



Research paper

Neural representation of pitch salience in the human brainstem revealed by psychophysical and electrophysiological indices

Ananthanarayan Krishnan*, Gavin M. Bidelman, Jackson T. Gandour

Department of Speech Language Hearing Sciences, Purdue University, West Lafayette, IN 47907, USA

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ABSTRACT

Acoustically, pitch is related to the temporal regularity or periodicity of a sound. Perceptual and electrophysiologic studies have revealed that pitch salience grows systematically with increasing stimulus periodicity. The aim of this study is to show that information relevant to pitch salience is already encoded in the phase-locked neural activity of brainstem neurons in order to demonstrate that the neural manifestation of pitch salience emerges well before cortical involvement. Brainstem frequency following responses (FFRs) were recorded from participants in response to linguistic tones, which varied only in their degree of pitch salience. Neural pitch strength was computed from FFRs using autocorrelation algorithms. In addition, behavioral frequency difference limens (F0 DLs) were measured from each participant to obtain a perceptual estimate related to pitch salience. Brainstem neural pitch strength increased systematically with increasing temporal regularity in stimulus periodicity, indicating more robust encoding for salient pitch. F0 DLs decreased with increasing stimulus periodicity revealing better pitch change detection for more salient stimuli. FFR neural pitch strength and behavioral F0 DLs were negatively correlated suggesting that subcortical processing can, in part, predict an individual's behavioral judgments of pitch salience. These data imply that changes to the acoustic periodicity of a stimulus directly influence brainstem encoding and the corresponding behavioral responses to pitch. We infer that information related to pitch salience may emerge early along the auditory pathway and is likely rooted in pre-attentive, sensory-level processing.

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1. Introduction

Pitch is a perceptual attribute that plays an important role in all aspects of hearing including the perception of speech, language and music. For many different types of complex sounds, including speech or music, the perceptual dimension of pitch and its salience is closely related to the strength of the temporal periodicity in the stimulus waveform. Indeed, it has been demonstrated that human listeners order complex sounds based on periodicity strength (Fastl and Stoll, 1979; Shofner and Selas, 2002; Yost, 1996b) and that the magnitude of pitch salience is primarily determined by the temporal information in the waveform fine structure (Shofner and Selas, 2002). Thus, there is considerable interest in how the auditory system detects and extracts pitch relevant information from the temporal regularity of periodic and quasi-periodic sounds.

One type of complex sound that allows for systematic manipulation of the fine temporal structure, and therefore the magnitude of pitch salience, is iterated rippled noise (IRN). IRN is produced by adding a delayed copy of a random noise to the original noise and then repeating this delay-and-add process n times (Bilsen, 1966; Yost, 1996a). Repeating this delay-and-add process produces both an increase in temporal regularity of the noise and a spectral ripple in its long-term power spectrum. A normalized autocorrelation function of IRN reveals a peak at the reciprocal of the delay, whose magnitude grows with increasing number of iterations reflecting the increasing periodicity.

Perceptually, IRN produces a pitch corresponding to the reciprocal of the delay, and its corresponding pitch salience that grows with increasing number of iterations (Patterson et al., 1996; Yost, 1978, 1996a; Yost and Hill, 1979). Functional brain imaging studies in humans show that activity of the cochlear nucleus, inferior colliculus and the primary auditory cortex increases as a function of the number of iteration steps (Griffiths et al., 1998, 2001). Intracranial electrode recordings reveal that discharge rates increase in auditory cortical neurons as a function of iteration steps in both primates (Bendor and Wang, 2005) and humans

* Corresponding author. Department of Speech Language Hearing Sciences, Purdue University, 1353 Heavilon Hall, 500 Oval Drive, West Lafayette, IN 47907 2038, USA. Tel.: +1 765 494 3793; fax: +1 765 494 0771.

E-mail addresses: rkrish@purdue.edu (A. Krishnan), gbidelma@purdue.edu (G.M. Bidelman), gandour@purdue.edu (J.T. Gandour).

(Schonwiesner and Zatorre, 2008). Using cortical evoked magnetic potentials in humans, the N1m and pitch onset responses show increases in amplitude with increasing iteration steps (Krumbholz et al., 2003; Soeta et al., 2005). These findings collectively suggest that the increase in pitch salience with increasing temporal regularity of the IRN stimulus is correlated with an increase in pitch-relevant neural activity in both cortical and subcortical auditory neurons.

Physiologically, recordings of responses to static (i.e., single pitch) and time-varying (i.e., dynamic pitch) IRN stimuli from auditory nerve fibers (Fay et al., 1983; ten Kate and van Bakkum, 1988) and cochlear nucleus neurons (Bilsen et al., 1975; Sayles and Winter, 2007; Shofner, 1991; 1999; Winter et al., 2001) show that the pitch of harmonic IRN is represented in the firing patterns of action potentials locked to either the temporal fine-structure or envelope periodicity. That is, there is temporal regularity in the fine structure of the neural firing patterns, and it produces peaks in the autocorrelogram. As measured by autocorrelation, these physiological data suggest that the pitch of IRN stimuli is based on temporal processing. Indeed, the pooled interspike interval distributions of auditory nerve discharge patterns in response to complex sounds resemble the autocorrelation function of the stimulus waveform, and the magnitude of the autocorrelation peak corresponds well with pitch salience (Cariani and Delgutte, 1996b).

In view of these results from psychophysical and physiologic studies, we hypothesized that the pitch relevant information preserved in the phase-locked neural activity underlying the scalp-recorded human frequency following response (FFR) may also increase in pitch strength with increase in the temporal regularity of an IRN stimulus, and in addition, that this measure may be correlated with pitch salience. The scalp recorded FFR reflects sustained phase-locked neural activity in a population of neural elements within the rostral brainstem (Glaser et al., 1976; Marsh et al., 1974; Smith et al., 1975; Worden and Marsh, 1968). FFRs have been shown to encode information about formants of speech sounds (Aiken and Picton, 2008; Krishnan, 1999, 2002; Krishnan and Parkinson, 2000) and pitch relevant information of both steady-state (Greenberg et al., 1987) and dynamic complex sounds including speech (Krishnan et al., 2004, 2005) and nonspeech IRN stimuli (Krishnan and Gandour, 2009; Krishnan et al., 2009a,b; Swaminathan et al., 2008a,b).

To the best of our knowledge, there are no previous studies in the human auditory brainstem that evaluate the relationship of neural pitch strength to temporal regularity of the stimulus, and concurrently, its relationship to perceptual pitch salience. Thus, the overall objective of this study is to determine whether neural representations relevant to pitch salience are evident at a subcortical, sensory level of pitch encoding. The specific aims of this study are to determine whether pitch strength, as reflected in the phase-locked neural activity generating the FFR, increases with increase in the iteration steps of a dynamic IRN stimulus; and whether this physiologic index of neural pitch strength is correlated with pitch salience obtained from psychophysical estimates from the same IRN stimulus.

2. Materials and methods

2.1. Participants

Seven (3 males, 4 females) adult native speakers of Mandarin Chinese participated in the experiment. All participants exhibited normal hearing sensitivity (better than 20 dB HL in both ears) at octave frequencies from 500 to 4000 Hz. In addition, participants reported no previous history of neurological or psychiatric

illnesses. As determined by a language history questionnaire (Li et al., 2006), each was born and raised in mainland China and none received formal instruction in English before the age of 9 ($M = 11.7$, $SD = 1.3$). Chinese participants were chosen given their vast experience with pitch, which in Mandarin, is used to signal word meaning at a syllable level (Yip, 2003). All participants were paid for their time and gave informed consent in compliance with a protocol approved by the Institutional Review Board of Purdue University.

2.2. Stimuli

Iterated rippled noise (IRN) was used to create a stimulus continuum, which varied only in pitch salience (from low to high). In its simplest form IRN stimuli is created using a broadband noise which is delayed by a fixed amount and added back on itself in a recursive manner overall multiple iterations (n). The algorithm is typically described using the nomenclature of IRN (d, g, n), where d is the delay in seconds, g is the gain (+ = add; - = subtract), and n is the number of iterations (i.e., loops) in the recursive process. This procedure produces the perception of a steady-state pitch corresponding to the reciprocal of the delay ($1/d$) whose salience increases with the number of iteration steps (n) (Yost, 1996b). Large n produces a clear, robust pitch, while small n produces noisy, weak pitch.

In this study, instead of using a single static delay-and-add network, we applied a time-varying delay-and-add algorithm to a filtered Gaussian noise (10–3000 Hz) to create IRN stimuli with a dynamic fundamental frequency (FO) contour whose pitch varies as a function of time (Denham, 2005; Krishnan et al., 2009a; Sayles and Winter, 2007; Swaminathan et al., 2008a). The pitch increases in a curvilinear fashion from about 100 to 135 Hz over the 250 ms stimulus duration. This was accomplished by implementing a mapping function so that each time instant can be delayed by a different amount. Time-varying pitch was used to mimic a prototypical linguistic pitch contour found in Mandarin Chinese (Krishnan et al., 2010; Xu, 1997). A schematic of the IRN circuit for $n = 2$ iterations is shown in Fig. 1.

The mapping signal is described by Equation (1) (Denham, 2005; Swaminathan et al., 2008a):

$$\begin{aligned} y_i(t) &= y_{i-1}(t) + gy_{i-1}(t - 1/f(t)); \quad \text{for } i = 1, 2, \dots, n \\ y_0(t) &= x(t), \quad \text{input signal} \end{aligned} \quad (1)$$

where $f(t)$ represents a polynomial equation of any degree modeling a linear/nonlinear FO contour, n is the number of iteration steps, and g is the gain ($-1 \leq g \leq 1$).

A fourth-order polynomial was used as the mapping function to mimic the dynamic FO contour of natural citation form Mandarin

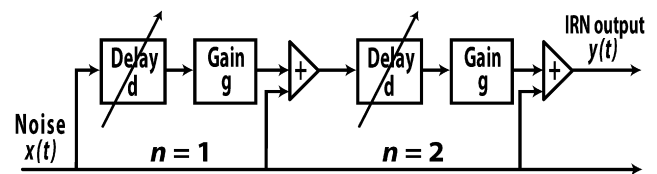


Fig. 1. Block diagram to create dynamic IRN stimuli. The parameters involved in creating IRN stimuli are delay d (in s), gain g (set to 1) and number of iteration steps n (2 in the example here). The arrow in the delay module suggests that each time sample of the original filtered (10–3000 Hz) Gaussian noise stimuli $x(t)$ is delayed by a different amount and added back to itself. The IRN stimulus allows for the use of parametrically defined time-varying delay functions that give rise to the perception of time-varying pitches.

Tone 2 (T2), as produced by a male speaker (Xu, 1997). The polynomial is described by Equation (2):

$$f(t) = 103.85 - (8.45/L)t - (76.32/L^2)t^2 + (297.91/L^3)t^3 - (185.34/L^4)t^4 \quad (2)$$

where L is the total duration of the stimulus (s). All stimuli were fixed in duration to 250 ms including a 10 ms rise/fall time (\cos^2 ramps). The gain in the IRN circuit was set to 1. Submitting the reciprocal of Equation (2) to the IRN circuit (Fig. 1) generates the $T2_{\text{IRN}}$ stimulus with time-varying pitch shown in Fig. 2C. Note the improvement in stimulus periodicity (Fig. 2A) and the emergence of clear spectral components corresponding to the F0 and its integer multiples as the number of iterations are increased (Fig. 2B). Consistent with this is the systematic increase in the magnitude of the autocorrelation function (ACF) around the fundamental pitch period (7.4–10 ms; $F0 = 100$ –135 Hz) as the number of iterations is increased (Fig. 2D, inset). Across iteration steps, the ACF peak height rises exponentially, and asymptotes by about $n = 12$ iterations.

Six versions of T2 were created using this same F0 contour at iteration steps of $n = 2, 4, 8, 12, 16,$ and 32 . At $n = 2$ the IRN stimulus produces a relatively noisy, weak pitch whereas at $n = 32$, a clear, robust pitch is heard (see Supplementary Material). The upper limit of $n = 32$ was chosen because pitch salience does not increase by any noticeable amount beyond this number of iteration steps (Yost, 1996b).

2.3. Psychophysical estimates of pitch salience

To quantify changes in pitch salience with increase in iteration steps, we adopted the F0 DL measure. This measure has been widely used in pitch discrimination experiments to quantify changes in pitch or pitch salience of complex sounds (Bernstein and Oxenham, 2003; Carlyon and Shackleton, 1994; Hall and Plack, 2009; Houtsma and Smurzynski, 1990; Shackleton and Carlyon, 1994). The rationale here is to utilize a behavioral index that is sensitive to changes in pitch salience. That is, pitch discrimination should improve with increasing salience of pitch (as iteration steps are increased). Testing consisted of six conditions (one for each iteration step, n) in which participants performed a three-interval forced choice task (3-IFC). For a given trial within a condition, they heard three sequential intervals, two containing a reference stimulus and one containing a comparison, assigned randomly. The reference $T2_{\text{IRN}}$ was fixed to produce a nominal pitch of the original T2 (see F0 contour, Fig. 2C); that of the comparison was always greater (i.e., higher onset F0 frequency). Hence the only difference between the standard and comparison pitch contours was that the latter was transposed to begin on a slightly higher pitch. Subjects were instructed to identify the interval in which the linguistic tone was perceived as having a higher pitch, i.e., a higher voice fundamental frequency. Discrimination thresholds were measured using a two-down, one-up adaptive tracking procedure (Levitt, 1971). Following two consecutive correct responses, the frequency difference between the reference and comparison T2 was decreased for the subsequent trial, whereas it was increased

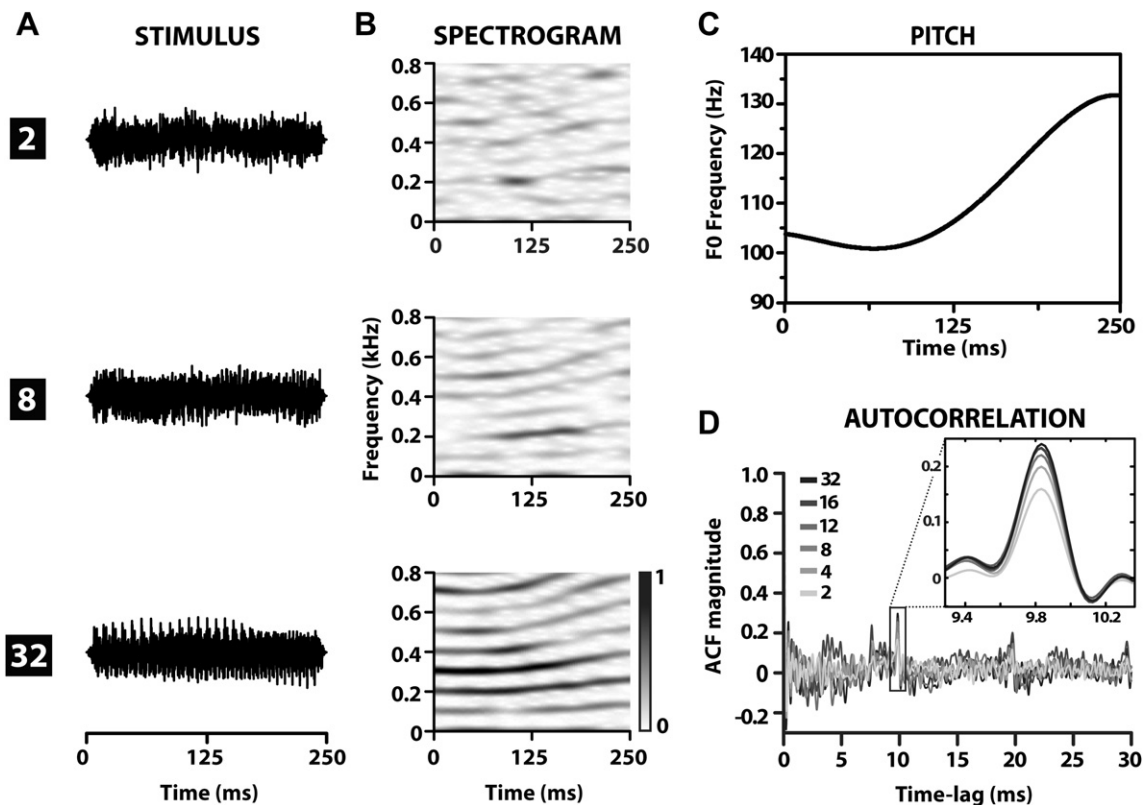


Fig. 2. IRN stimuli used to evoke brainstem responses to a linguistic pitch which varied in salience. The delay used to generate the IRN stimuli was systematically varied over the 250 ms duration of the stimuli so that the reciprocal of the delays produced a time-varying F0 according to citation form Mandarin Tone 2 (T2) (C). By using a different number of iterations (n) in the IRN generating circuit, we vary the F0 contour's pitch salience. Waveforms (A), spectrograms (B), and stimulus ACFs (C) for low ($n = 2$), medium ($n = 8$), and high ($n = 32$) number of iteration steps reveal more robust periodicity and spectral information with increasing n (waveforms and spectrograms for $n = 4, 12, 16$ not shown). ACF magnitude around the fundamental pitch period of the stimuli ($F0 = 100$ –135 Hz; period = 7.4–10 ms) increases monotonically with the number of iteration steps (n) indicating that acoustic periodicity improves with increasing n (D, inset). The spectrograms' normalized magnitudes are represented using the gray scale gradient; darker shades indicate larger spectral magnitudes. ACF, autocorrelation function; F0, fundamental frequency; IRN, iterated rippled noise.

following a single incorrect response. Frequency difference between reference and comparison intervals was varied using a geometric step size of 1.414 between response reversals. For each condition, 16 reversals were measured and the geometric mean of the last 12 was taken as the individual's frequency difference limen (F0 DL), that is, the minimum frequency difference needed to detect a change in pitch. Four estimates were made per condition and the mean of the last three were used to compute the participant's final F0 DL threshold for a given iteration step.

2.4. FFR recording protocol and analysis

FFRs were recorded from each participant in response to monaural stimulation of the right ear at 80 dB SPL through a magnetically shielded insert earphone (Etymotic, ER-3A). Neural responses were recorded differentially between a non-inverting (+) electrode placed on the midline of the forehead at the hairline (Fz) and inverting electrodes (–) placed on (i) the right mastoid (A2); (ii) the left mastoid (A1); and (iii) the 7th cervical vertebra (C7). Another electrode placed on the mid-forehead (Fpz) served as the common ground. FFRs were recorded simultaneously from the three different electrode configurations, and subsequently averaged for each stimulus condition to yield a response with a higher signal-to-noise ratio. All inter-electrode impedances were maintained at or below 1 k Ω . Each response waveform represents the average of 3000 stimulus presentations over a 280 ms acquisition window.

To analyze the robustness of encoding to stimuli differing in pitch salience, we quantified the neural *pitch strength* of each response waveform. From each FFR, the normalized autocorrelation function (ACF; calculated over the entire duration of the response) was computed in order to determine the dominant periodicities

contained within the response. The height of the first peak in the ACF away from time-lag zero was taken as the magnitude of neural pitch strength (Krishnan et al., 2005). In all cases, this peak fell at a time-lag of \sim 10 ms, the fundamental pitch period of the input stimulus (see ACFs, Fig. 3). Such autocorrelation metrics have shown a high correspondence with the pitch salience of a stimulus in both behavioral studies with humans and single-unit neurophysiologic studies in animal models (Cariani and Delgutte, 1996a; Yost, 1996b).

3. Results

3.1. Characteristics of FFR response with increasing iteration steps (n)

Grand averaged FFR waveforms (Panel A), narrow band spectrograms (Panel B), and, ACFs (Panel C) computed from grand averaged FFRs are shown as a function of iteration steps in Fig. 3. The FFR waveforms show clearer periodicity and larger amplitude with increasing iterations (compare $n = 2$ to $n = 32$). Spectrograms, likewise, reveal clearer and more robust spectral components at the fundamental frequency and its integer multiples with increasing number of iteration steps. Consistent with these observations, ACF peak magnitude (10 ms), reflecting the degree of neural phase-locking to the fundamental pitch period, increases monotonically with iteration steps thus indicating more robust brainstem phase-locked activity for stimuli with salient pitch.

3.2. Psychophysical experiment

Mean behavioral frequency limens (F0 DL) and their corresponding neural pitch strength derived from FFRs are shown for each of the six iteration steps in Fig. 4. In general, at low iterations

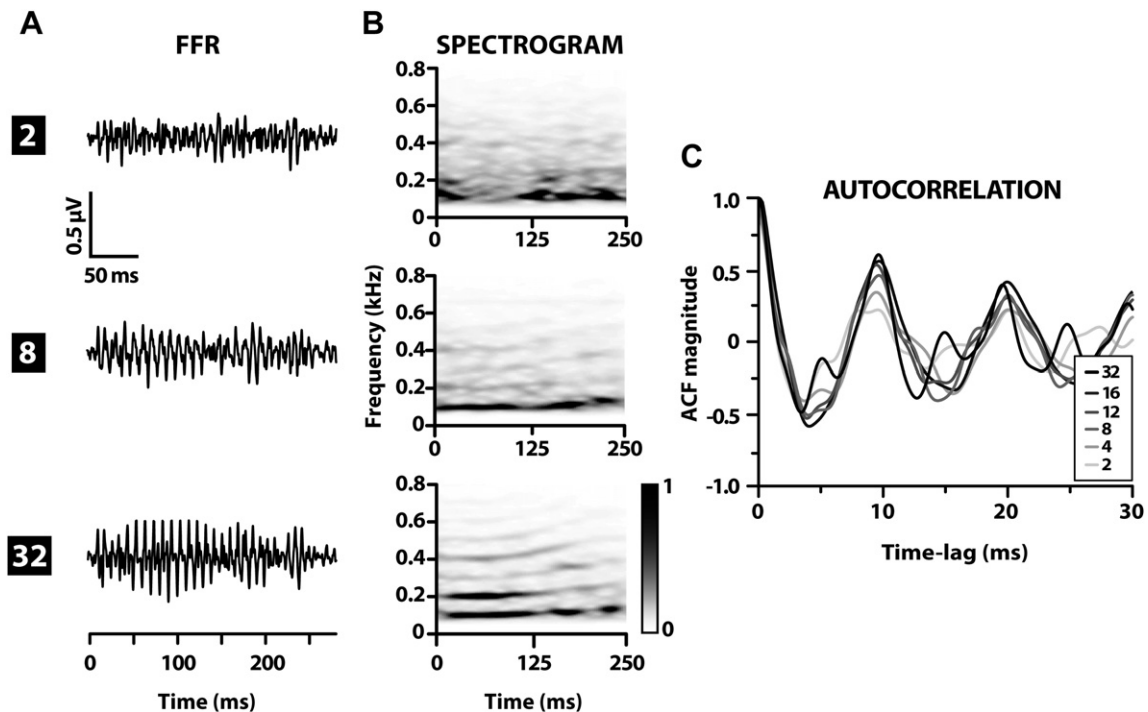


Fig. 3. FFR waveforms (A), spectrograms (B), and ACFs (C) as a function of iteration steps (n) computed from grand averaged brainstem responses. Spectrograms were computed by sliding a 50 ms analysis window by a 1 ms increment and computing the FFT in each time bin. Normalized magnitudes are indicated by the gray scale gradient; darker shades indicate stronger encoding of pitch relevant harmonics (i.e., more pronounced phase-locked activity). Minimal periodicity is observed in FFRs at low iteration steps ($n = 2$; top row). By $n = 8$ iterations, FFR phase-locked activity captures periodicity related to the fundamental frequency (F0) and its harmonics (middle row). Robust encoding is even more pronounced at $n = 32$ iterations when the stimulus is maximally salient (bottom row). Complementary results are seen in time-domain measures. Temporal waveforms and ACFs derived from the FFRs reveal increasing periodicity in the neural response with increasing iteration steps thus indicating more robust brainstem activity for salient pitch. ACF, autocorrelation function; FFR, frequency following response.

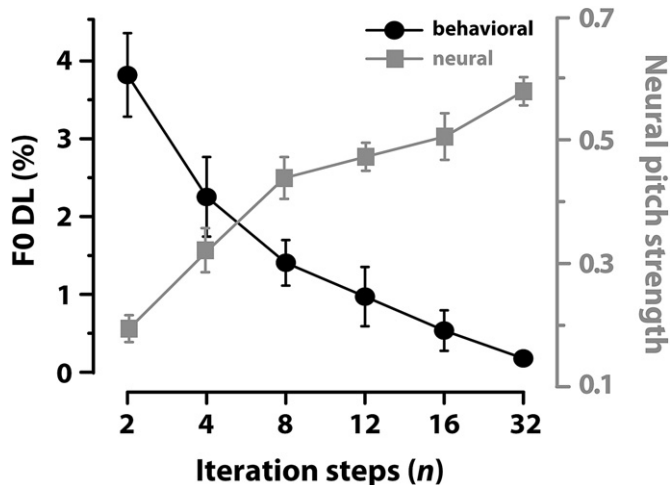


Fig. 4. Behavioral frequency difference limens (F0 DLs) and neural pitch strength derived from FFRs as a function of stimulus pitch salience (i.e., iteration steps, n). For low iteration steps (e.g., $n = 2, 4$), the pitch salience of the stimulus is minimal, requiring large differences in frequency to detect a change in pitch (i.e., large F0 DL). At high iteration steps (e.g., $n = 16, 32$), the stimuli have salient pitch and detection is markedly better (i.e., small F0 DL). Complementary results are seen in the neural data; neural pitch strength increases monotonically with increasing salience of the stimulus.

steps (e.g., $n = 2, 4$), F0 DLs were larger than at higher iteration steps (e.g., $n = 16, 32$) and decrease monotonically with increasing n . Complementary results are seen in the neural data, that is, FFR neural pitch strength increases monotonically with increasing iteration steps.

A mixed-model ANOVA with subjects as a random factor and iteration step as a fixed factor was performed on the F0 DLs to assess how pitch change detection differs depending on the pitch salience of the input stimulus. Results revealed a significant main effect of iteration step ($F_{5,30} = 16.44, p < 0.0001$) on behavioral F0 DLs. Post hoc Student–Newman–Keuls (SNK) adjusted multiple comparisons ($\alpha = 0.05$) revealed that individuals had significantly smaller F0 DLs for iteration steps $n \geq 4$ than for $n = 2$, and for iteration steps $n \geq 12$ than for $n = 4$. In other words, participants were better at detecting changes in pitch at higher iteration steps.

3.3. FFR experiment

A similar ANOVA was performed on neural pitch strength derived from FFRs to assess how subcortical encoding of pitch related information differs depending on the pitch salience of the input stimulus. Results revealed a significant effect of iteration step on neural pitch strength ($F_{5,30} = 21.99, p < 0.0001$). Post hoc SNK adjusted multiple comparisons revealed that individuals had significantly larger neural pitch strength for iteration steps $n \geq 4$ than for $n = 2$; $n \geq 8$ than for $n = 4$; and $n = 32$ than for $n = 12$.

Weighted least squares regression was used to determine to what extent subcortical processing could predict an individual's behavioral judgments based on pitch salience. Weights were calculated as the inverse of the variance at each observation. Variance estimates were obtained by regressing the residuals of F0 DL measurements against the predictor variable neural pitch strength. Weighted least squares regression was used to ensure that lower iteration steps, which produced more variable F0 DLs, would not influence the fit of the regression model. Fig. 5 displays behavioral F0 DLs plotted against neural pitch strength derived from FFRs. The fitted model predicts that for every 0.1 increase in brainstem pitch encoding, behavioral F0 DLs decrease (i.e., improve) by approximately 0.5%.

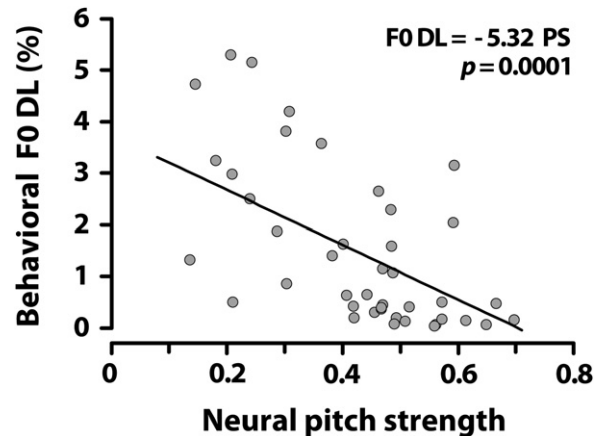


Fig. 5. Behavioral frequency difference limens (F0 DL) vs. neural pitch strength derived from FFRs. Stimuli with weak, noisy pitch (e.g., $n = 2$) elicit lower neural pitch strength in brainstem responses and subsequently require larger frequency differences to detect a change in pitch. Stimuli with clear, robust pitch (e.g., $n = 32$) elicit large FFR pitch strength and require much smaller differences to detect a change in pitch. Weighted least squares regression reveals that for every 0.1 increase in brainstem pitch encoding F0 DL improves (i.e., decreases) by approximately 0.5%.

4. Discussion

The major finding of this study shows that neural pitch strength, as reflected in the brainstem FFR, and pitch salience, as reflected by the F0 DL estimates, improve systematically with increasing temporal regularity of the IRN stimulus. Moreover, a strong correspondence is observed between growth in neural pitch strength and pitch salience with increasing temporal regularity of the IRN stimulus. The growth in FFR pitch strength (derived from peak magnitude of the FFR autocorrelation function) with increasing iteration steps may be interpreted to suggest an increase in the degree of neural phase-locking to the pitch relevant periodicity resulting from increased temporal regularity in the stimulus. This view is compatible with previous perceptual (Patterson et al., 1996; Yost, 1996b) and physiologic (Bilsen et al., 1975; Sayles and Winter, 2007; Shofner, 1991, 1999; Winter et al., 2001) experiments that suggest that pitch of static and dynamic IRN stimuli is based on an autocorrelation-like temporal processing where the magnitude of the autocorrelation peak increases with iteration steps, and provides a strong measure of temporal regularity, a stimulus attribute closely tied to pitch salience.

Our novel finding of a strong correlation between neural pitch strength and behavioral measures related to pitch salience suggests that information relevant to pitch salience may be extracted and preserved early along the auditory pathway in the pre-attentive, sensory-level processing at the level of the human brainstem. This is plausible given that the phase-locked neural activity underlying pitch representation in the brainstem is sensitive to changes in the temporal regularity in the IRN stimulus.

This finding further converges with earlier auditory electrophysiological studies linking neural activity and pitch salience. The latency and amplitude of the pitch onset response (a cortical evoked response) varies systematically with the pitch salience of an IRN stimulus (Krumbholz et al., 2003; Soeta et al., 2005), suggesting that the neural activity underlying the generation of the pitch onset response is involved in extracting an initial estimate of the pitch salience of the sound. A strong correspondence is observed between the neural pitch strength of complex sounds and their pitch salience for auditory nerve responses (Cariani and Delgutte, 1996a,b) and human brainstem FFRs in response to consonant and dissonant pitch intervals in music (Bidelman and Krishnan,

2009). Together, these studies suggest a strong correspondence between the neural metric of pitch strength and the behavioral measure of pitch salience. We therefore infer that the growth in pitch salience with increasing iteration steps (i.e., acoustic periodicity) may be explained by improved neural encoding of pitch relevant periodicities in the brainstem, as reflected by our measure of pitch strength. The failure of functional magnetic resonance imaging to identify representations for pitch salience in subcortical structures (Hall and Plack, 2009; Penagos et al., 2004) presumably reflects the fact that subcortical representations of pitch or pitch salience exist on a much finer temporal scale (milliseconds) than that (seconds) provided by hemodynamic imaging methods.

5. Conclusions

The scalp-recorded human FFR provides a non-invasive window to view neural processes underlying pitch encoding of complex sounds at the level of the auditory brainstem. By comparing neural pitch strength and a perceptual measure of pitch salience associated with changing temporal regularity of a complex sound we are able to probe the nature of the relationship between strength of neural encoding and the resulting perceptual salience of the sound. The strong correlation observed herein between the neural and behavioral measures supports the view that pitch encoding at a subcortical, sensory level of processing plays an important role in shaping pitch perception.

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Appendix. Supplemental material

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.heares.2010.04.016.

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