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CASE STUDIES IN NEUROSCIENCE

Sensory Processing

Case studies in neuroscience: cortical contributions to the frequency-following response depend on subcortical synchrony

Travis White-Schwoch,[1] Jennifer Krizman,[1] Trent Nicol,[1] and Nina Kraus[1,2]

[1]*Auditory Neuroscience Laboratory, Department of Communication Sciences, Northwestern University, Evanston, Illinois; and*
[2]*Departments of Neurobiology and Otolaryngology, Northwestern University, Evanston, Illinois*

Abstract

Frequency-following responses to musical notes spanning the octave 65–130 Hz were elicited in a person with auditory neuropathy, a disorder of subcortical neural synchrony, and a control subject. No phaselocked responses were observed in the person with auditory neuropathy. The control subject had robust responses synchronized to the fundamental frequency and its harmonics. Cortical onset responses to each note in the series were present in both subjects. These results support the hypothesis that subcortical neural synchrony is necessary to generate the frequency-following response—including for stimulus frequencies at which a cortical contribution has been noted. Although auditory cortex ensembles may synchronize to fundamental frequency cues in speech and music, subcortical neural synchrony appears to be a necessary antecedent.

NEW & NOTEWORTHY A listener with auditory neuropathy, an absence of subcortical neural synchrony, did not have electrophysiological frequency-following responses synchronized to an octave of musical notes, with fundamental frequencies ranging from 65 to 130 Hz. A control subject had robust responses that phaselocked to each note. Although auditory cortex may contribute to the scalp-recorded frequency-following response in healthy listeners, our results suggest this phenomenon depends on subcortical neural synchrony.

auditory neuropathy; auditory processing; electrophysiology; frequency-following response; subcortical

INTRODUCTION

Historically, the scalp-recorded frequency-following response (FFR) was thought to reflect subcortical neural synchrony, originating chiefly in the inferior colliculus of auditory midbrain. This hypothesis was supported by lesion studies in humans and animal models (1, 2), comparative neurophysiological studies (3), EEG/magnetoencephalography (MEG) source modeling (4–6), and reasoning based on the phase and lag of the response (reviewed in Ref. 7). Recent neuroimaging evidence suggests a role for the auditory cortex, however. In particular, MEG and functional magnetic resonance imaging (fMRI) evidence suggest the right-hemisphere auditory cortex contributes a phaselocked response to the stimulus fundamental frequency (F0) (8–10). This observation has reopened questions about the FFR's origins and motivated some to reinterpret FFR results heretofore characterized as subcortical phenomena (for review, see Ref. 11).

We think this confusion is, in part, an unintended consequence of the tendency to elicit FFRs to stimuli with F0's circa 100 Hz (reviewed in Ref. 12), a parameter chosen because it corresponds to typical speech (13). Unfortunately, this region is also a "gray area" for single-neuron phaselocking, at the upper cusp of cortical neuron phaselocking (14, 15), yet well within the range of thalamic and midbrain phaselocking (16, 17). There is also evidence that auditory cortex ensembles can synchronize in this range (18). This ambiguity has led several authors to suggest eliciting electrophysiological FFRs to higher-frequency sounds to rule out cortical contributions (see, inter alia, Ref. 19).

We recently reported a double dissociation between two patients, one with bilateral auditory cortex lesions and another with auditory neuropathy, a disorder of subcortical synchrony. We showed that subcortical synchrony is necessary and sufficient to generate an FFR, whereas cortical function is neither necessary nor sufficient to generate an FFR

Correspondence: N. Kraus (nkraus@northwestern.edu).
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(20). A limitation of this report was that we measured responses to a single speech sound with an F0 of 100 Hz, leaving open the possibility that an ostensible FFR could be observed to lower-frequency stimuli—that is, stimuli with a periodicity likely to elicit strong single-unit phaselocking in auditory cortex—in patients with neuropathy. This prediction would be consistent with the cortical contribution hypothesis and the broader view that FFR generators depend on the interactions between stimuli, recording modality, and dipole orientation (11).

Here, we retested the patient with neuropathy using an octave of musical notes with fundamental frequencies (F0's) spanning 65–130 Hz. These responses were compared with those in a control subject with normal hearing and subcortical auditory function. We chose stimuli in this frequency range because these encompass the phaselocking ranges of auditory cortex and inferior colliculus neurons. Figure 1 shows results predicted from different hypotheses about the FFR's generators. The "cortical contribution hypothesis" predicts that the listener with neuropathy should show phaselocked activity in response to all stimuli, despite the lack of subcortical synchrony (Fig. 1, *top*). In contrast, the "subcortical synchrony hypothesis," that subcortical synchrony is necessary for an FFR regardless of stimuli, predicts that the listener with neuropathy should exhibit no phaselocked activity in response to any stimuli (Fig. 1, *middle*). A third, "mixed-source hypothesis," which our stimulus range allows us to test, predicts a gradual roll-off in phaselocking observed at the scalp, similar to the low-pass nature of the auditory system. This would manifest as phaselocked activity in response to lower-frequency stimuli, but not higher-frequency stimuli (Fig. 1, *bottom*).

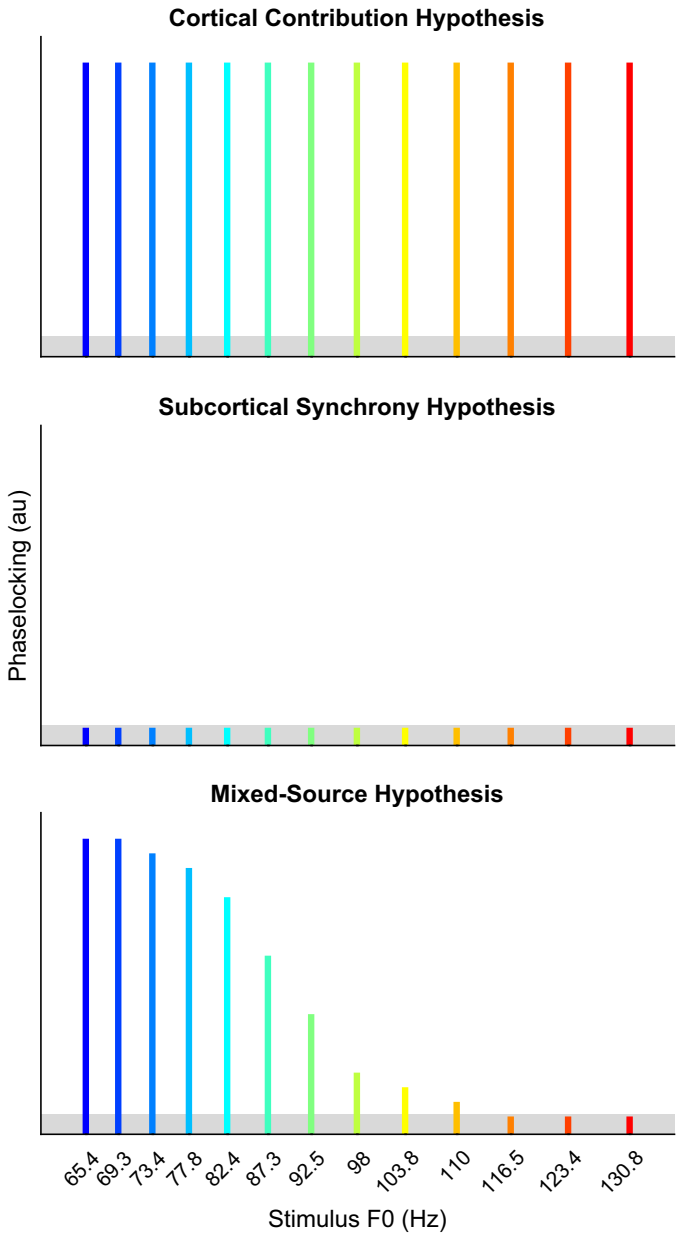

Figure 1. Predicted results from three hypotheses about frequency-following response (FFR) generators. Each line shows the degree of phaselocking to the fundamental frequency of each stimulus in a hypothetical response, plotted in arbitrary units. The gray shaded area signifies the noise floor. The "cortical contribution hypothesis" predicts phaselocked scalp-recorded activity in response to each stimulus fundamental frequency (F0) despite a lack of subcortical synchrony (*top*). The "subcortical synchrony hypothesis" predicts no phaselocked response to stimulus F0, even though the lower-frequency stimuli are within the range of cortical phaselocking (*middle*). That is, all responses are below the noise floor. The third, "mixed-source hypothesis" predicts the person with neuropathy has responses to the lower-frequency, but not higher-frequency stimuli, owing to the low-pass nature of the auditory system; that is, a strong cortical contribution ebbs as the auditory cortex's phaselocking limit is exceeded (*bottom*). au, arbitrary units.

MATERIALS AND METHODS

This study compares auditory-evoked responses in two subjects: IT, an adult woman with auditory neuropathy, and OLA (control subject), an adult woman with normal hearing. We have reported on IT's perceptual abilities previously (21, 22). Briefly, she has excellent speech perception in quiet but struggles mightily in noise. She reports inconsistent sound awareness, particularly of unexpected alerts such as calls, bells, whistles, and timers. IT enjoys listening to music, however, and cites classical and jazz as favorite genres, with a marked disinterest in country and electronica. Procedures for the current study were approved by the Institutional Review Board of Northwestern University, and subjects provided written informed consent to participate in the research.

Auditory brainstem responses (ABRs) were elicited to a 100-μs click presented at 80-dB sound pressure level (SPL) in both rarefaction and condensation polarities at 31.1 Hz via a Neuroscan Stim2 system. Responses were recorded with a Neuroscan Synamps system, with filters set from 100 to 2,000 Hz; 1,500 artifact-free trials were recorded to each polarity in the right and left ears.

FFR stimuli were 13 musical notes, with fundamental frequencies spanning the octave from 65 to 130 Hz: C2 (F0 = 65.4 Hz), C$^{\#}$2 (69.3 Hz), D2 (73.4 Hz), D$^{\#}$2 (77.8 Hz), E2 (82.4 Hz), F2 (87.3 Hz), F$^{\#}$2 (92.5 Hz), G2 (98 Hz), G$^{\#}$2 (103.8 Hz), A2 (110 Hz), A$^{\#}$2 (116.5 Hz), B2 (123.4 Hz), and C3 (130.8 Hz).

We wanted stimuli that were ecologically valid and, like speech, spectrally rich. To this end, each note was a 200-ms

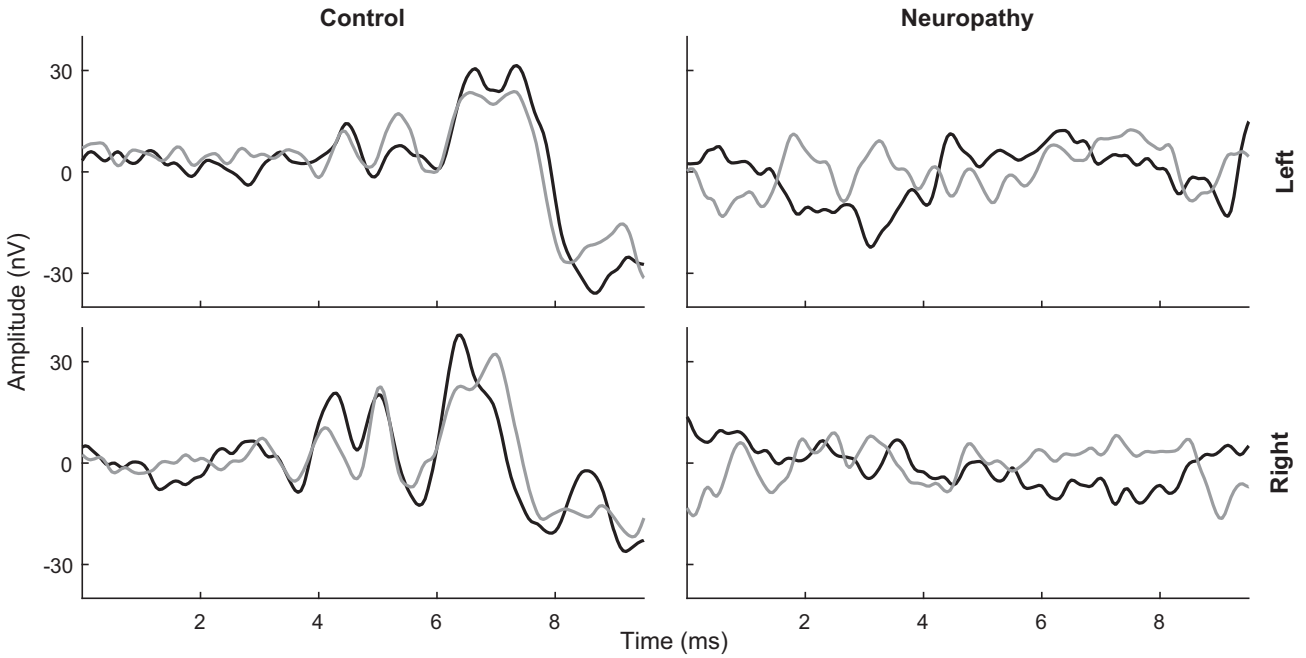

Figure 2. Auditory brainstem responses (ABRs) are shown for the control subject (*left*) and IT (*right*). ABRs are shown to rarefaction (black) and condensation (gray) clicks in the left (*top*) and right (*bottom*) ears. Consistent with the diagnosis of auditory neuropathy, IT has no ABR. IT, an adult woman with auditory neuropathy.

sample from a Rhodes piano. The stimuli were delivered bilaterally at 70 dB SPL and in alternating polarity via shielded earphones at a rate of 3.18 Hz. Stimuli were presented in pseudorandom order by the Gentask module of Neuroscan Stim2, and 1,500 sweeps of each stimulus were recorded (750/polarity). Electrophysiological responses were recorded using a vertical montage (Cz active, Fpz ground, A1/A2 references) with open filters via a Neuroscan SynAmps system. Responses to alternating polarities were added to accentuate responses to the F0 and its lower harmonics (12). The epoch window was set to −50 to 250 ms re stimulus onset.

For FFRs, we were interested in phase-locked responses to the fundamental frequency and its harmonics. Consequently, responses were bandpass-filtered from 50 to 2,000 Hz (second-order Butterworth) to exclude the cortical onset response (P1/N1). For cortical onset responses (P1/N1), responses were bandpass-filtered from 0.1 to 40 Hz (second-order Butterworth).

FFR spectra were calculated using FFTs with a 10-ms ramp time. Spectral amplitudes were calculated over 5-Hz bins. We also used a complementary approach called the phaselocking factor (PLF)[1]. This analysis calculates the consistency of the phase of the EEG activity for each trial and allows the construction of "phase spectrograms." These figures illustrate the degree to which the response is synchronized across trials in circumscribed time-frequency bins, as opposed to a phase-independent illustration of spectral energy. We set a threshold for the minimum PLF at which the response is significantly synchronized using circular statistics (23). In particular, we calculated $Threshold = \sqrt{-\frac{\ln(\alpha)}{N}}$, with N set to the number of stimulus trials (1,500) and α set to the Type 1 error rate (set to a conservative 0.001).

RESULTS

To confirm an absence of subcortical synchrony in IT, ABRs were elicited to clicks. Consistent with the auditory neuropathy phenotype (24–26) and our previous reports on IT (20, 21), she had no ABR to either rarefaction or condensation clicks in either ear. In contrast, the control subject had normal ABRs to each polarity bilaterally. ABRs are shown in Fig. 2.

Response spectra for the bandwidth encompassing the stimulus F0 and harmonics are shown in Fig. 3, along with spectra of the stimuli. OLA, the control subject, has robust responses phaselocked to the fundamental frequency and its first few harmonics. Her response F0's show a systematic frequency progression that matches the ascending F0's of the stimuli. IT's responses, in contrast, show no discernable pattern. They are dominated by lower-frequency noise; the spectral maxima do not correspond to the stimuli. Critically, IT's responses show no evidence of phaselocked energy at the F0's of the lowest-frequency stimuli, which are the responses most likely biased to cortical generators (*top* panels). Fn1

IT's and OLA's spectral responses were compared statistically using a linear model, predicting the amplitude of the F0 and first five harmonics as a function of subject (IT or OLA), musical note (C2 through C3), and spectral peak (F0

[1]As used in studies of scalp-recorded EEG in human, "phaselocking" refers to the extent to which the phase of scalp-recorded EEG is similar across trials. This is different from the "phaselocking" in the neurophysiology community, which refers to the extent to which a neuron synchronizes its action potentials to the period or repetition rate of a stimulus.

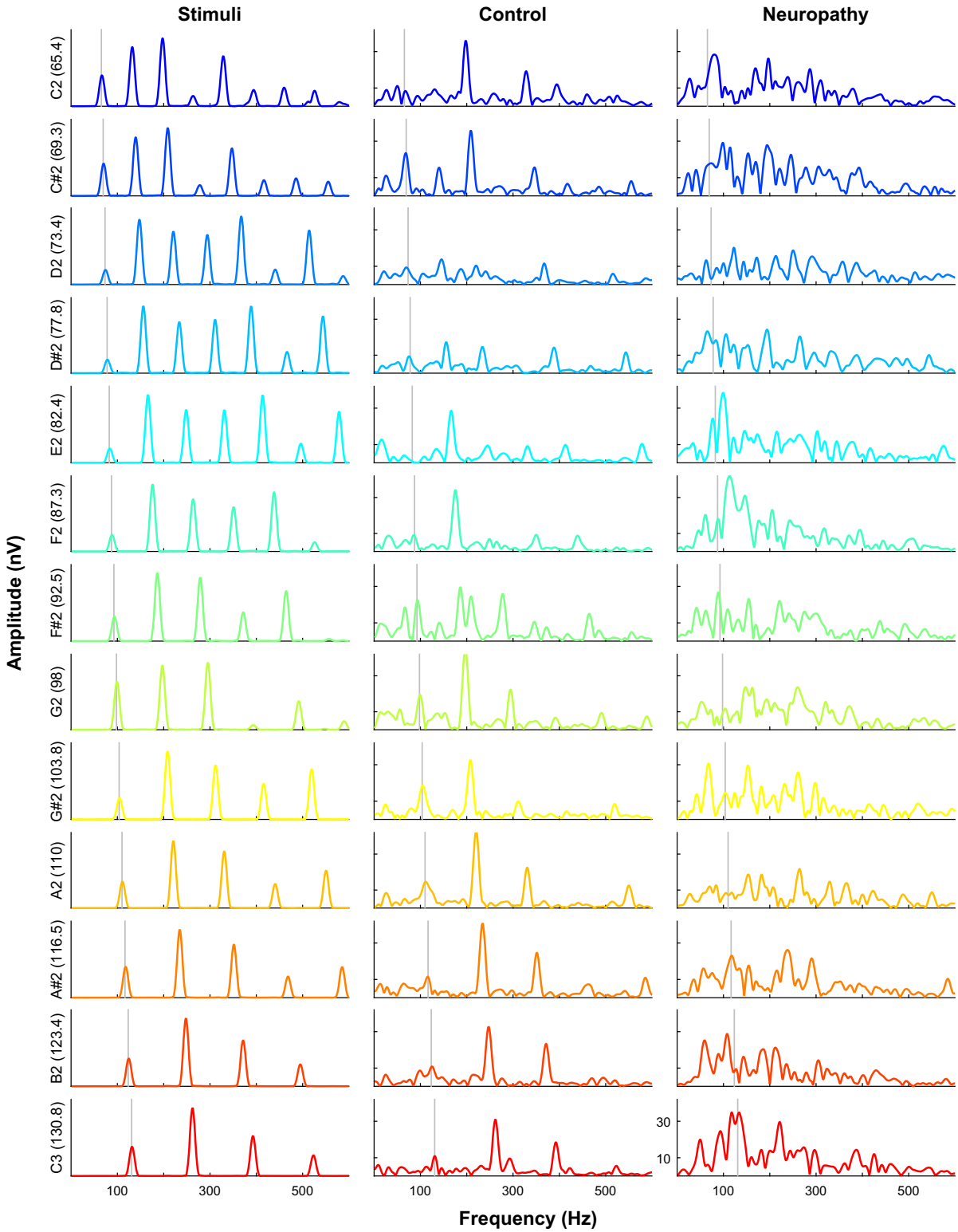

Figure 3. Spectra are shown for the stimuli (*left*), the control subject's responses (*middle*), and IT's responses (*right*). The control subject has strongly synchronized responses to each stimulus's fundamental frequency (F0) and/or its harmonics. IT's responses bear no resemblance to the stimulus spectra, indicating an absence of phaselocking. The *y*-axis scale indicated in the bottom-right panel is in nanovolts and is used for both subjects' responses to each stimulus; the stimulus spectra are plotted with arbitrary units. Colors are assigned to stimuli as in Fig. 1. In each panel, the gray fiducial line shows the F0 of that stimulus. IT, an adult woman with auditory neuropathy.

through H6). Consistent with previous reports (27), the amplitude varied as a function of note, decreasing in amplitude overall as the stimulus F0 increased (β_{Note} = −0.32 nV, 95% CI = [−0.60, −0.05 nV], P = 0.023). Also consistent with previous reports (28, 29), the amplitude tended to decrease for higher harmonics (β_{Harmonic} = −2.43 nV, 95% CI = −3.04, −1.82 nV], P <0.001). Crucially, regardless of stimulus or harmonic, OLA's response amplitudes were, on average, 6.5 nV larger than IT's (β_{Subject} = −6.45 nV, 95% CI = [−8.53, −4.36 nV], P <0.001).

Next, we computed the spectral signal-to-noise ratio (SNR) of responses to each stimulus F0 and its first several harmonics. We computed the amplitude of responses to each spectral peak in the response and divided it by the amplitude of the same frequency bin in the prestimulus region (12). Results are shown in Fig. 4. OLA, the control subject, consistently had a larger SNR than IT. The majority of IT's responses are in the noise floor (i.e., a y-axis value of 0 on Fig. 4). OLA's F0 responses show a pattern of varying amplitudes, whereas her responses to higher-frequency harmonics are consistently large up until the sixth harmonic. Also shown for each harmonic are OLA and IT's mean SNRs across the stimuli. On average, OLA always has response spectra above the noise floor, whereas IT always has responses below the noise floor. IT had a significantly larger proportion of spectral peaks below the noise floor, evaluated using Fisher's exact test (Table 1).

As a complementary analysis to the response spectra, Fig. 5 shows phase spectrograms for OLA and IT's responses. White regions correspond to time-frequency bins, where the responses are not reliably synchronized; of regions that synchronized, deeper umbers show more phase synchrony.

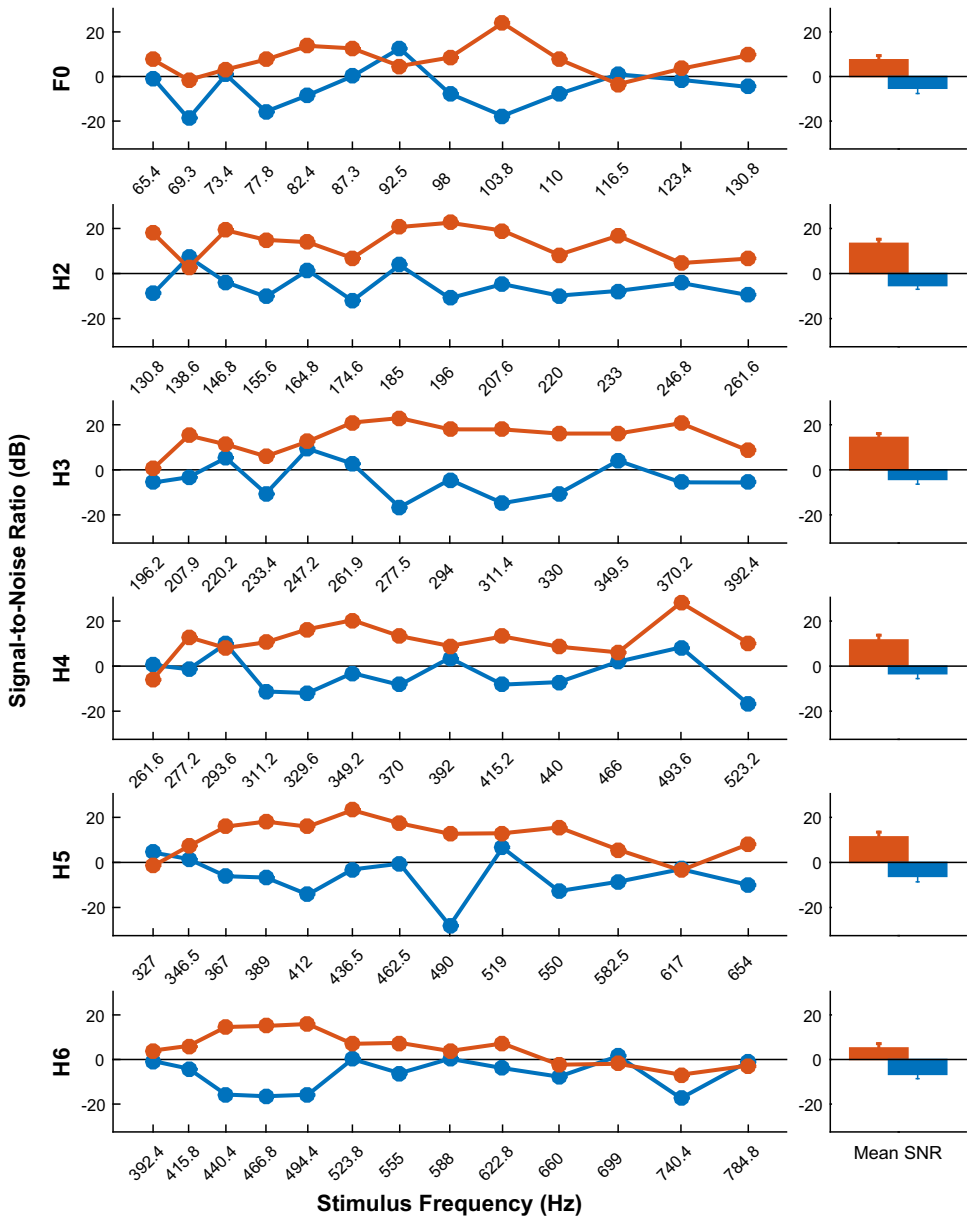

Figure 4. Signal-to-noise ratios (SNRs) of responses to the fundamental frequency (F0) and its harmonics for both subjects are shown in dB. SNRs for the response to each note frequency (*x*-axis) (*left*). The average SNR of each response to that particular harmonic (error bars indicate 1 SE) (*right*). OLA (orange) consistently has spectral responses above the noise floor (0 dB); IT's responses (blue) are consistently below the noise floor. IT, an adult woman with auditory neuropathy; OLA, an adult woman with normal hearing (control subject).

Table 1. *Harmonics above and below the noise floor in the control subject (OLA) and person with neuropathy (IT)*

	Control		Neuropathy		Fisher's Test
Harmonic	Above	Below	Above	Below	*P* Value
F0	11	2	4	9	0.01
H2	13	0	1	12	<0.001
H3	13	0	3	10	<0.001
H4	12	1	5	8	0.01
H5	11	2	3	10	0.004
H6	9	4	3	10	0.04

Shown for each harmonic are the number of responses to the 13 stimuli above or below the noise floor. Fisher's exact test shows that OLA has significantly more harmonics above the noise floor than IT (see Fig. 4 for an illustration of spectral SNRs for each stimulus). F0, fundamental frequency; IT, an adult woman with auditory neuropathy; OLA, an adult woman with normal hearing (control subject); SNR, signal-to-noise ratio.

OLA's response consistently synchronizes to the harmonics of each stimulus, particularly the middle harmonics. In contrast, IT has no synchronized response; in the lower left of each of her phase spectrograms is a small burst of synchronized energy that reflects the cortical onset response, on par with that of OLA.

Time-domain responses are shown in Fig. 6. In the responses filtered for the FFR (*top*), OLA, the control subject, had robust responses to each musical note. Her responses are characterized by a strong onset response (corresponding to the ABR) and synchronized frequency-following responses that reflect the periodicity of each stimulus. In contrast, IT has no evoked activity in responses filtered for the FFR. Noteworthy is that the amplitude of the pre- and poststimulus regions is identical: her responses are only noise.

Responses were also filtered for cortical onset responses (i.e., P1/N1). OLA and IT both have robust cortical responses, as shown in Fig. 6. Response morphology for both is slightly unusual, likely due to the rapid presentation rate. Consistent with previous reports on IT's cortical function in difficult listening scenarios (20, 21), her responses are somewhat later than expected in typical adults. Nevertheless, they are clearly present. These responses confirm that IT's auditory system responded to each stimulus. Her responses simply reflect that a sound had occurred, however. They do not indicate synchronization to stimulus features.

DISCUSSION

Scalp-recorded electrophysiological responses were elicited to musical notes spanning the octave from 65 to 130 Hz in two subjects. IT, the subject with auditory neuropathy, had no phaselocked responses to these notes; yet, she had reliable cortical onset responses. In contrast, the control subject had both cortical onset responses and strongly synchronized, phaselocked responses, coding the stimulus F0's and their harmonics. These results support the view that subcortical synchrony is necessary to generate the FFR. Although neuroimaging evidence suggests that, in healthy subjects, the right-hemisphere auditory cortex can generate phaselocked responses to stimulus F0, our results suggest that subcortical synchrony is a critical antecedent underlying this phenomenon. That is, subcortical synchrony is necessary to generate a scalp-recorded frequency-following response even within the bandwidth of cortical phaselocking.

One concern raised in the interpretation of existing FFR literature is that the stimulus F0's tend to be within the range of cortical phaselocking. We addressed this issue by attempting to elicit responses to stimuli in this "gray area" in a patient who has no FFR to stimuli with an F0 of 100 Hz. Consistent with our previous results (20), the patient with auditory neuropathy did not have responses synchronized to the stimulus F0 or its harmonics. This suggests that even for stimuli with F0s below 100 Hz, subcortical synchrony is necessary and sufficient to generate an electrophysiological FFR. Although our results do not rule out the possibility of cortical contributions in healthy listeners, they also suggest it is an oversimplification to attribute the low-frequency FFR solely to the auditory cortex. This is consistent with a network-based view of auditory processing (30, 31) and the notion that FFR sources can depend on the mix of stimulus, recording modality, and dipole (11).

In contrast to the FFR, IT had robust and reliable cortical onset responses to each sound. These were recorded simultaneously as the FFRs. This provides an important control by demonstrating that we could elicit *some* electrophysiological activity in IT—just not an FFR. We view the cortical potential as an "onset detector" that reflects the presence or absence of a stimulus but does not explicitly reflect its periodicity. Cortical responses tolerate more timing jitter in the ascending auditory system compared with FFRs, which makes sense because they reflect phaselocking an order of magnitude lower.

The control subject had a robust FFR to each stimulus that was strongly phaselocked to the F0. Careful inspection of her responses, though, reveals an interesting pattern (Fig. 3). In particular, amplitude of her F0 response waxes and wanes as the stimulus F0 ascends. Tichko and Skoe (27) measured FFRs to triangle tones, with F0s from 16.35 to 880 Hz and showed a similar nonlinearity with stimulus frequency. Our control subject's pattern of response amplitudes is consistent with their results. Tichko and Skoe attributed this phenomenon to phase cancellation depending on the mix of sources that maximally respond to each frequency. Our results are consistent with this view and suggest two extensions: *1*) a similar pattern is observed with more harmonically complex stimuli, and *2*) regardless of the source mix, subcortical synchrony is necessary to generate responses in the first place. It is also noteworthy that, even for the stimuli where the control subject had relatively small F0 responses, she had strongly synchronized responses reflecting stimulus harmo-nics.

In contrast, IT had very noisy responses in the subcortical frequency band, as shown in the SNR plots in Fig. 4 and the time-domain plots in Fig. 6. IT's system may respond with a lack of inhibition that causes these large noise responses. This hypothesis is consistent with previous work showing she has excessively large cortical evoked responses to speech (20, 21). An alternate explanation ascribes Tichko and Skoe's phenomenon of waxing and waning F0 amplitudes to inhibition across auditory centers rather than phase cancellation of dipoles. It is possible that a coordinated, strongly synchronized response inhibits extraneous (i.e., out-of-phase) activity to provide for efficient neural coding.

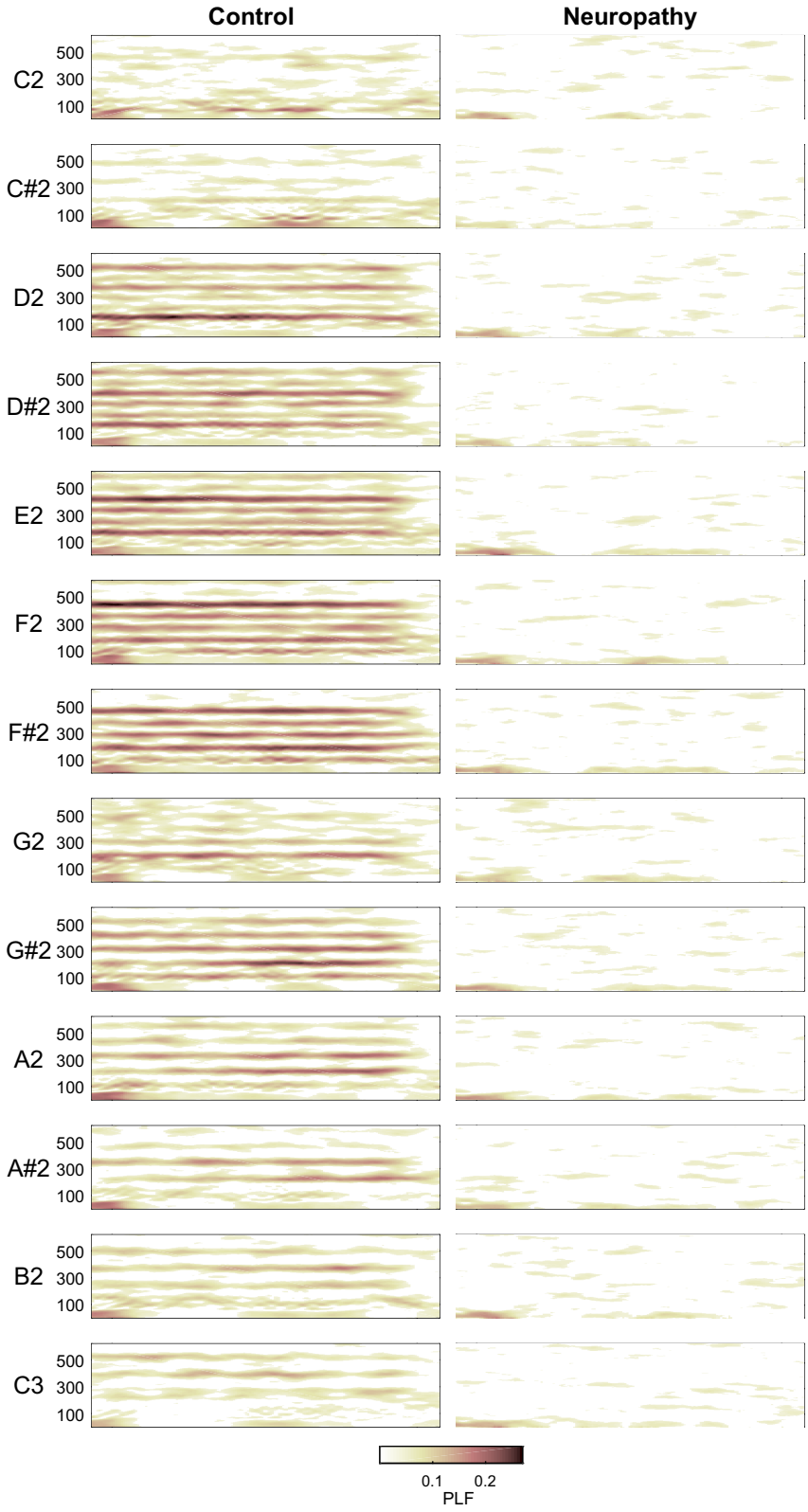

Figure 5. Phase spectrograms show OLA (*left*) and IT's (*right*) responses to each note. Darker colors indicate more consistent responses across trials. OLA shows synchronized responses to the fundamental frequency (F0) and harmonics of each note; IT's responses show no synchronized activity across trials, indicated by the disorganized, light umber splotches and much more white, which indicates an absence of phase-locking synchrony. IT, an adult woman with auditory neuropathy; OLA, an adult woman with normal hearing (control subject).

As in any case study, our inferences are based on observations in one subject. These results may not generalize and so it would be ideal to replicate these results in additional subjects with auditory neuropathy. Such a study would also be important because the auditory neuropathy phenotype can result from several pathophysiologies, including pre- and postsynaptic insults (32). We do not have a good understanding of IT's underlying pathophysiology, although based on her case history we suspect her auditory neuropathy is genetic (21). What patients with auditory neuropathy have in common is an

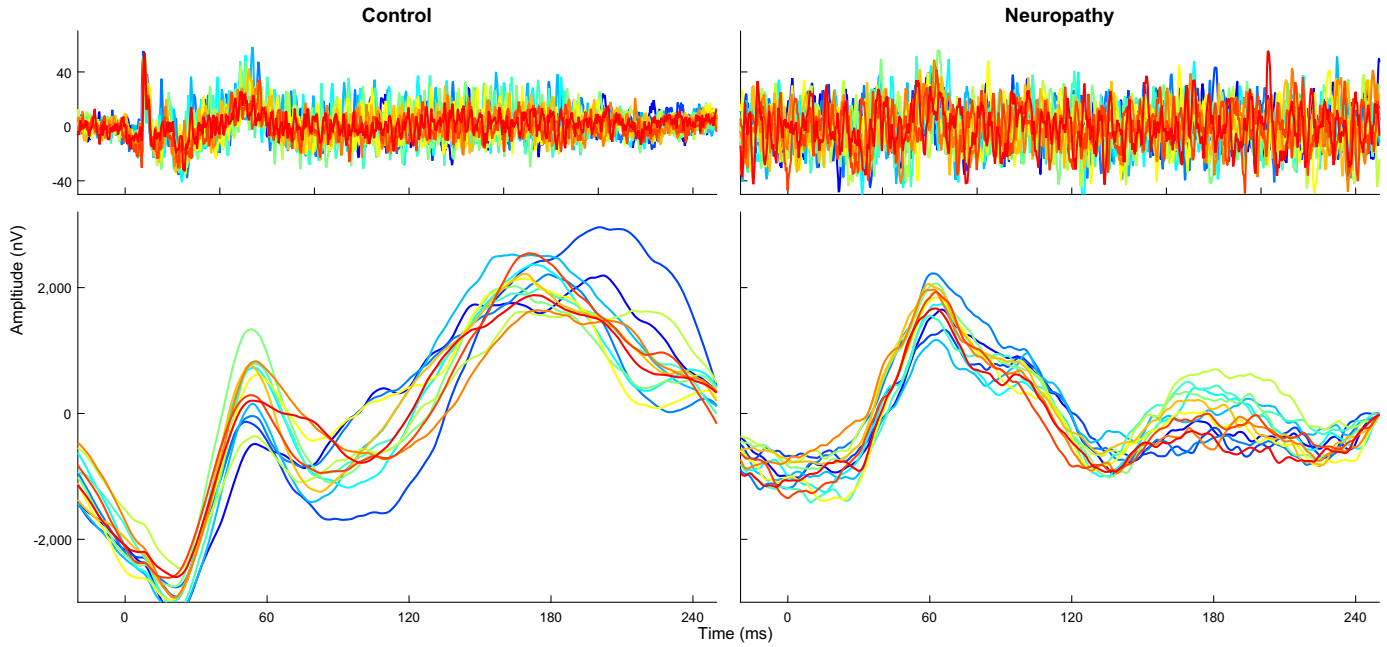

Figure 6. Time-domain responses are shown for each stimulus, filtered for the frequency-following response (FFR) (*top*) and cortical onset responses (*bottom*). OLA has strongly synchronized FFRs to each tone, showing a sharp onset response and sustained activity, reflecting the periodicity of the stimuli. She also has reliable cortical onset responses to each stimulus. In contrast, IT has no FFR despite evident cortical onset responses to each stimulus. Colors are assigned to stimuli as in Fig. 1. IT, an adult woman with auditory neuropathy; OLA, an adult woman with normal hearing (control subject).

absent ABR that cannot be explained by peripheral hearing loss. Our results predict patients with neuropathy would likewise have an absent FFR, a notion consistent with the suggestion that the FFR is sensitive to milder forms of neural dyssynchrony (e.g., 33).

We also did not evaluate IT's perceptual discrimination of the musical stimuli. Therefore we cannot comment on whether her lack of phaselocking caused difficulties perceiving and/or discriminating pitches within this range. Zeng et al. (34) reported that patients with neuropathy exhibit pronounced difficulty discriminating low-frequency sounds, requiring two tones to be nearly an octave apart to discriminate them. The extent to which the FFR reflects pitch perception remains an open question (cf. 35). Future work can directly compare neurophysiological processing and perception in patients with neuropathy, which may help elucidate the functional role(s) of subcortical synchrony for pitch perception.

Highly precise, synchronized activity in the subcortical auditory system may orchestrate consistent temporal coding for fast information in the rest of the auditory system. This interpretation aligns with perceptual evidence that listeners with auditory neuropathy struggle on tasks that require highly precise temporal processing such as gap detection (36) and interaural timing difference detection (34). Listeners with neuropathy also exhibit profound difficulties in speech-in-noise recognition tasks, supporting the view that subcortical synchrony is necessary to hear in noise (21, 22). Subcortical neural synchrony also appears to govern FFRs, including within the frequency bandwidth of cortical phaselocking. Together, our work suggests that FFRs reflect these subcortical mechanisms important for auditory perception.

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Additional contact information: www.brainvolts.northwestern.edu.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

T.W.-S., J.K., T.N., and N.K. conceived and designed research; T.W.-S. performed experiments; T.W.-S., J.K., T.N., and N.K. analyzed data; T.W.-S., J.K., T.N., and N.K. interpreted results of experiments; T.W.-S. prepared figures; T.W.-S. drafted manuscript; J.K., T.N., and N.K. edited and revised manuscript; T.W.-S., J.K., T.N., and N.K. approved final version of manuscript

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