Exponential modeling of human frequency-following responses to voice pitch

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Abstract

Objective: Recent studies have shown that the frequency-following response (FFR) to voice pitch can be a useful method to evaluate the signal-processing mechanisms and neural plasticity in the human brainstem. The purpose of this study was to examine the quantitative properties of the FFR trends with an exponential curve-fitting model. Design: FFR trends obtained with increasing number of sweeps (up to 8000 sweeps) at three stimulus intensities (30, 45, and 60 dB nHL) were fit to an exponential model that consisted of estimates of background noise amplitude, asymptotic response amplitude, and a time constant. Five objective indices (Frequency Error, Slope Error, Tracking Accuracy, Pitch Strength and RMS Ratio) were used to represent different perspectives of pitch processing in the human brainstem. Study Sample: Twenty-three native speakers (16 males; age = 24.7 ± 2.1 years) of Mandarin Chinese were recruited. Results: The results demonstrated that the exponential model provided a good fit ($r^2 = 0.89 ± 0.10$) to the FFR trends with increasing number of sweeps for the five objective indices. Conclusions: The exponential model, combined with the five objective indices, can be used for difficult-to-test patients and may prove to be useful as an assessment and diagnostic method in both clinical and basic research efforts.

Key Words: Frequency-following response; Voice pitch; Exponential model; Number of sweeps

The scalp-recorded frequency-following response (FFR) to voice pitch has become widely accepted as a useful method for studying the signal-processing mechanisms and the neural plasticity of the human brainstem for normal and pathological populations. Recent studies have shown that neurons in the human brainstem are malleable elements and can be affected by the listener’s language experience (Krishnan et al, 2005, 2009; 2010; Swaminathan et al, 2008), long-term musical training (Johnson et al, 2008; Musacchia et al, 2007; Strait et al, 2009; Wong et al, 2007), and short-term auditory training (Russo et al, 2005; Song et al, 2008). As measured through FFR, some children with autism spectrum disorders (Russo et al, 2008) and reading and spelling difficulties (Chandrasekaran et al, 2009) have shown decreased accuracy in tracking changes in voice pitch. Developmental trajectories of the FFR to voice pitch have also been described through studies in normal-hearing children (Johnson et al, 2008) and infants (Jeng et al, 2010). Given the increasing clinical utilities of the FFR to voice pitch, the amount of time needed to complete a recording becomes an important issue to address. The purpose of this study was to quantify the dependency of the FFR to voice pitch on the number of sweeps through the use of an exponential model. A major factor affecting the quality of recordings is the signal-to-noise ratio (SNR). It is known that SNR is affected by number of sweeps; therefore, number of sweeps was chosen as the quantitative factor in determining its role on quality of the FFR to voice pitch. It is also understood that for any individual participant, a specific number of sweeps cannot guarantee a given SNR.

One challenge in recording an FFR to voice pitch is the relatively low SNR of the response waveform taken from an individual.
The FFR reflects a small amplitude response, usually on the order of hundreds of nanovolts (Gardi et al, 1979; Krishnan et al, 2004; Jeng et al, 2010; Li & Jeng, 2011), whereas the background noise (physiological and non-physiological) is larger, usually in the range of 10–20 μV. Among many possible ways to improve the SNR of a recording, signal averaging is one of the most commonly used approaches in clinics and research laboratories. Signal averaging takes advantage of the time-locked feature between the onset of the stimulus and that of the computer analysis sweeps. With progressively more sweeps included in the average, the background noise (due to its nature of randomness) will be averaged toward a zero mean. In contrast, neural responses to the external auditory event are time-locked to the stimulus onset and will be summed with increasing number of sweeps. That is, in order to successfully identify an FFR, a certain number of stimulus presentations and recording sweeps will be needed to reduce the background noise to an extent such that the FFR is distinguishable from the background noise. Although it is almost impossible to pre-determine an exact number of sweeps for a given population, a reasonable range can be estimated using a post hoc analysis of recordings containing a large number of sweeps. Effects of the number of sweeps can then be assessed by including progressively higher numbers of sweeps into the average (e.g. comparing sub-averages of the first 500, 1000, 1500, 2000, and up to 8000 sweeps).

For conventional auditory evoked potentials such as the auditory brainstem response (ABR) to click stimuli, it has been reported that the SNR changes according to the following formula (Hood, 1998; Hall, 2006; Thornton, 2007).

\[
\text{SNR} = \frac{\text{response amplitude}}{\text{noise amplitude}} \times (\text{number of sweeps})^{1/2}
\]

That is, SNR changes with the square root of the number of sweeps. SNR will increase quickly in the beginning of a recording and reach an asymptotic value when more sweeps are included. Also, according to this formula, SNR is affected by at least three factors. The first factor is the response amplitude, which is inherent to the integrity and excitability of the auditory system for each individual. Although the amplitude of a response varies between individuals (due to the properties of the individual’s volume conduction and the location and orientation of the ABR sources relative to the electrode montage), response amplitude usually does not vary dramatically within an individual and is primarily affected by the intensity of the stimulus token. The second factor is the amplitude of noise, which can be physiological (e.g. ongoing brain activities that are not synchronized to the stimulus) or non-physiological (e.g. ambient noise) in origin. Note that, in deriving the SNR, the units for measuring the response and noise amplitudes are the same. The third factor is number of sweeps. As stated above, noise amplitude in the average declines with an increasing number of sweeps and, consequently, SNR is improved.

Although the square-root relationship between the amplitude of noise and the number of sweeps has been well established (Don & Elberling, 1994, 1996), in the presence of an evoked potential, response trends of a specific aspect of the evoked potential will likely deviate from the original square-root relationship, which is solely determined by the decrement of noise. Several mathematical models have been used to capture the response trends of various neural activities in the auditory system (Miller et al, 2006; Nourski et al, 2005). For example, Don and Elberling (1996) reported the usefulness of employing quantitative measures of ABR peak amplitude and residual background noise in the decision to stop averaging. Nourski and colleagues (2005) also successfully used an exponential model to describe the time course of the effects of acoustic noise on electrically evoked auditory compound action potentials in guinea pigs’ auditory nerves. For responses elicited by the sustained portion of a stimulus, such as the FFR to voice pitch, it has not yet been determined if the same formula would provide a good fit to the FFR trends.

There are two general approaches that can be used to quantify the repeating pattern (i.e. periodicity) of a sampled signal. One is to measure the strength of the overall periodicity of a sampled signal in the temporal domain by using an autocorrelation algorithm (Krishnan et al, 2005; Wong et al, 2007; Jeng et al, 2011). Briefly, this method employs an autocorrelation function that multiplies a sampled signal with a time-shifted copy of itself. Strength of the overall periodicity of the sampled signal is then determined by calculating the peak-to-trough amplitude within a certain range of time shifts in the normalized autocorrelation output. The other approach is to examine how accurately the spectral energy of a response follows the fundamental frequency (\(f_0\)) contour of the stimulus by using a narrow-band spectrogram algorithm (Russo et al, 2008; Song et al, 2008; Jeng et al, 2011). Briefly, this algorithm analyses the spectral components of an incoming signal by using a sliding-window technique. In this study, we used a window size of 50 ms and a step size of 1 ms when plotting the narrow-band spectrogram of a sampled signal. For each time bin (i.e. each windowed segment of the sampled signal), this algorithm searches for the frequency that contains the largest spectral density in a pre-defined frequency range. An \(f_0\) contour of the sampled signal was then constructed by concatenating the fundamental frequencies estimated from each of the time bins. When an FFR is present, spectral components of a recording that are in close proximity to the \(f_0\) contour of the stimulus would have relatively larger and distinguishable spectral energy than the frequency components that are further from the \(f_0\) contour of the stimulus. Thus, small spectral energies in the frequency range around the \(f_0\) contour of the stimulus token could be quantitatively analysed.

To better quantify the response trends of the FFR to voice pitch from the time and frequency domains, both pitch-extraction algorithms were used. Specifically, five objective indices: Frequency Error, Slope Error, Tracking Accuracy; Pitch Strength and RMS (root-mean-square) Ratio were included (Krishnan et al, 2005; Russo et al, 2008; Skoe & Kraus, 2010; Song et al, 2009; Wong et al, 2007) to represent different aspects of pitch processing in the human brainstem. The first index, Frequency Error, represents a measure of the accuracy of pitch-encoding during stimulus presentation. Slope Error indicates the brainstem’s ability to preserve the overall shape of the pitch contour of the stimulus signal. Tracking Accuracy reflects the overall faithfulness of pitch tracking between

<table>
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<th>Abbreviations</th>
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<tr>
<td>ABR</td>
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<tr>
<td>(A_{AS})</td>
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<tr>
<td>(A_{\text{noise}})</td>
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<td>(f_0)</td>
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<td>FFR</td>
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<td>SNR</td>
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\[\text{SNR} = \frac{\text{response amplitude}}{\text{noise amplitude}} \times (\text{number of sweeps})^{1/2}\]
the stimulus and response f0 contours. Pitch Strength denotes the robustness of the phase-locking phenomenon in the human brainstem. RMS Ratio represents the dB relationship of the RMS amplitude of a response to that of noise.

Materials and Methods

Experimental protocols and procedures used in this study were approved by the China Medical University Hospital (Taichung, Taiwan) Institutional Review Board. All recordings were obtained in an acoustically-treated chamber in the Auditory Electrophysiology Laboratory at the China Medical University Hospital.

Participants

Twenty-three adult participants (16 males; mean ± S.D. = 24.7 ± 2.1 years), with hearing sensitivity ≤ 20 dB HL at octave frequencies from 125 to 8000 Hz, were recruited. All participants were native speakers of Mandarin Chinese.

Stimulus parameters and calibration

A monosyllabic Mandarin Chinese speech token /yi/, meaning aunt, with a rising pitch (117–166 Hz) was utilized to evoke the FFR. This stimulus token had a duration of 250 ms with 10-ms rise and fall times of the stimulus envelope. Stimulus presentation and trigger synchronization was controlled by custom-made software written in LabView 8.0 (National Instruments, Austin, USA). For each recording, the stimulus token was presented up to about 8800 times with a silent interval of 45 ms between the offset of a stimulus token and the onset of the next. All stimulus tokens were routed through a silent interval of 45 ms (i.e. the same silent interval used in the FFR control condition) was not performed due to time constraints. Continuous recordings were then digitized at a rate of 20000 samples/s using a 12-bit analog-to-digital converter (National Instruments, DAQ 6062E). Continuous recordings were obtained using custom-written LabView software and stored on a computer for offline analysis.

To enhance the detectability and visibility of the FFR and minimize the contamination of stimulus artifact, a few procedural steps and precautions were exercised in this study. First, all waveforms were recorded in an acoustically-attenuated and electromagnetically-shielded sound booth to reduce environmental noise. Second, the insert earphone and the stimulation cable were electromagnetically shielded to minimize electromagnetic leakage from the stimulation equipment to the recording cables. Finally, to better visualize the FFR on a spectrogram, a high-order bandpass filter was used to 'extract' the spectral energy within the frequency region of interest (e.g. 100 to 1500 Hz). One drawback of applying a high-order filter, in this case a 500-pole digital filter, is that it introduces a noticeable filter delay in the output. To accommodate the 250 data-point filter delay (i.e. 12.5 ms delay with a recording sampling rate of 20 000 samples/s), all recordings began at least three seconds before the first stimulus token was delivered to the listener’s ear. The filter delay was corrected in data analysis of all recordings. It was also important to note that a control condition (i.e. sound tube plugged and removed from the listener’s ear canal) which had been used in previous studies (e.g. Jeng et al., 2010, 2011) demonstrated that the recordings obtained were physiological in nature. For the current study, the same stimulation and recording techniques were used; however, the control condition was not performed due to time constraints.

Data analysis

All data were analysed using MatLab 2008a (MathWorks, Natick, USA). To better isolate spectral energies at the f0 contours, continuous recordings were digitally bandpass filtered using a brickwall, linear-phase finite-impulse-response filter (cutoff frequency 100–1500 Hz, 50th order). Filtered recordings were segmented into sweeps of 250 ms in length. An individual sweep was rejected if it contained voltages greater than ± 25 μV. During each recording condition, the rejection rate was less than 10% and a total of 8000 accepted sweeps were included for averaging. Recordings obtained from a distinct number of sweeps, starting from the first sweep, were averaged. The numbers of sweeps used in averaging were 1, 10, 20, 50, 100, 200, 500, 800, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3500, 4000, 5000, 6000, 7000, and 8000. Each averaged waveform was subject to the following analytical procedures. First, cross-correlation of the stimulus and an averaged waveform was performed to identify the time shift that produced the maximum cross-correlation value within the 3–10 ms response window (Galbraith et al., 2001; Russo et al., 2005). Second, a 250-ms segment of the recording was extracted from the averaged waveform starting from the time shift that produced the maximum cross-correlation value. Finally, the same analytical procedures were applied to all other averaged waveforms. Data obtained from each stimulus level were analysed separately.
Extraction of f0 contours

A narrow-band spectrogram was used to extract the pitch information of a sampled signal. All averaged recordings were first segmented using a 50-ms Hanning window with a step size of 1 ms which resulted in a total of 201 time bins to be analysed. Each time bin was zero-padded to 1 s and provided a 1-Hz resolution in the spectrogram. For each time bin, the frequency that corresponded to the maximal peak of the spectral density was searched within a pre-defined frequency range and determined as the f0 estimate for that time bin. This procedure was repeated for all time bins. All f0 estimates were concatenated to constitute the f0 contour of an averaged recording. A pre-defined frequency range (107–176 Hz) was used to fit with the specific pitch contour of the stimulus and allow a buffer of 10 Hz for error measurements. The same technique was applied to the stimulus token and averaged recordings.

Objective indices

Five objective measures (Frequency Error, Slope Error, Tracking Accuracy, Pitch Strength, and RMS Ratio) were used to quantify the pitch-tracking accuracy and phase-locking magnitude of the responses. These objective indices are described as follows. (1) Frequency Error represented the accuracy of pitch-encoding during stimulus presentation. This index was computed as the absolute Euclidian distance between the stimulus and recording f0 contours for each time bin and averaged across the 201 time bins. (2) Slope Error indicated the degree to which the shapes of the pitch contours were preserved in the brainstem, and was derived by subtracting the slope of the regression line of the stimulus f0 contour from the regression slope of the recording f0 contour. The estimated slope of the stimulus token used in this study was 275 Hz/s. (3) Tracking Accuracy denoted the overall faithfulness of pitch tracking between the stimulus and response f0 contours and was calculated by finding the linear regression ‘r’ value on a recording-versus-stimulus f0 contours plot. (4) Pitch Strength measured the robustness of phase-locking in the brainstem and was derived from an autocorrelation function that allowed the measurement of overall periodicity of a sampled signal. Specifically, each recording was multiplied by a copy of itself with increasing time shifts. For each time shift, an autocorrelation value was calculated and finding was multiplied by a copy of itself with increasing time shifts. (5) RMS Ratio provided an estimate of the FFR amplitude relative to that of the ongoing neural activity not synchronized to the stimulus. FFR amplitude was calculated by finding the RMS amplitude of the extracted 250-ms segment of an averaged waveform. To obtain an estimate of the background physiological noise, waveforms were extracted from a 10-ms pre-stimulus interval to determine the amount of brainstem activities not synchronized to the stimulus. RMS Ratio was then calculated as the dB ratio of the FFR RMS amplitude relative to that of the noise.

Exponential curve fitting on the FFR trends of pitch-encoding

Measurements of each of the objective indices (Frequency Error, Slope Error, Tracking Accuracy, Pitch Strength, and RMS Ratio) were analysed as a function of number of sweeps. For Frequency Error and Slope Error, which had descending trends with increasing number of sweeps, the following model was used to describe the dependency of the FFR to voice pitch on the number of sweeps included in the averaging procedure.

\[ A(n) = A_{\text{noise}} \left( e^{-\frac{n}{\tau}} \right) - A_{AS} \]  

where \( A \) is an objective measure (i.e. Frequency Error or Slope Error) of the FFR to voice pitch; \( n \) is the number of sweeps included in the averaging process; \( A_{\text{noise}} \) represents the amplitude of noise and is derived from the fitted curve of the FFR trend of a specific objective index when the number of sweeps equals 1 (i.e. units of \( A_{\text{noise}} \) remain the same for each of the five objective indices); \( A_{AS} \) represents the asymptotic amplitude of the response and is computed from the fitted curve of the exponential model with the number of sweeps being 8000; \( e \) is Euler’s number: 2.7182; \( \tau \) is the ‘time’ constant of the fitted curve that denotes the number of sweeps needed to reach its 63% asymptotic amplitude. Calculation and derivation of the 63% asymptotic amplitude is based on the mathematical principle that the exponential function, with a base of \( e \), is identical to its derivative (Courant & Robbins, 1996; Goldstein et al, 2009). For example, when \( n \) equals \( \tau \), an ascending exponential function with zero noise will be: \( A(n) = A_{AS} (1 - e^{-\frac{n}{\tau}}) = A_{AS} (1 - e^{-1}) = 0.63 A_{AS} \).

For Tracking Accuracy, Pitch Strength, and RMS Ratio, which had ascending trends with increasing number of sweeps, an alternative model was used to describe the response trends of these objective indices. Note \( A_{\text{noise}} \) and \( A_{AS} \) were exchanged in place due to the nature of an ascending exponential trend.

\[ A(n) = A_{AS} (1 - e^{-\frac{n}{\tau}}) - A_{\text{noise}} \]

Results

Temporal and spectral energies of the FFR to voice pitch were visualized by plotting the averaged time waveforms and spectrograms of each recording. Figure 1 shows a typical set of the FFR time waveforms (A) and spectrograms (B) at three different stimulus intensities. Each row represents the time waveforms and spectrograms of a recording that were averaged by including a certain number of sweeps. In this example, the FFR was difficult to distinguish from the background noise with less than 1000 sweeps for the three stimulus intensities. However, the FFR became visually identifiable when the number of sweeps was progressively increased up to about 8000 sweeps.

Quantitative analyses of the FFR to voice pitch

In order to quantify the FFR to voice pitch, responses were analysed using the methods noted above. Figure 2 represents an example of the f0 contour of a response (left panel) and the autocorrelation output (right panel) of a recording obtained at 60 dB nHL. This response was obtained by including 8000 sweeps in the averaging process. In terms of the accuracy of pitch tracking (left panel), the f0 contour of the response generally followed the f0 contour of the stimulus. In terms of the strength of phase-locking, autocorrelation output of the same recording (right panel) demonstrated overall periodicity of the recording. Pitch Strength of the response
was calculated from the peak-to-trough amplitude starting from the positive peak (within the 5–10 ms time shifts) to the following negative trough in the normalized autocorrelation output. The response $f_0$ contour and autocorrelation curve seen in this figure are typical of those observed in the 23 participants across the three stimulus intensities.

**FFR trends with respect to different objective indices**

As the FFR to voice pitch contains enriched information of pitch-encoding mechanisms in the human brainstem, the five objective indices used in this study quantified the FFR from different perspectives. Figure 3 plots the mean Frequency Error (A), Slope Error (B), Tracking Accuracy (C), Pitch Strength (D), and RMS Ratio (E) as a function of number of sweeps.

Relatively large values of Frequency Error (A) were observed when the averaging included only a limited number of sweeps. When the number of sweeps was increased, Frequency Error declined dramatically and appeared to reach a steady-state, asymptotic amplitude. At 60 dB nHL, Frequency Error was about 18 Hz for 10 sweeps, declined with increasing number of sweeps, and then reached a steady-state of about 7 Hz at around 5000–8000 sweeps. Frequency Error at 45 and 30 dB nHL showed similar trends and declined from about 16 to 9 Hz, and 18 to 11 Hz, respectively. Although three stimulus intensities showed similar values of Frequency Error at low numbers of sweeps (e.g. ≤10 sweeps), the
Exponential modeling of the FFR trends

To better quantify the decreasing and increasing trends of pitch processing in the human brainstem as a function of number of sweeps, data obtained from the 23 participants were fit to either a descending or ascending exponential model as noted above. Figure 4 shows the exponential curves that best fit the pitch-encoding trends of Frequency Error, Slope Error, Tracking Accuracy, Pitch Strength, and RMS Ratio at three different stimulus intensities. Equations and goodness of fit ($r^2$) are displayed in each panel. The exponential model used in this study provided a good fit to the pitch-encoding trends in the human brainstem, with a mean $r^2$ value of 0.89 and standard deviation of 0.10, across the five objective indices and three stimulus intensities. For clarity, dotted and dashed lines were used in each panel to indicate the estimates of the noise amplitude ($A_{noise}$) and response asymptotic amplitude ($A_{AS}$) of the fitted curve, respectively. The $A_{noise}$ and $A_{AS}$ values were calculated from the fitted curves of the FFR trends when the numbers of sweeps were 1 and 8000, respectively.

Frequency Error (Figure 4, A) of the fitted curves had asymptotic amplitudes (i.e. $A_{AS}$) of 10.78, 7.23, and 6.09 Hz at 30, 45, and 60 dB nHL, respectively. The fact that Frequency Error reached a smaller asymptotic value at higher stimulus intensities indicated the dependency of the Frequency Error measurement on stimulus intensities. Estimates of the noise amplitudes (i.e. $A_{noise}$) of the fitted curves for Frequency Error were 16.02, 14.31, and 16.37 Hz for 30, 45, and 60 dB nHL, respectively. The unfavorable noise amplitudes of Frequency Error reflected the poor signal-to-noise ratios when only a limited number of sweeps was included in the averaging procedures. In addition to the $A_{AS}$ and $A_{noise}$ estimates, another important parameter in our exponential model was the $\tau$ value which indicated the number of sweeps needed to reach its 63% asymptotic amplitude of the response. The $\tau$ values of the fitted curves for Frequency Error were 3940, 3110, and 1578 sweeps at 30, 45, and 60 dB nHL, respectively. It is important to note that the $\tau$ values decreased with increasing stimulus intensity. This finding indicated that higher stimulus intensities (e.g. 60 dB nHL) produced a faster improvement in pitch-tracking acuity (i.e. less Frequency Error) in the human brainstem than lower stimulus intensities (e.g. 30 dB nHL).

Slope Error (Figure 4, B) showed similar trends to Frequency Error. The asymptotic amplitudes were 182.66, 101.91, and 82.67 Hz/s at 30, 45, and 60 dB nHL, respectively. The unfavorable noise amplitudes of Slope Error reflected the poor SNRs when only a limited number of sweeps was included in the averaging procedures. In addition, the $A_{AS}$ and $A_{noise}$ estimates of the fitted curves at 30, 45, and 60 dB nHL were 234.15, 190.02, and 206.37 Hz/s, respectively.
limited number of sweeps were included. The $\tau$ values of the fitted curves for Slope Error were 3310 sweeps at 30 dB nHL, decreased to 2030 sweeps at 45 dB nHL, and 1932 sweeps at 60 dB nHL. Note that higher stimulus intensities produced a faster improvement (i.e. less Slope Error) in preserving the shape of the stimulus $f_0$ contour in the FFR than lower stimulus intensities.

Tracking Accuracy (Figure 4, C) of the fitted curves demonstrated an ascending trend with increasing number of sweeps. Tracking Accuracy of the fitted curves had asymptotic amplitudes of 0.41, 0.72, and 0.75 at 30, 45, and 60 dB nHL, respectively. Noise amplitudes of the fitted curve for Tracking Accuracy were 0.24, 0.30, and 0.15 at 30, 45, and 60 dB nHL, respectively. The $\tau$ values of the fitted curves were 5527 sweeps at 30 dB nHL, decreased to 2633 sweeps at 45, and 1299 sweeps at 60 dB nHL. Higher stimulus intensities produced better pitch-tracking accuracy (i.e. larger asymptotic amplitudes) at a faster rate (i.e. smaller $\tau$ values) than lower stimulus intensities.

Pitch Strength (Figure 4, D) showed similar trends as those observed in Tracking Accuracy. The asymptotic amplitudes of the fitted curve for Pitch Strength were 0.54, 0.54, and 0.63 at 30, 45, and 60 dB nHL, respectively. Noise amplitudes of the fitted curves were 0.20, 0.27, and 0.16 at 30, 45, and 60 dB nHL, respectively. The $\tau$ values of the fitted curves for Pitch Strength were 9634 sweeps at 30 dB nHL, which decreased to 3737 sweeps at 45 dB nHL, and 1767 sweeps at 60 dB nHL. Note that higher stimulus intensities produced a larger enhancement (i.e. larger asymptotic amplitudes) of neural phase-locking in the human brainstem at a faster rate (i.e. smaller $\tau$ values) than lower stimulus intensities.

RMS Ratio (Figure 4, E) showed similar trends as those observed in Tracking Accuracy and Pitch Strength.

**Figure 3.** FFR trends revealed by plotting the mean values of Frequency Error (A), Slope Error (B), Tracking Accuracy (C), Pitch Strength (D), and RMS Ratio (E) as a function of number of sweeps. Stimulus intensities are plotted using different symbols. Vertical error bars indicate one standard error.
Table 1. Means and standard deviations of the FFR amplitude, noise amplitude and RMS Ratio at three stimulus intensities.

<table>
<thead>
<tr>
<th>Number of sweeps</th>
<th>30 dB nHL</th>
<th>45 dB nHL</th>
<th>60 dB nHL</th>
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<tr>
<td></td>
<td>FFR amplitude (nV)</td>
<td>Noise amplitude (nV)</td>
<td>RMS Ratio (dB)</td>
</tr>
<tr>
<td>8000</td>
<td>35 (4)</td>
<td>38 (14)</td>
<td>+0.43 (2.93)</td>
</tr>
<tr>
<td>6000</td>
<td>35 (5)</td>
<td>45 (18)</td>
<td>−0.07 (3.00)</td>
</tr>
<tr>
<td>4000</td>
<td>45 (6)</td>
<td>56 (24)</td>
<td>−0.49 (2.84)</td>
</tr>
<tr>
<td>2000</td>
<td>63 (12)</td>
<td>76 (27)</td>
<td>−0.99 (1.75)</td>
</tr>
<tr>
<td>1000</td>
<td>93 (20)</td>
<td>101 (22)</td>
<td>−0.75 (1.61)</td>
</tr>
<tr>
<td>500</td>
<td>133 (28)</td>
<td>173 (48)</td>
<td>−1.92 (1.41)</td>
</tr>
<tr>
<td>200</td>
<td>215 (45)</td>
<td>294 (97)</td>
<td>−2.09 (1.99)</td>
</tr>
<tr>
<td>100</td>
<td>313 (70)</td>
<td>421 (121)</td>
<td>−2.26 (1.79)</td>
</tr>
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FFR amplitude is the RMS (root-mean-square) amplitude of the FFR time waveform. Noise amplitude is the RMS amplitude of the 10-ms prestimulus interval of the averaged time waveform. RMS Ratio is the dB relationship of the FFR amplitude relative to that of noise.

Dependence of the FFR trends on stimulus intensity and objective index

To better illustrate the dependence of the FFR on stimulus intensity and the choice of objective indices, the asymptotic amplitude ($A_{eys}$), noise amplitude ($A_{nois}$), and $t$ values of the fitted curves are summarized in Table 2. As reflected from the $t$ values of the fitted exponential model, response trends of pitch-encoding in the human brainstem were dependent on both the stimulus intensity and the choice of objective indices. Specifically, higher stimulus intensities (e.g. 60 dB nHL) demonstrated a faster improvement in SNR (i.e. smaller $t$ values) with increasing number of sweeps than lower stimulus intensities (e.g. 30 dB nHL). The five objective indices were all feasible and effective in quantifying the FFR trends. Note Tracking Accuracy had the smallest $t$ value (1229 sweeps at 60 dB nHL) across the five objective indices and the three stimulus intensities.

Discussion

As the FFR has shown its potential in basic research and clinical applications, parameters that can be used to determine the number of sweeps (i.e. amount of time) needed to obtain an FFR become important factors to examine. This study collected up to 8000 accepted sweeps and examined the response trends of the FFR to voice pitch in normal-hearing adults. Results demonstrated that the exponential model used in this study provides a good fit ($r^2$ value: mean $\pm$ S.D. = 0.89 $\pm$ 0.10, median = 0.93, range = 0.69–0.98) to the FFR trends. This finding supports the use of an exponential model to mathematically analyse the FFR trends.

Exponential modeling of the FFR trends of pitch-encoding in the human brainstem

It has been reported that amplitude of noise decreases with the square root of the number of sweeps (Hood, 1998; Hall, 2006; Thornton, 2007). However, when a response is present in addition to noise, response trends with increasing number of sweeps may be further influenced by the physiological properties of the response. That is, in the presence of a specific neural potential, trends of the response will likely deviate from the original square-root relationship that is solely determined by the decrement of noise. Several exponential models have also been reported to track the time course of various neural activities in the auditory system (Miller et al., 2006; Nourski et al., 2005). For example, Nourski and colleagues (2005) successfully used an exponential model to describe the time course of the effects of acoustic noise on electrically evoked auditory compound action potentials in the guinea pig’s auditory nerve. Our study expands the use of the exponential model to track the changes of the FFR to voice pitch with increasing number of sweeps in normal-hearing adults. Additionally, the model used in this study provides a good fit of the FFR trends across the five objective indices and three stimulus intensities. This finding supports the use of an exponential model to delineate the response trend of pitch-encoding in the human brainstem. One important advantage of utilizing an exponential model to describe the FFR trends is that it allows an objective method to mathematically analyse and compare the amplitude of such a response across different testing conditions and populations of interest. It is also important to note that, although each of the objective indices represents a different aspect of pitch processing in the human brainstem, they may not be totally independent from each other. For example, averaged recordings with lower values of Frequency Error will likely have lower Slope Error and higher Tracking Accuracy.

This modeling approach also improves the consistency and proficiency in selecting a pre-determined threshold criterion (or a combination of several criteria) for recording FFRs. It should be noted that a recording can be terminated for different reasons. In developing a statistical model for ABR, Don and Elberling (1996) proposed that a recording could be terminated based on several conditions: (1) when the criterion for residual average background noise is met or (2) when the target neural response between the background noise has been achieved. Although a statistical model has not been used in the present study, successful results of the exponential model fitting to the FFR trends permits the use of a normal quantitative analysis. The absence of an FFR would be apparent in conditions where the criterion for residual averaged background noise is met or when allowed test time is exhausted. It is also important to note that the FFR trends of the five objective indices may change if a different set of experimental parameters are used. However, one would not need to conduct their own modeling to evaluate FFR trends but could achieve the same results if FFR and noise amplitudes are comparable to the numbers listed in Table 2.
Figure 4. Exponential curve-fitting to the FFR trends with respect to five objective indices: Frequency Error (A), Slope Error (B), Tracking Accuracy (C), Pitch Strength (D), and RMS Ratio (E). The three columns represent data obtained at three different stimulus intensities. Data of each index were fit to an exponential model with descending or ascending trends (solid curves). The fitted equation, along with the coefficient of determination ($r^2$), is shown in each panel. Dotted and dashed lines in each panel indicate the estimated amplitude of background noise ($A_{\text{noise}}$) and asymptotic amplitude of the response ($A_{\text{AS}}$), respectively.
Table 2. Curve fitting coefficients of an exponential model to the FFR trends of pitch-encoding with respect to the five objective indices (Frequency Error, Slope Error, Tracking Accuracy, Pitch Strength, and RMS Ratio) at three stimulus intensities.

<table>
<thead>
<tr>
<th>Stimulus intensity</th>
<th>Frequency Error (Hz)</th>
<th>Slope Error (Hz/s)</th>
<th>Tracking Accuracy (τ)</th>
<th>Pitch Strength</th>
<th>RMS Ratio (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A_{AS}</td>
<td>A_{noise}</td>
<td>τ</td>
<td>A_{AS}</td>
<td>A_{noise}</td>
</tr>
<tr>
<td>30 dB nHL</td>
<td>10.78</td>
<td>16.02</td>
<td>3940</td>
<td>182.66</td>
<td>263.45</td>
</tr>
<tr>
<td>45 dB nHL</td>
<td>7.23</td>
<td>14.31</td>
<td>3110</td>
<td>101.91</td>
<td>243.15</td>
</tr>
<tr>
<td>60 dB nHL</td>
<td>6.09</td>
<td>16.37</td>
<td>1578</td>
<td>82.67</td>
<td>271.53</td>
</tr>
</tbody>
</table>

A_{AS}: asymptotic amplitude of the FFR trends; A_{noise}: amplitude of the background noise; τ: ‘time’ constant of the fitted curve that indicates the number of sweeps needed to reach its 63% asymptomatic amplitude; RMS Ratio: dB ratio of the FFR RMS amplitude relative to that of noise. Note τ has the same unit (number of sweeps) for Frequency Error, Slope Error, Tracking Accuracy, Pitch Strength, and RMS Ratio. †Indicates the smallest τ value across the five objective indices and three stimulus intensities.

One interesting finding derived from the exponential model is that the asymptotic amplitude of the response (i.e. A_{AS}) does not reach a zero mean at any of the three stimulus intensities. For example, the A_{AS} value of Frequency Error is largest at 30 dB nHL and smallest at 60 dB nHL. The A_{AS} values of Slope Error show a similar trend to Frequency Error. (i.e. do not reach a zero mean at the three stimulus intensities). This finding indicates that at higher stimulus intensities (e.g. 60 dB nHL), neural responses are more synchronized to the stimulus frequency when compared to lower stimulus intensities (e.g. 30 dB nHL). This phenomenon is also observed in the A_{AS} values of Tracking Accuracy and Pitch Strength. Although the non-zero A_{AS} values of Frequency Error, Slope Error, Tracking Accuracy, and Pitch Strength at 60 dB nHL can be explained by the residual errors of the less synchronized neural responses in the brainstem, it is possible that higher stimulus intensities (e.g. 80 dB nHL) will produce A_{AS} values that are very close or equal to zero. If so, the non-zero A_{AS} values observed in this study simply represent the FFR dependence on stimulus intensity. It is also possible that, even at stimulus intensities higher than 60 dB nHL, the A_{AS} values still do not reach a zero mean. In this case, the non-zero A_{AS} values would further represent the upper limits of the pitch-tracking acuity and phasing-locking phenomenon in the human brainstem.

Effects of number of sweeps and stimulus intensity

When recording an auditory evoked potential, it is necessary to identify the physiological response of small-amplitude from the relatively large-amplitude background noise. While the amplitude of a response can be enhanced by a careful design of experiments, amplitude of background noise can be reduced through a variety of techniques. The most efficient way of reducing noise is likely to eliminate the noise from its source, which can be physiological (e.g. muscle artifact) or non-physiological (e.g. environmental noise and stimulation artifact) in nature. For example, muscle artifact can be reduced by making sure that the participant is relaxed and receives appropriate head support during experiments. Environmental noise can be minimized by conducting experiments in an acoustically-isolated and electrically-treated chamber. Stimulus artifact can be minimized through careful selection of the stimulation and recording parameters as well as the use of an electromagnetically-shielded earphone. After the various sources of background noise have been eliminated, the SNR of a recording can be further improved by including more sweeps in the averaging process (Hood, 1998; Hall, 2006; Thornton, 2007). In order to determine the appropriate range of number of sweeps needed to reduce the noise to an acceptable level, this study used an exponential model to examine the response trends of the FFR to voice pitch. It is found that, when given equal levels of background noise, the number of sweeps needed to stop a recording is dependent on the stimulus intensity and the choice of objective indices. For example, if FFR recordings are performed at 60 dB nHL and Tracking Accuracy is used to signal the presence of a response, the exponential model provides the specific A_{AS}A_{noise} and τ values that can be used to compute the number of sweeps needed to complete a recording. For example, if 75% of the response asymptotic value is desired, approximately (1.39 τ = 1.39 × 1229 = 1708) sweeps will be needed. If 90% or more is satisfactory, approximately (2.30 τ = 2.30 × 1229 = 2827) sweeps will be required. Similarly, if anywhere between 75–90% of the asymptotic value is set as the threshold criterion, roughly 1700 to 2800 sweeps will be needed to obtain an FFR to voice pitch. This result is consistent with the number of sweeps that are commonly used in FFR literature (Galbraith et al, 1994, 2000, 2001; Jeng et al, 2010, 2011; Krishnan, 2007; Krishnan et al, 2004, 2005, 2010; Li & Jeng, 2011; Skoe & Kraus, 2010; Song et al, 2009; Wong et al, 2007).

Dependence of the FFR to voice pitch on stimulus intensity is also observed (i.e. FFR amplitude increases with stimulus intensity). An interesting finding observed in this study is that higher stimulus intensities (e.g. 60 dB nHL) produce a faster SNR improvement than lower stimulus intensities (e.g. 30 dB nHL). This finding can be explained, at least partially, by the fact that high stimulus intensities produce better neural-firing efficiency and less temporal jitter in single neuron recordings in the auditory nerve (Miller et al, 2006; Imennov & Rubinstein, 2009), and brainstem nuclei (Keller & Takahashi, 2000; Voytenko & Galazuk, 2008). Briefly, firing efficiency can be computed as a ratio of the number of neuronal spikes elicited and the number of times the stimulus is presented. Jitter is often considered as the temporal uncertainty of spike timing and can be calculated as the standard deviation of the spiking times. At high stimulus intensities, neurons in the brainstem will probably produce a larger number of spikes (i.e. greater firing efficiency) that are closely synchronized with the onset of the stimulus (i.e. less temporal jitter). As the scalp-recorded FFR to voice pitch requires synchronized neural responses, higher stimulus intensities will probably produce a ‘cleaner’ response. Such clean responses from individual neurons in response to high intensities will probably build up and reveal the presence of a response more quickly than those obtained at low stimulus intensities. In the current study, all five objective indices showed a faster SNR improvement (i.e. smaller τ values) at high stimulus intensities than low stimulus intensities. This finding is consistent with the effect of stimulus intensity reported in FFR literature (Gardi et al, 1979; Krishnan & Parkinson, 2000). For example, Gardi and colleagues (1979) recorded FFRs to 10-ms tone bursts.
in normal-hearing adults and neonates at 25–65 dB nHL and found that the largest FFR amplitude was produced at 65 dB nHL for both the neonates and adults. Krishnan and Parkinson (2000) recorded FFRs to 80-ms frequency sweeps (400–600 Hz) at 65–95 dB nHL in normal-hearing adults and found that the largest response amplitude was produced at 95 dB nHL. Although higher stimulus intensity produces larger response amplitude, we limited our stimulus to ≤60 dB nHL (due the relatively long duration of stimulus presentation used in this study, e.g. 295 ms × 8000 sweeps = 39 minutes) in order to avoid any possible damage to the listener’s hearing.

Clinical implications
Although Mandarin tones are used to elicit FFRs in this study, the exponential model could realistically be applied to any complex sound with a variable pitch contour; thus it has utility beyond a Mandarin speaking population and can be useful to any clinician interested in obtaining an objective measurement of pitch processing in the human brainstem. It is important to note that different populations (e.g. musicians, native speakers of tonal versus non-tonal languages, normal-hearing children and infants, children with specific hearing or language disorders) and stimuli with different pitch contours (e.g. a falling pitch rather than a rising pitch) may have different response properties in pitch processing and therefore exhibit FFR trends with different $A_{50}$ $A_{\text{noise}}$, and $r$ values. Equations derived from these trends of a specific population can be useful in developing objective methods and experimental protocols to determine the presence of an FFR and to complete a recording by applying a pre-determined stopping criterion or a combination of them. It is anticipated that future studies focusing on examining the exponential trends of the FFR in a variety of populations will shed light on signal-processing mechanisms and neural plasticity of the human brainstem.

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References
Miller C.A., Abbas P.J., Robinson B.K., Nourski K.V., Zhang F. et al. 2006. Electrical excitation of the acoustically sensitive auditory nerve:

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