between FFRs during the fragment and the average of pre- and postfragment FFRs (for details see MATERIALS AND METHODS).

Fig.
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od, 600–
B: exam
ral fragment
BIC-stimulation
mulation condition
R$_{Env}$ (*right*).

o test whether the FDI under the BIC-stim
d that under the Corgap-stimulation con
mmon neural mechanism, Pearson correl
DI between the two conditions were conducte
d FFR$_{Env}$, separately. As shown in Fig. 3*B*, n
rrelation was found between the two stimula
ns for either FFR$_{TFS}$ or FFR$_{Env}$.

To compare the effect of introduction of a BIC or
the FFR$_{TFS}$ and on the FFR$_{Env}$, the FFR$_{TFS}$-FFR
trix was examined, in which FFR$_{TFS}$ was presented
xis and FFR$_{Env}$ was presented on the *x*-axis (Fig.
n in ig. 4, the majority of the BIC FFR$_{TFS}$ FDIs
the BIC FFR$_{Env}$ FDIs (most filled circles are a
nal). However, this pattern was not present for Co

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his study showed that a steady-state narrowband noise
cit remarkable FFRs in the auditory midbrain IC, whi
e end point integrating inputs from lower auditory brain
structures for binaural processing (Li and Kelly 1992;
et al. 1999; Shackleton et al. 2005; Shackleton and
2006; Yin et al. 1987). Since FFRs are based on
phase-locked responses of neuron populations to ins
waveforms of acoustic stimuli (Chandrasekaran and Kraus
2010; Du et al. 2009a, 2009b, 2011, 2016 sh and Worden
1969; Moushegian et al. 1970 08; Weinberger
al. 1970; Word arrowb

0.5   1   1.5

Fragment Detection Index
(FFR   )
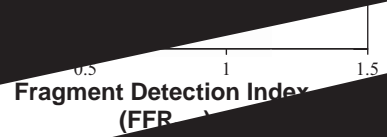
features of a narrowband noise. The results support the concept that FFRs efficiently convey both TFS information (e.g., Chandrasekaran and Kraus 2010; Du et al. 2011; Galbraith 1994; Krishnan 2002; Krishnan and Gandour 2009; Russo et al. 2004) and envelope information (also called envelope-following response) (e.g., Aiken and Picton 2006, 2008; Dolphin and Mountain 1992, 1993; Hall 1979; Shinn-Cunningham et al. 2013; Supin and Popov 1995; Zhu et al. 2013).

More importantly, this study for the first time provides evidence showing that introduction of a BIC reduces both the FFR_{TFS} and FFR_{Env}. Since introducing a BIC does not substantially change monaural inputs, the FFR reduction must be based on binaural interactions, which have been demonstrated previously (Du et al. 2009b). The BIC-induced FFR reduction may be the neural correlate underlying perceptual detection of the BIC (Akeroyd and Summerfield 1999; Boehnke et al. 2002; Huang et al. 2008, 2009a, 2009b; Kong et al. 2012, 2015; Li et al. 2009, 2013).

When the FDI is used to estimate the degree of FFR changes caused by introducing a fragment (BIC or Corgap), the BIC-induced FDI for FFR_{TFS} is larger than that for FFR_{Env}, indicating that introduction of a BIC causes more reduction in FFR_{TFS} than in FFR_{Env}. The Boehnke et al. (2002) study showed that the envelope information is not as important as the TFS information in determining the detection of the BIC detection. Clearly, further perceptual work is needed to verify whether the processing of FFR_{TFS} contributes more to the BIC detection than the processing of FFR_{Env}. However, the Corgap-induced FDI for FFR_{TFS} is not significantly different from that for FFR_{Env}. Since IAC-based binaural processing plays a role in both sound localization (Coffey et al. 2006; Franken et al. 2014; Soeta and Nakagawa 2006) and target-object detection against masking (Durlach et al. 1986; Palmer et al. 1999), further perceptual work is also needed to verify whether FFR_{TFS} signals are more involved in sound localization and target unmasking than FFR_{Env} signals. Smith et al. (2002) have suggested that TFS signals and envelope signals are most important for pitch/location perception and speech recognition, respectively. It is of interest to know whether this functional dichotomy between TFS and envelope is associated with certain differences in sensitivity to the BIC between FFR_{TFS} and FFR_{Env}.

The IC is the end point converging inputs from lower auditory brain stem structures (Palmer et al. 1999; Shackleton et al. 2005; Shackleton and Palmer 2006; Yin et al. 1987). Previous studies have suggested that binaural integration occurs in the IC (Du et al. 2009b; Kelly and Li 1997; Li and Kelly 1992). Does the IAC-based binaural integration follow a simple linear summation (cross-correlation) function? The results of this study indicate that for either FFR_{TFS} or FFR_{Env} the BIC-induced FDI is independent of the Corgap-induced FDI. Thus the BIC-induced changes in FFRs cannot be explained by a simple signal input reduction.

Summary. In the IC, a narrowband noise can efficiently induce FFRs that contain both the FFR_{TFS} and FFR_{Env} components, signaling the center frequency and bandwidth, respectively. Introduction of a BIC reduces both FFR_{TFS} and FFR_{Env}, and the FFR reductions cannot be explained by a simple reduction in linear summation of signal inputs from the two ears.

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