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Research Paper

# Correlation between the frequency difference limen and an index based on principal component analysis of the frequency-following response of normal hearing listeners

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Subcortical phase locking tends to reflect performance differences in tasks related to pitch perception across different types of populations. Enhancement or attenuation in its strength may correspond to population excellence or deficiency in pitch perception. However, it is still unclear whether differences in perceptual capability among individuals with normal hearing can be predicted by subcortical phase locking. In this study, we examined the brain-behavior relationship between frequency-following responses (FFRs) evoked by pure/sweeping tones and frequency difference limens (FDLs). FFRs are considered to reflect subcortical phase locking, and FDLs are a psychophysical measure of behavioral performance in pitch discrimination. Traditional measures of FFR strength were found to be poorly correlated with FDL. Here, we introduced principal component analysis into FFR analysis and extracted an FFR component that was correlated with individual pitch discrimination. The absolute value of the score of this FFR principal component (but not the original score) was negatively correlated with FDL, regardless of stimulus type. The topographic distribution of this component was relatively constant across individuals and across stimulus types, and the inferior colliculus was identified as its origin. The findings suggest that subcortical phase locking at certain but not all FFR generators carries the neural information required for the prediction of individual pitch perception among humans with normal hearing.



## 1. Introduction

Pitch is a sound attribute that is essential for conveying musical melody, expressing conversational mood, and providing semantic cues via tonic differentiation in tone languages (Bendor and Wang, 2006; Yost, 2009). Increasing evidence suggests that subcortical structures may play an important role in the processing of linguistic and musical pitch (Krishnan and Gandour, 2009; Bidelman, 2013). Temporal cues, to which the perception of tone pitch at low frequencies is often attributed (e.g. Moore, 2012), are well preserved at the auditory periphery and brainstem, but they are represented more by non-synchronized firing rates in thalamus and auditory cortex (Wang et al., 2008). Therefore, a comprehensive understanding of pitch perception in humans requires evaluation at subcortical levels, especially the auditory brainstem.

One way to study whether subcortical temporal cues may represent pitch perception in humans is to examine the relevance of neural phase locking to behavioral performance (Plack et al., 2014), either among various populations or among individuals within one population. The human frequency-following response (FFR), a non-invasively recorded brainstem potential, reflects periodicity in stimulus sounds and serves as an electrophysiological measure of subcortical phase locking (reviewed in Krishnan, 2007). The strength of the FFR seems to differ between populations that show performance differences in tasks related to pitch perception. For instance, musicians and tone language speakers possess

*Abbreviations:* APWF, a posteriori Wiener filtering; DISS, global dissimilarity; EEG, Electroencephalography; FDL, frequency difference limen; FEM, finite element model; FFR, frequency-following response; GFP, global field power; IC, inferior colliculus; MNI, Montreal Neurological Institute; PC, principal component; PCA, principal component analysis; SNR, signal-to-noise ratio; TANOVA, topographic analysis of variance

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improved perceptual capability regarding pitch (Bidelman et al., 2013), and their FFRs are enhanced relative to those observed in non-musicians (Wong et al., 2007; Musacchia et al., 2007; Bidelman et al., 2011a) or non-tone language speakers (Krishnan et al., 2005; Jeng et al., 2011). Likewise, FFRs are relatively deficient in populations like the elderly (Clinard and Cotter, 2015) and individuals with sensorineural hearing loss (Ananthakrishnan et al., 2016), who have degraded pitch perception (Moore and Peters, 1992). Furthermore, short-term training has been shown to increase FFR strength and improve performance in tasks requiring pitch perception (Song et al., 2008; Carcagno and Plack, 2011). These findings suggest a connection between subcortical phase locking and performance in pitch-related tasks.

Here we examined whether there exists a brain-behavior relationship between subcortical phase locking and behavioral performance in pitch perception among young normal hearing individuals. Results of relevant studies are mixed. Krishnan et al. (2012) reported a significant correlation between FFR strength and behavioral performance in pitch discrimination. However, this correlation was driven by manipulation of the pitch salience of the stimuli. Similarly, Marmel et al. (2013) reported a significant correlation between FFR strength and pitch discrimination capability. However, their study involved multiple populations including the elderly and the hearing impaired. Therefore, the reported correlation may be caused by the factors (aging and hearing loss) that involve individuals of different populations and may not be convincingly generalized to listeners with normal hearing. Clinard et al. (2010) investigated a population comprised of individuals with normal hearing and did not find a significant brain-behavior relationship (even though the age range was large). Nor did Bidelman et al. (2011b) find a significant correlation between behavioral performance in fundamental frequency discrimination and the strength of FFRs evoked by three of the four musical notes with slightly different fundamental frequencies (even though the subjects included both musicians and non-musicians). Note that they reported a significant correlation between behavioral performance and the strength of FFRs evoked by one of the notes, across all subjects and among musicians. Owing to the stimulus specificity, their findings are insufficient to support a firm brain-behavior relationship among normal hearing individuals or musicians. To our knowledge, it is still uncertain whether subcortical phase locking bears neural information for predicting individual pitch perception among young individuals with normal hearing, especially those without special musical training.

FFRs, especially those evoked by pure tones, originate from multiple nuclei in the auditory brainstem (Stillman et al., 1978; Gardi et al., 1979; Davis and Britt, 1984). Thus, it is conceivable that FFR source waves from structurally and/or functionally different generators represent individual pitch perception to different extents. In addition, the interference of cochlear microphonics, which may only minimally represent pitch perception, is almost inevitable (Sohmer and Pratt, 1977; Hou and Lipscomb, 1979; Chimento and Schreiner, 1990). In order to further investigate the relationship between subcortical phase locking and individual pitch perception, it is necessary to focus on FFR components that can represent individual pitch perception and to exclude the interference of those that cannot. However, traditional measures of FFR strength essentially refer to the magnitude of the mixture of all FFR source waves. Therefore, they may be vitiated by cancellations among the multiple source waves and fail to reflect the strength of the FFR components of interest.

In the present study, we hypothesized that individual differences in pitch perception between young individuals with normal hearing may be represented by differences in subcortical phase locking. This hypothesis was examined in two experiments aimed at investigating the brain-behavior correlation between FFRs and frequency difference limens (FDLs). The aim of experiment 1 was to search for a neural index reflecting individual rankings in pitch discrimination capability, and the aim of experiment 2 was to explore the physiological basis of this index. In experiment 1, FDLs were measured at a low frequency, and FFRs were evoked by pure/sweeping tones. It was predicted that the correlations between FDL and traditional measures of FFR strength would be weak and insignificant. Principal component analysis (PCA) was then used to analyze the individual differences in FFRs among all subjects. Since the PCA projected the FFRs onto several orthogonal bases where the data variance maximized, the FFR source waves mixed in the scalp-recorded responses were likely to be separated. It was predicted that at least one principal component (PC) would be correlated with FDL. In experiment 2, topographic distributions of various PCs were obtained from multichannel data acquired for a subset of the subjects for the same stimulation as in experiment 1. As the PC(s) that was significantly correlated with FDL likely originated from a structurally and functionally compatible configuration of neural generators, it was predicted that the FDL-correlated PC(s) would be greater in field power than those not correlated with FDL and would have a relatively consistent topographic distribution across subjects. Probable underlying neural generators were then identified with source reconstruction based on the equivalent dipole model.

Sweeping tones in addition to pure tones were used to evoke FFRs in this study. Previous reports have confirmed that the FFR can dynamically track the time-variant frequency contours of both sweeping tones (Krishnan and Parkinson, 2000; Clinard and Cotter, 2015) and speech sounds (Krishnan et al., 2005). Here, sweeping tones provided a chance to (1) test the repeatability of the findings, (2) help confirm the dominance of subcortical contributions in the recorded FFRs through a relatively precise estimation of FFR latency, and (3) examine the possible effect of a frequency shift in stimuli on FFR indices.

## 2. Methods

### 2.1. Subjects

Seventeen students (seven females; mean $\pm$ SD age, 21 $\pm$ 3 years) from Tsinghua University and its affiliated high school participated in experiment 1, and eight of them (four females) participated in experiment 2. All subjects were native mandarin Chinese speakers with normal hearing. Pure tone thresholds for tested ears were all below 20 dB hearing level at octave frequencies from 250 to 8000 Hz. None of the subjects had a history of neurological or psychiatric diseases. None received formal musical training. All subjects were paid for their time and gave informed consent to the experiment protocol approved by the Institutional Review Board at Tsinghua University (IRB00008273).

### 2.2. Stimuli

Stimuli in the behavioral section were pure tones at frequencies equal to or higher than 146.8 Hz. Stimuli in the electrophysiological section included five types: pure tones at 146.8 Hz (PT), ascending and descending sweeping tones between 146.8 and 164.8 Hz (Up1 and Down1), and ascending and descending sweeping tones between 146.8 and 207.7 Hz (Up2 and Down2). 146.8 Hz, 164.8 Hz, and 207.7 Hz are respective pitches of musical tones D3, E3, and G♯3. Therefore, the stimuli used in this study sounded like “musical notes and glides”.

Behavioral measurements were run on a custom platform controlled by a program written in Matlab (R2013b; MathWorks).