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CASE STUDIES IN NEUROSCIENCE | *Sensory Processing*

Case studies in neuroscience: subcortical origins of the frequency-following response

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White-Schwoch T, Anderson S, Krizman J, Nicol T, Kraus N. Case studies in neuroscience: subcortical origins of the frequency-following response. *J Neurophysiol* 122: 844–848, 2019. First published July 3, 2019; doi:10.1152/jn.00112.2019.—The auditory frequency-following response (FFR) reflects synchronized and phase-locked activity along the auditory pathway in response to sound. Although FFRs were historically thought to reflect subcortical activity, recent evidence suggests an auditory cortex contribution as well. Here we present electrophysiological evidence for the FFR's origins from two cases: a patient with bilateral auditory cortex lesions and a patient with auditory neuropathy, a condition of subcortical origin. The patient with auditory cortex lesions had robust and replicable FFRs, but no cortical responses. In contrast, the patient with auditory neuropathy had no FFR despite robust and replicable cortical responses. This double dissociation shows that subcortical synchrony is necessary and sufficient to generate an FFR.

NEW & NOTEWORTHY The frequency-following response (FFR) reflects synchronized and phase-locked neural activity in response to sound. The authors present a dual case study, comparing FFRs and cortical potentials between a patient with auditory neuropathy (a condition of subcortical origin) and a patient with bilateral auditory cortex lesions. They show that subcortical synchrony is necessary and sufficient to generate an FFR.

auditory cortex lesions; auditory evoked potentials; auditory neuropathy; electrophysiology; frequency-following response

INTRODUCTION

The frequency-following response (FFR) has emerged in neuroscience as a means to understand auditory behaviors such as speech and music perception, real-world listening, and experience-dependent plasticity in auditory processing (Krizman and Kraus 2019). FFRs have long been thought to originate primarily in subcortical auditory nuclei, with the inferior colliculus of the auditory midbrain serving a chief role; indeed, FFRs recorded directly from the midbrain strongly resemble those recorded at the scalp (White-Schwoch et al. 2017) and cooling the inferior colliculus eliminates FFRs (Smith et al. 1975). This hypothesis is also supported by evidence in humans. Sohmer et al. (1977) showed that FFRs were absent in nine patients with brainstem lesions. Bidelman (2015, 2018) recorded FFRs with high-density, multichannel EEG and used source modeling to show that FFRs reflect sustained auditory midbrain activity.

Recent magnetoencephalography (MEG) evidence indicates a role for the right hemisphere auditory cortex in generating FFRs to the fundamental frequency (F0), along with contributions from the brainstem, midbrain, and thalamus (Coffey et al. 2016; see Zhao and Kuhl 2018 for additional MEG evidence pointing to subcortical sources of the FFR). Some authors have suggested these MEG results should be considered when interpreting EEG FFRs (Coffey et al. 2016, 2017; Holmes and Herrmann 2017; but see Bidelman 2018), the prevailing approach for recording FFRs. This raises the question: Is the auditory midbrain necessary and sufficient to generate an FFR?

To provide clarity to the origins of the scalp-recorded FFR, we conducted a dual case study. Specifically, we conducted an electrophysiological test battery in two patients who provide rare opportunities to test multiple hypotheses about the origins of the FFR.

MATERIALS AND METHODS

This study compares auditory-neurophysiological responses in two patients: NR, who has bilateral auditory cortex lesions, and IT, who has auditory neuropathy. Details on their case histories are presented in the RESULTS section, but both have essentially normal cochlear function (see Figs. 1 and 2). Both patients provided informed, written consent to participate in the project, and procedures were approved by the Institutional Review Board of Northwestern University.

Auditory brainstem responses (ABRs), FFRs, and cortical potentials were recorded in both patients.

The stimulus for ABRs was a 100-μs click presented at 80 dB SPL and 31.1 Hz and recorded with a Bio-Logic NavPro system. Clicks were presented in rarefaction (and, for IT, also condensation) polarity, and 2,000 artifact-free responses were recorded. Responses were filtered from 100 to 1,500 Hz online. We also have records of an ABR latency-intensity function for NR (see Fig. 1*C*), which used rarefaction clicks at 13.3 Hz with similar filtering, and also on a Bio-Logic NavPro.

The stimulus for FFRs and cortical potentials was a 170-ms [da] used in previous studies (Anderson et al. 2012). In addition to the [da] collected in quiet, we presented it in background noise, a six-talker babble track (timed to avoid phase synchrony with the [da]). We wanted a second, more challenging stimulus condition to compare with responses in quiet. This would let us both test whether responses

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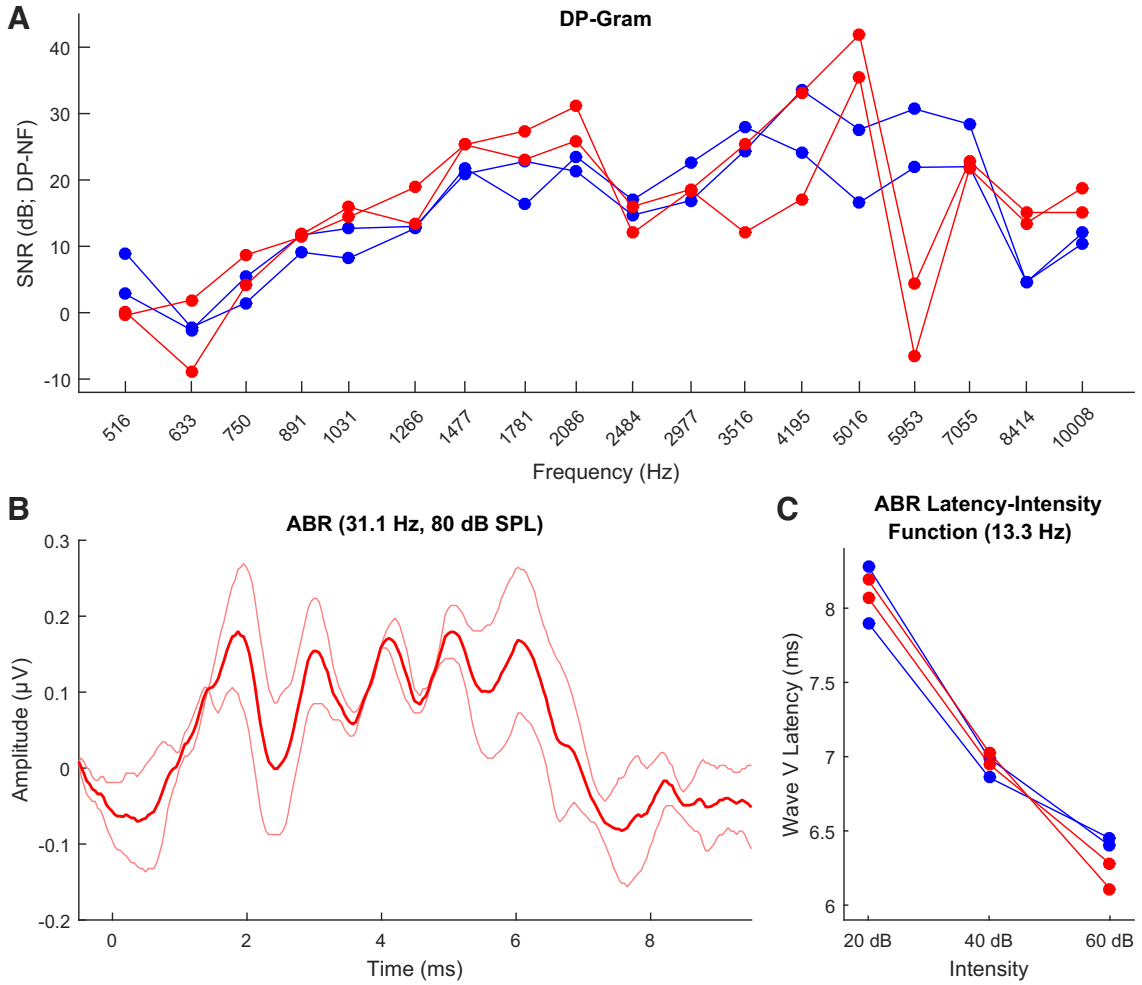

Fig. 1. Results from subject NR's audiology testing. *A*: distortion product otoacoustic emission results for the right (red) and left (blue) ears from 516 to 10,008 Hz. Plotted is the signal-to-noise ratio of the emission (distortion product minus noise floor, DP-NF). Overall NR has normal cochlear function, with a possible notch noted in the right ear. He may have a mild sensorineural hearing loss from chemotherapy. *B*: auditory brainstem responses (ABRs) collected in the Auditory Neuroscience Laboratory in response to a rarefaction click presented at 31.1 Hz and 80 dB SPL. Thin lines show two runs of the click ABR with the bold line showing their average. While the morphology is somewhat idiosyncratic, the response is reliable. *C*: ABR latency-intensity study provided to us by NR's audiologist. Both ears show normal responses to changes in intensity (note this click was delivered at 13.3 Hz). DP-gram, distortion product otoacoustic emission level as a function of F2 frequency.

are absent or present and test for changes in response morphology as a function of listening condition (cf. White-Schwoch et al. 2015). We chose noise given evidence that patients with neuropathy have extreme difficulties understanding speech in noise (Kraus et al. 2000).

For FFRs, the [da] was presented at 3.9 Hz at 80 dB SPL in alternating polarities; 6,000 artifact-free responses were collected in the quiet and background noise conditions from Cz, filtered from 70 to 2,000 Hz, and epoched from 0 to 210 ms re stimulus onset. The signal-to-noise ratio for the noise condition was +10 dB. NR's FFRs were recorded in a Neuroscan SynAmps system and IT's FFRs were recorded in a Biosemi Active2 system.

Spectra were computed via fast Fourier transforms. For cortical responses, the [da] was presented at 1 Hz at 80 dB SPL in alternating polarity; 500 artifact-free responses were collected in each condition from Cz, filtered from 1 to 40 Hz, and epoched from −100 to 500 ms re stimulus onset. The signal-to-noise ratio for the noise condition was +10 dB. Both responses were recorded in a Neuroscan SynAmps system; NR's responses were recorded with a 32-channel cap and IT's with a single channel at Cz.

RESULTS

The first case, NR, is a 28-yr-old man with bilateral auditory cortex lesions following treatment for acute lymphoblastic leukemia. His treatment included a breathing tube that was dislodged, causing hypoxia, followed by a medically induced coma, multiple rounds of chemotherapy, and a bone marrow transplant. Following his treatment he experienced hearing difficulties. His medical team conducted an MRI and the radiologist's report identified bilateral temporal lobe lesions.

NR is cortically deaf: he lacks awareness of sounds and cannot understand speech or music. He also exhibits signs of mild visual agnosia. Cognitive abilities are otherwise normal. Due to his poor ability to detect sounds, NR could not complete a behavioral audiogram. However, NR had normal distortion product otoacoustic emissions (DPOAEs; see Fig. 1*A* for a distortion product otoacoustic emission level as a function of F2 frequency graph) and auditory brainstem responses (ABRs; Fig. 1, *B* and *C*), indicating an origin central to the auditory midbrain for his deafness. Consistent with the diagnosis of cortical deafness, NR had absent cortical auditory evoked potentials (Fig. 3*E*).

Yet, NR had robust and highly replicable FFRs (Fig. 3*A*). Latencies and amplitudes were within normal limits and similar to healthy, age-matched controls (Anderson et al. 2012).

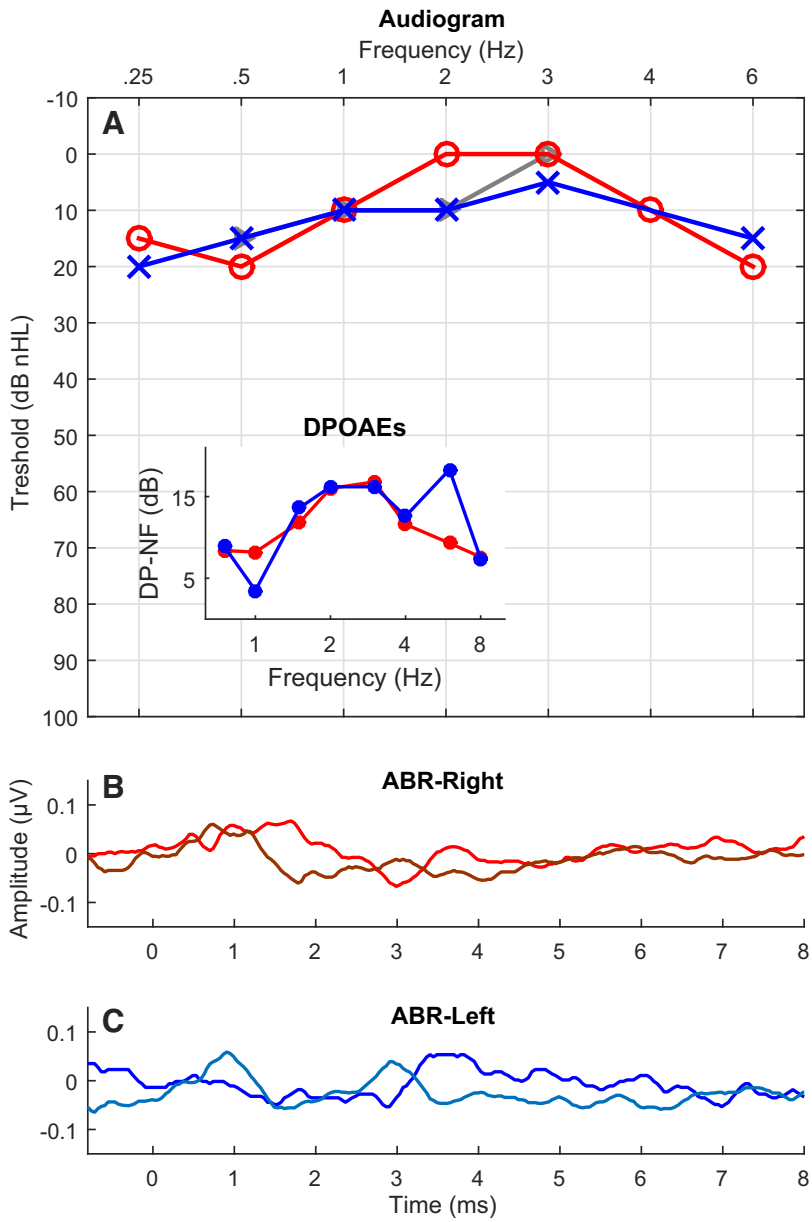

Fig. 2. Results from subject IT's audiology testing. *A*: audiogram shows normal hearing thresholds. Right ear is shown in red, left ear in blue, and bone-conduction testing in gray. The *inset* shows distortion product otoacoustic emissions (DPOAEs) in the right and left ears, which are robust. *B* and *C*: auditory brainstem responses (ABRs) were elicited at 31.1 Hz and 80 dB SPL in rarefaction (bright colors) and condensation (duller colors) in the right and left ears, respectively. Consistent with her diagnosis of auditory neuropathy, IT had absent ABRs.

NR had robust responses to the fundamental frequency in both quiet and background noise (Fig. 3*B*), which is noteworthy because MEG source modeling ascribes the FFR to the 100-Hz F0 of this stimulus, at least in part, to the auditory cortex (Coffey et al. 2016). NR's robust response to the F0 suggests that multiple sources can contribute to the F0 component of the FFR, consistent with MEG source analysis (Coffey et al. 2016)—and NR's response shows that cortex is not necessary for generating low-frequency components of the FFR. NR's case is consistent with studies in cats that were lesioned in either the inferior colliculus or auditory cortex and showed that inferior colliculus was necessary and sufficient to generate FFRs (Kiren et al. 1994).

The second case, IT, is a 41-yr-old woman with auditory neuropathy, meaning she has intact outer hair cell function in the cochlea but an absent auditory brainstem response due to dyssynchronous subcortical firing (Starr et al. 1996). IT has tremendous difficulty understanding speech in adverse listening conditions, such as noisy environments, but has normal speech perception in quiet. She also reports some difficulty with sound awareness, albeit not to the extent of NR, and difficulty understanding unfamiliar accents. IT had a normal audiogram (Fig. 2*A*) and normal DPOAEs (Fig. 2, *inset*) but an absent ABR bilaterally (Fig. 2, *B* and *C*). Additionally, and consistent with her absent ABR, IT had no FFR (Fig. 3, *B* and *D*).

Yet she had robust and highly replicable cortical responses (Fig. 3*F*). Her response in quiet was somewhat larger than typically observed in adults (cf. Cunningham et al. 2000), albeit later, and her response in noise was particularly delayed. This may reflect cortical-subcortical interactions, particularly for coding speech features in noise. Her cortical response is also evocative of that found in older adults, where larger responses are thought to reflect compensatory mechanisms (Bidelman et al. 2014; Roque et al. 2019). Moreover, her response likely lacks normal brainstem inhibitory processes. It is noteworthy that her response in noise is especially delayed

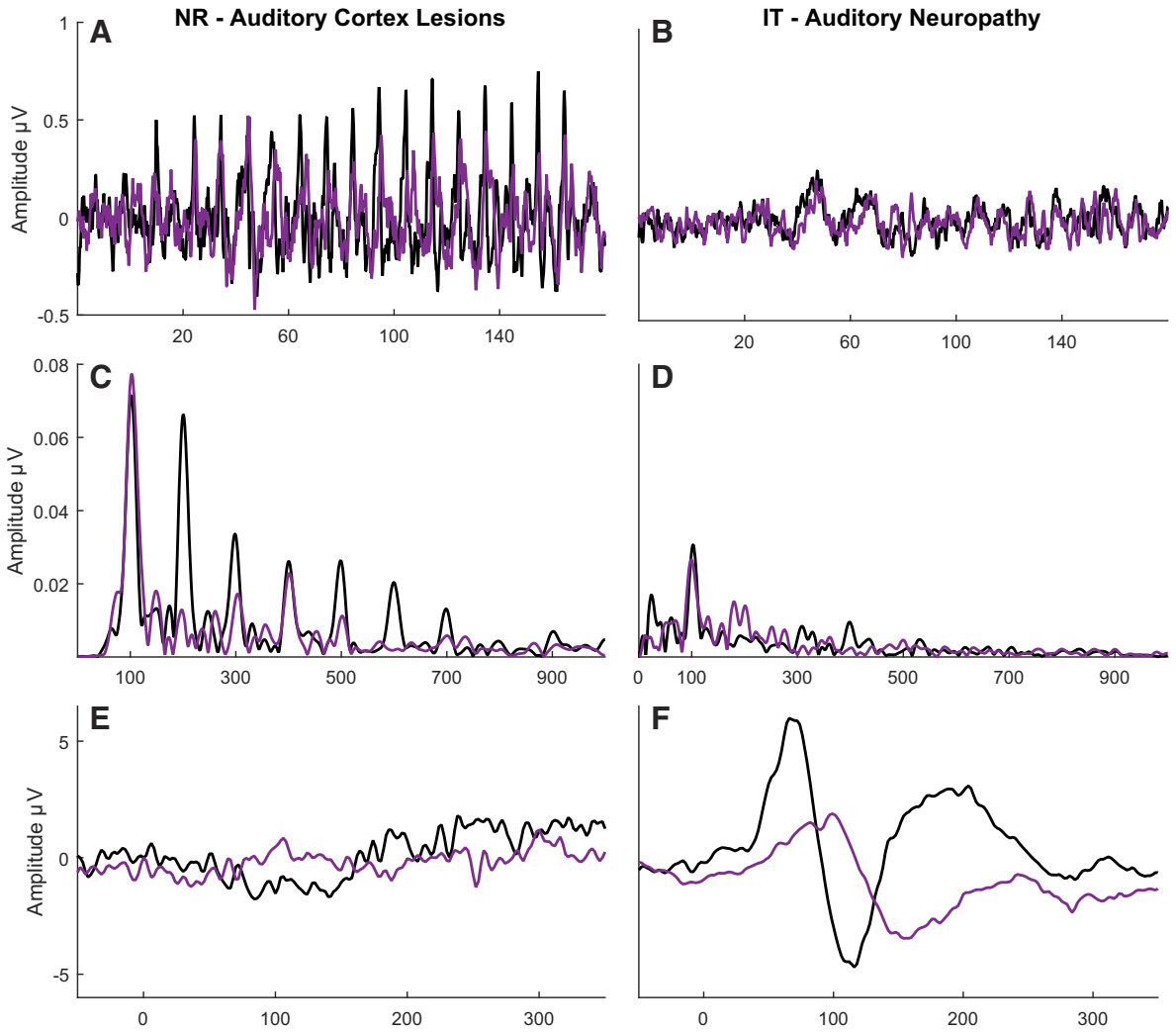

Fig. 3. Subcortical and cortical responses are shown for both subjects NR and IT. Each panel is organized analogously. The *top two rows* show frequency-following response (FFR) to "da" in quiet (black) and noise (purple) in the time and frequency domains, respectively. NR has robust responses in both conditions, including to the fundamental frequency (F0) at 100 Hz, which were within normal limits (Anderson et al. 2012). IT has no FFR. The *bottom row* shows cortical responses to the same stimuli. NR has no cortical response but IT has a robust onset response both in quiet and noise.

given her difficulties understanding speech in noise. Cortical-subcortical interactions may partially drive cortical responses to speech in noise. Still, overall, her case is consistent with the notion that a functioning auditory cortex is not sufficient to generate an FFR.

DISCUSSION

Together, NR and IT show a double dissociation: auditory cortex is necessary for cortical responses but unnecessary for FFRs. Highly precise subcortical synchrony is necessary for FFRs but unnecessary for cortical responses. The auditory midbrain and cortex may specialize to fill distinct roles in auditory perception. If the cortex does not receive synchronous input from the midbrain, the signal will be temporally smeared, such that the cortex will not be able to reconstruct it. Indeed, listeners with neuropathy exhibit profound deficits with fast temporal processing (Kraus et al. 1984, 2000; Starr et al. 1996; Zeng et al. 1999). In contrast, NR's case shows that this fine temporal resolution can be intact but is insufficient for speech communication or music perception.

One drawback of this study is that we do not have detailed anatomical information about NR's lesions. We have the radiologist's report, which indicates bilateral temporal lobe lesions but does not provide detailed information about the possibility of residual auditory fields. We note the complete absence of a cortical evoked potential, which is consistent with auditory cortex lesions (Özdamar et al. 1982). Nevertheless, with our current data we cannot rule out the possibility of residual cortical contributions to his FFR, although we think it unlikely that such a contribution would contribute to the FFR but not generate any cortical evoked potential (i.e., consist only of 100 Hz phaselocking).

In IT's case we similarly do not have a precise localization of the "site of lesion" — her neuropathy may be pre- and/or postsynaptic. We note evidence of a middle latency response visible in her FFR tracings (in the 25–75 ms rage; see Fig. 3*B*) consistent with functioning thalamic and corticothalamic pathways (Kraus et al. 1982, 1988) and reinforcing evidence of a subcortical neuropathy. Still, a number of subcortical insults and lesions can produce the auditory

neuropathy phenotype (Kraus et al. 1984; Starr et al. 1996, 2003).

This is neither to gainsay cortical contributions to healthy subjects' FFRs, nor to undermine the strong, long-term influence of cortical processing on subcortical auditory function. As with any case study, our results depend on rare circumstances that may not generalize to all subjects. Noteworthy, however, is their consistency with early FFR work in humans (Sohmer et al. 1977), recent source modeling work (Bidelman 2015, 2018), and lesion studies in animals (Kiren et al. 1994). When considered in tandem with previous work, these case studies show that accurate and synchronous encoding of the auditory midbrain is necessary and sufficient to generate an electrophysiological FFR.

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GRANTS

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

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

REFERENCES

Anderson S, Parbery-Clark A, White-Schwoch T, Kraus N. Aging affects neural precision of speech encoding. *J Neurosci* 32: 14156–14164, 2012. doi:10.1523/JNEUROSCI.2176-12.2012.

Bidelman GM. Multichannel recordings of the human brainstem frequency-following response: scalp topography, source generators, and distinctions from the transient ABR. *Hear Res* 323: 68–80, 2015. doi:10.1016/j.heares.2015.01.011.

Bidelman GM. Subcortical sources dominate the neuroelectric auditory frequency-following response to speech. *Neuroimage* 175: 56–69, 2018. doi:10.1016/j.neuroimage.2018.03.060.

Bidelman GM, Villafuerte JW, Moreno S, Alain C. Age-related changes in the subcortical-cortical encoding and categorical perception of speech. *Neurobiol Aging* 35: 2526–2540, 2014. doi:10.1016/j.neurobiolaging.2014.05.006.

Coffey EB, Herholz SC, Chepesiuk AM, Baillet S, Zatorre RJ. Cortical contributions to the auditory frequency-following response revealed by MEG. *Nat Commun* 7: 11070, 2016. doi:10.1038/ncomms11070.

Coffey EBJ, Musacchia G, Zatorre RJ. Cortical correlates of the auditory frequency-following and onset responses: EEG and fMRI evidence. *J Neurosci* 37: 830–838, 2017. doi:10.1523/JNEUROSCI.1265-16.2016.

Cunningham J, Nicol T, Zecker S, Kraus N. Speech-evoked neurophysiologic responses in children with learning problems: development and behavioral correlates of perception. *Ear Hear* 21: 554–568, 2000. doi:10.1097/00003446-200012000-00003.

Holmes E, Herrmann B. Revisiting the contribution of auditory cortex to frequency-following responses. *J Neurosci* 37: 5218–5220, 2017. doi:10.1523/JNEUROSCI.0794-17.2017.

Kiren T, Aoyagi M, Furuse H, Koike Y. An experimental study on the generator of amplitude-modulation following response. *Acta Otolaryngol Suppl* 511: 28–33, 1994.

Kraus N, Bradlow AR, Cheatham MA, Cunningham J, King CD, Koch DB, Nicol TG, McGee TJ, Stein LK, Wright BA. Consequences of neural asynchrony: a case of auditory neuropathy. *J Assoc Res Otolaryngol* 1: 33–45, 2000. doi:10.1007/s101620010004.

Kraus N, Özdamar Ö, Hier D, Stein L. Auditory middle latency responses (MLRs) in patients with cortical lesions. *Electroencephalogr Clin Neurophysiol* 54: 275–287, 1982. doi:10.1016/0013-4694(82)90177-8.

Kraus N, Özdamar Ö, Stein L, Reed N. Absent auditory brain stem response: peripheral hearing loss or brain stem dysfunction? *Laryngoscope* 94: 400–406, 1984. doi:10.1288/00005537-198403000-00019.

Kraus N, Smith DI, McGee T. Midline and temporal lobe MLRs in the guinea pig originate from different generator systems: a conceptual framework for new and existing data. *Electroencephalogr Clin Neurophysiol* 70: 541–558, 1988. doi:10.1016/0013-4694(88)90152-6.

Krizman J, Kraus N. Analyzing the FFR: a tutorial for decoding the richness of auditory function. *Hear Res*. First published August 8, 2019. doi:10.1016/j.heares.2019.107779.

Özdamar Ö, Kraus N, Curry F. Auditory brain stem and middle latency responses in a patient with cortical deafness. *Electroencephalogr Clin Neurophysiol* 53: 224–230, 1982. doi:10.1016/0013-4694(82)90027-X.

Roque L, Gaskins C, Gordon-Salant S, Goupell MJ, Anderson S. Age effects on neural representation and perception of silence duration cues in speech. *J Speech Lang Hear Res* 62, 4S: 1099–1116, 2019. doi:10.1044/2018_JSLHR-H-ASCC7-18-0076.

Smith JC, Marsh JT, Brown WS. Far-field recorded frequency-following responses: evidence for the locus of brainstem sources. *Electroencephalogr Clin Neurophysiol* 39: 465–472, 1975. doi:10.1016/0013-4694(75)90047-4.

Sohmer H, Pratt H, Kinarti R. Sources of frequency following responses (FFR) in man. *Electroencephalogr Clin Neurophysiol* 42: 656–664, 1977. doi:10.1016/0013-4694(77)90282-6.

Starr A, Michalewski HJ, Zeng F-G, Fujikawa-Brooks S, Linthicum F, Kim CS, Winnier D, Keats B. Pathology and physiology of auditory neuropathy with a novel mutation in the MPZ gene (Tyr145->Ser). *Brain* 126: 1604–1619, 2003. doi:10.1093/brain/awg156.

Starr A, Picton TW, Sininger Y, Hood LJ, Berlin CI. Auditory neuropathy. *Brain* 119: 741–753, 1996. doi:10.1093/brain/119.3.741.

White-Schwoch T, Davies EC, Thompson EC, Woodruff Carr K, Nicol T, Bradlow AR, Kraus N. Auditory-neurophysiological responses to speech during early childhood: effects of background noise. *Hear Res* 328: 34–47, 2015. doi:10.1016/j.heares.2015.06.009.

White-Schwoch T, Nicol T, Warrier CM, Abrams DA, Kraus N. Individual differences in human auditory processing: insights from single-trial auditory midbrain activity in an animal model. *Cereb Cortex* 27: 5095–5115, 2017. doi:10.1093/cercor/bhw293.

Zeng F-G, Oba S, Garde S, Sininger Y, Starr A. Temporal and speech processing deficits in auditory neuropathy. *Neuroreport* 10: 3429–3435, 1999. doi:10.1097/00001756-199911080-00031.

Zhao TC, Kuhl PK. Linguistic effect on speech perception observed at the brainstem. *Proc Natl Acad Sci USA* 115: 8716–8721, 2018. doi:10.1073/pnas.1800186115.