Multiple Cases of Auditory Neuropathy Illuminate the Importance of Subcortical Neural Synchrony for Speech-in-noise Recognition and the Frequency-following Response

Travis White-Schwoch,[1] Samira Anderson,[2] Jennifer Krizman,[1] Silvia Bonacina,[1] Trent Nicol,[1] Ann R. Bradlow,[3] and Nina Kraus,[1,4]

Objectives: The role of subcortical synchrony in speech-in-noise (SIN) recognition and the frequency-following response (FFR) was examined in multiple listeners with auditory neuropathy. Although an absent FFR has been documented in one listener with idiopathic neuropathy who has severe difficulty recognizing SIN, several etiologies cause the neuropathy phenotype. Consequently, it is necessary to replicate absent FFRs and concomitant SIN difficulties in patients with multiple sources and clinical presentations of neuropathy to elucidate fully the importance of subcortical neural synchrony for the FFR and SIN recognition.

Design: Case series. Three children with auditory neuropathy (two males with neuropathy attributed to hyperbilirubinemia, one female with a rare missense mutation in the *OPA1* gene) were compared to age-matched controls with normal hearing (52 for electrophysiology and 48 for speech recognition testing). Tests included standard audiological evaluations, FFRs, and sentence recognition in noise. The three children with neuropathy had a range of clinical presentations, including moderate sensorineural hearing loss, use of a cochlear implant, and a rapid progressive hearing loss.

Results: Children with neuropathy generally had good speech recognition in quiet but substantial difficulties in noise. These SIN difficulties were somewhat mitigated by a clear speaking style and presenting words in a high semantic context. In the children with neuropathy, FFRs were absent from all tested stimuli. In contrast, age-matched controls had reliable FFRs.

Conclusion: Subcortical synchrony is subject to multiple forms of disruption but results in a consistent phenotype of an absent FFR and substantial difficulties recognizing SIN. These results support the hypothesis that subcortical synchrony is necessary for the FFR. Thus, in healthy listeners, the FFR may reflect subcortical neural processes important for SIN recognition.

Key words: Auditory development, Auditory neuropathy, Cochlear Implants, Frequency-following response, Speech-in-noise recognition.

Abbreviations: ABR, auditory brainstem response (eABR, electrically evoked ABR); ASSR, auditory steady state response; CAEP, cortical auditory-evoked potential; CI, cochlear implant; D, days; F0, fundamental frequency; F1, first formant (F2, second formant, etc.); FFR, frequency-following response; HINT-C, Hearing-in-Noise Test for Children; M-LNT, Multisyllabic Lexical Neighborhood Test; MEG, magnetoencephalography; MLR, middle-latency response; Mo, month; NU-CHIPS, Northwestern University-Children's Perception of Speech; OAEs, otoacoustic emissions (DPOAEs, distortion product OAEs; TEOAEs, transient evoked OAEs); PBK, Phonetically Balanced Kindergarten Test; SDT, speech detection threshold; SIN, speech in noise; SPL, sound pressure level; SRT, speech reception threshold; WRS, word recognition score; Yr, year.

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[1]Auditory Neuroscience Laboratory, Department of Communication Sciences, Northwestern University, Evanston, Illinois; [2]Department of Hearing and Speech Sciences, University of Maryland College Park, College Park, Maryland; [3]Speech Communication Research Group, Department of Linguistics, Northwestern University, Evanston, Illinois; and [4]Departments of Neurobiology and Otolaryngology, Northwestern University, Evanston, Illinois.
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INTRODUCTION

This article addresses two related issues in auditory neuroscience: the role of subcortical neural synchrony in supporting recognition of speech in noise (SIN) and in generating the frequency-following response (FFR). Our premise is that subcortical synchrony is critical for both. This hypothesis can be tested in case studies of patients with auditory neuropathy—a lack of subcortical synchrony that manifests as an absent auditory brainstem response (ABR) without necessarily affecting audiometric thresholds (Kraus et al. 1984; Starr et al. 1996).

A direct connection between subcortical synchrony and SIN recognition has been documented in listeners with normal hearing, insofar as the FFR reflects subcortical neural activity. Four lines of evidence support this contention. First, among healthy individuals of multiple ages, individual differences in FFRs correlate with individual differences in SIN performance (Anderson et al. 2010b; Anderson et al. 2011; Anderson et al. 2013c; Thompson et al. 2019; Bidelman & Momtaz 2021; but see Schoof & Rosen 2016). Similarly, individual differences in FFRs correlate with performance on nonverbal tests of processes thought to support SIN recognition, such as temporal fine structure perception (Ruggles et al. 2012; Parthasarathy et al. 2020). Second, clinical populations who often experience SIN difficulties, such as older adults, children with learning problems, and individuals with a brain injury, also exhibit poor FFRs (Clinard et al. 2010; Anderson et al. 2012; White-Schwoch et al. 2015; Thompson et al. 2018; Bidelman et al. 2019). Third, expert populations such as musicians tend to exhibit stronger FFRs and better SIN performance (Parbery-Clark et al. 2009a; Parbery-Clark et al. 2009b; Bidelman et al. 2011; Coffey et al. 2017a; but see Boebinger et al. 2015). Finally, randomized control trials show auditory-cognitive training instills parallel gains in FFRs and SIN performance (Song et al. 2012; Anderson et al. 2013d; Anderson et al. 2014). Still, much of this work is correlational. Documenting absent FFRs and SIN difficulties in patients with compromised subcortical synchrony would provide strong reinforcement of the hypothesis that synchrony is critical for SIN recognition.

At the same time, interpretations of a potential mechanistic connection between the FFR and SIN have been complicated by questions about what exactly the FFR reflects. In particular, longstanding dogma that the FFR reflects subcortical neural activity has been challenged by neuroimaging evidence proposing a right-hemisphere auditory cortex contribution (Coffey et al. 2016; Coffey et al. 2017b). Nevertheless, an adult listener with auditory neuropathy but relatively normal hearing thresholds had no FFR despite a robust cortical auditory-evoked potential (CAEP) (White-Schwoch et al. 2019; White-Schwoch et al. 2021).

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In contrast, an adult male with bilateral auditory cortex lesions exhibited a normal FFR. While these case studies do not negate a cortical contribution to healthy listeners' FFRs, they do suggest subcortical synchrony is necessary and sufficient to generate one.

There is also considerable evidence that auditory neuropathy causes difficulties understanding SIN (reviewed by Rance 2005). The aforementioned listener with neuropathy, but relatively normal hearing, has excellent word and sentence recognition in quiet, but in noise has both variable and poor performance (Kraus et al. 2000; White-Schwoch et al. 2020). Neuropathy patients' difficulty in noise also lends credence to emerging hypotheses that milder forms of dyssynchrony, such as those introduced by normal aging or noise exposure, might account for hearing-in-noise difficulties (Kujawa & Liberman 2009; Sergeyenko et al. 2013).

Several etiologies cause the neuropathy phenotype (Moser & Starr 2016) and even the same presumed etiology can manifest as vastly different clinical presentations (Berlin et al. 2010; Harrison et al. 2015). Yet our work to date has relied on a single, idiopathic case. It is therefore necessary to expand our work demonstrating an absent FFR in a neuropathy patient to multiple patients with multiple sources of neuropathy. It is also necessary to demonstrate concomitant SIN recognition difficulties in these same patients to reinforce the link between subcortical synchrony and SIN recognition.

Here we do just that. We present three patients with auditory neuropathy to test the generalizability of the hypothesis that subcortical synchrony is necessary for the FFR. We include detailed case histories to highlight the diversity of the neuropathy population. In Experiment 1, we report on two patients with neuropathy attributed to hyperbilirubinemia, a leading cause of the disorder. In Experiment 2, we report on a patient whose neuropathy is attributed to a rare missense mutation in the *OPA1* gene. Our results show that, while subcortical neural synchrony is subject to multiple sources of disruption that manifest in heterogeneous clinical profiles, the consequences of this dyssynchrony for the FFR and SIN recognition are consistent.

EXPERIMENT 1

Materials and Methods

All procedures were approved by the Northwestern University Institutional Review Board in accordance with the Declaration of Helsinki. Patients' parents provided written consent for them to participate in research.

Subjects

Neuropathy • Two patients with auditory neuropathy attributed to hyperbilirubinemia, R.C. and N.E., participated in Experiment 1. R.C. is a 2-year-old male and N.E. is a 6-year-old male. Detailed case histories and audiological data* are presented in Results section.

Controls • For electrophysiological data, the control subjects are age-matched males pulled from the Auditory Neuroscience Laboratory database (Skoe et al. 2015; Krizman et al. 2019). Only males were selected as controls because of sex differences in FFRs (Krizman et al. 2019; Krizman et al. 2020). There were four 2-year-old boys in the database with a mean age of 2.67 years (SD, 0.22 years). There were 27 6-year-old boys in the database with a mean age of 6.65 years (SD, 0.26 years). All had normal distortion product otoacoustic emissions (DPOAEs) from 0.5 to 4 kHz and reported no history of hearing loss or neurodevelopmental disorder. In addition, all had normal ABRs to a 100-μs square wave rarefaction click†. For speech recognition testing, the pool(s) of control subjects differed based on the paradigm, with details provided later.

Electrophysiology

FFRs were elicited to a 40-ms synthesized /d/; see Supplemental Digital Content 1, http://links.lww.com/EANDH/A896 for details on the stimuli. Stimuli were delivered and responses were collected through a Bio-Logic Navigator Pro System (Natus Medical Incorporated, San Carlos, CA). The /d/ was presented at 80 dB SPL to the right ear through the system's stock insert earphone in alternating polarities. A vertical montage of three Ag–AgCl electrodes was used (Cz active, A2 reference, and Fpz ground). Responses were sampled at 12 kHz, filtered online from 100 to 2000 Hz, and averaged over a 75-ms epoch with a 15.8-ms prestimulus region. Artifact rejection was at ±23.8 μV. Two blocks of 3000 artifact-free stimuli were collected in each subject. Responses to alternating polarities were added, accentuating the FFR to the envelope of the speech syllable, which is dominated by its periodicity and lower harmonics (FFR_{ENV}; see Coffey et al. 2019 and Krizman & Kraus 2019 for a discussion of terminology).

Speech Recognition

A number of standard speech and phoneme recognition tests were available from R.C.'s and N.E.'s audiological records. We have reproduced available data in the Results section.

N.E., the 6-year-old boy, also completed two tests of speech recognition in noise in our laboratory. These tests were designed for pediatric populations to evaluate both speech recognition and potential benefits from different talker, contextual, and noise scenarios.

The first, the Clear Speech Test, was designed to measure sentence-in-noise recognition and estimate the benefit derived from speaking in an intentionally clear style ("clear speech"). The test and stimuli are described in detail by Bradlow et al. (2003). Briefly, stimuli were four lists of 16 sentences taken from the Bamford-Kowal-Bench corpus (Bench et al. 1979). The sentences were recorded by a female talker in clear and conversational styles. Sentences were mixed with broad-band (speech-spectrum shaped) noise and presented at −4 and −8 dB signal to noise ratios (SNRs). The number of correctly identified target words was recorded (N = 50/list, 3 to 4/sentence). Bradlow et al. (2003) provided control data on 18 typically developing children with normal hearing between the ages of 8 to 12 years (mean 10.4 years, SD 1.3 years). The Clear Speech Test was adapted for use in cochlear implant (CI) users by Liu et al. (2004), from which we pulled comparison data from 8 adults between the ages of 25 to 70 years (mean 50.4 years, SD 16.4 years). These data are included because N.E. used a CI, and we wanted to control for the potential effects of electric hearing on the test.

*Clinical data from audiological records were extracted using WebPlot Digitizer (Rohatgi 2020).

†Our laboratory's standard ABR protocol involves only rarefaction clicks for normal-hearing subjects as a screening. Consequently, we do not have alternating-polarity clicks in our normal hearing control subjects.

The second, the Style-by-Context Test, was designed to tease apart potential word-in-noise recognition benefits derived from talker style (conversational versus clear speech) and the semantic context of the utterance (low versus high context). The test was adapted from Fallon et al. (2002), who found that 5-year-old children recognize approximately 10% more target words in noise when presented in a high semantic context (e.g., *Farm animals stay in a barn.*) versus a low semantic context (e.g., *He read about the barn.*). The modification (described in detail in Bradlow & Alexander 2007) added a speaking style contrast (clear or conversational speech) resulting in four sets of 15 sentence stimuli. All 60 sentences were recorded by one female talker and presented to each child (15 from each condition). The proportion of final words correctly recognized was recorded (N = 60). The controls were 30 children ages 8 to 12 years (mean 10.6 years, SD 1.3 years) with normal hearing.

RESULTS

Case Histories and Clinical Presentations

R.C. • R.C. is a 2.8-year-old male with auditory neuropathy attributed to hyperbilirubinemia. He was born premature at 33 weeks gestational age and had mild jaundice for which he received phototherapy, which was effective. A few days later, when R.C. was 11 days old and nearing discharge from intensive care, he contracted necrotizing enterocolitis that caused a bowel perforation and, as a consequence, remained in intensive care where he received a blood transfusion. Jaundice reappeared and when he was 27 days old total serum bilirubin reached 26.1 mg/dl, which prompted an additional course of intensive phototherapy.

When he was approximately 2.6 months old he was discharged from intensive care and received his first hearing screening. He passed OAEs but failed ABRs and was referred to audiology for follow-up testing. When he was tested in our laboratory, his receptive language skills corresponded to an 18 to 21-month-old and his expressive language skills correspond to a 15- to 18-month-old. He had used bilateral hearing aids for about 11 months (Phonak micro eXtra). His parents had pursued extensive audiological testing and shared the results, along with his neonatal medical history. Audiological test results are summarized in Figure 1 and Table S1, Supplemental Digital Content 1, http://links.lww.com/EANDH/A896.

N.E. • N.E. is a 6-year-old male with auditory neuropathy attributed to hyperbilirubinemia that caused kernicterus. He was born at 33 weeks and spent 11 days in the intensive care unit. N.E.'s mother was diagnosed with a kidney infection when pregnant and treated with gentamycin. When N.E. was 4 days old his total serum bilirubin level was 21.7 mg/dl. He did not receive a blood transfusion but received intensive phototherapy and antibiotics.

He passed a bilateral OAE screening at birth. We do not have records on when N.E. received his first ABR; however, we suspect it was quite early in life and responses were not detected. When N.E. was 10 months, he used hearing aids for 1 month to no avail. When he was 1 year old, however, he received a CI in the left ear (Cochlear N24 with SPrint processor). The family immediately noticed a considerable benefit from the CI and, when N.E. was 6, was contemplating a right-ear implant. When we evaluated him, we attempted FFRs in his unimplanted ear. He listened bimodally for SIN recognition testing.

N.E.'s audiograms over time are shown in Figure 2. His right ear showed air conduction thresholds anywhere from 40 to 70 dB HL. At age 10.9 months, his left ear showed similar, albeit slightly poorer sensitivity. Two months later, no response

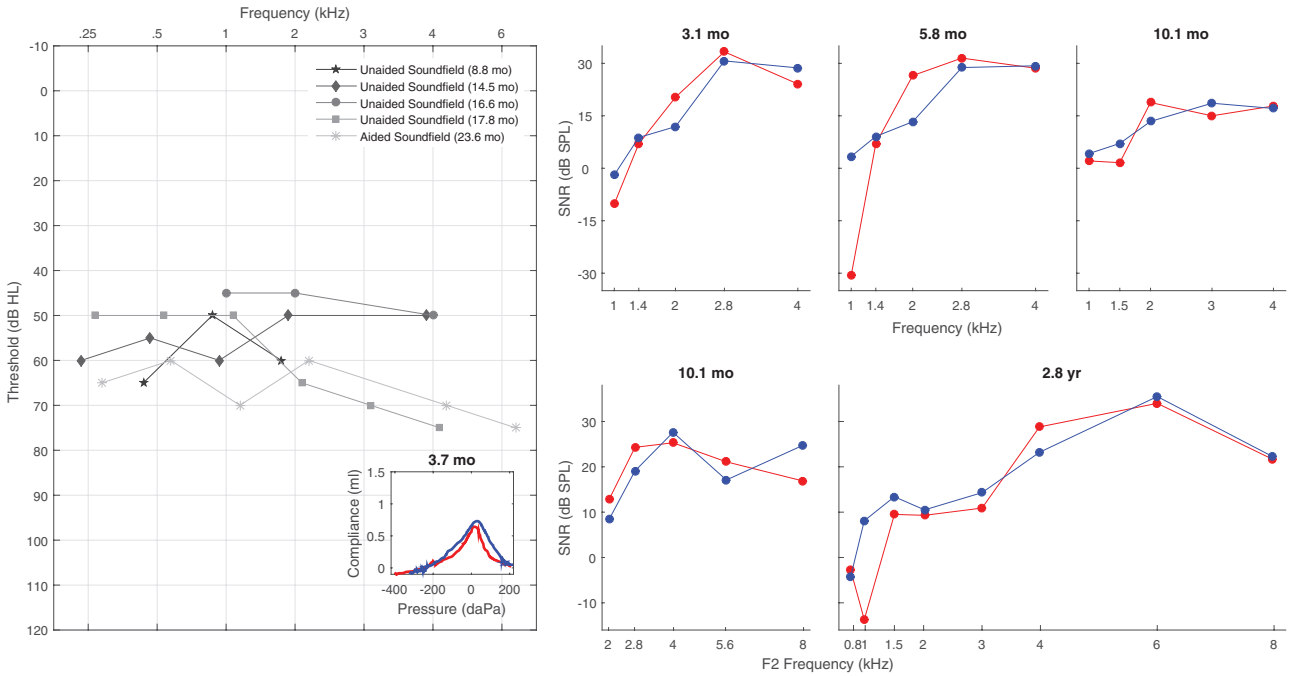


Fig. 1. R.C.'s hearing. (Left) Five screening audiograms were conducted in sound field during his first 2 yr. Screening thresholds are plotted for each test in greyscale, as indicated by the legend. Note audiograms have been jittered slightly about the x-axis to allow visualization of multiple datapoints at a given frequency-threshold point. Audiograms are consistent with a moderate to severe sensorineural hearing loss. (Inset) Tympanograms show normal compliance bilaterally. (Right/Top) TEOAEs conducted during the first year of life are robust. (Right/Bottom) DPOAEs conducted at 10 months and 2.8 years are robust. DPOAEs, distortion product otoacoustic emissions; TEOAEs, transient-evoked otoacoustic emissions.

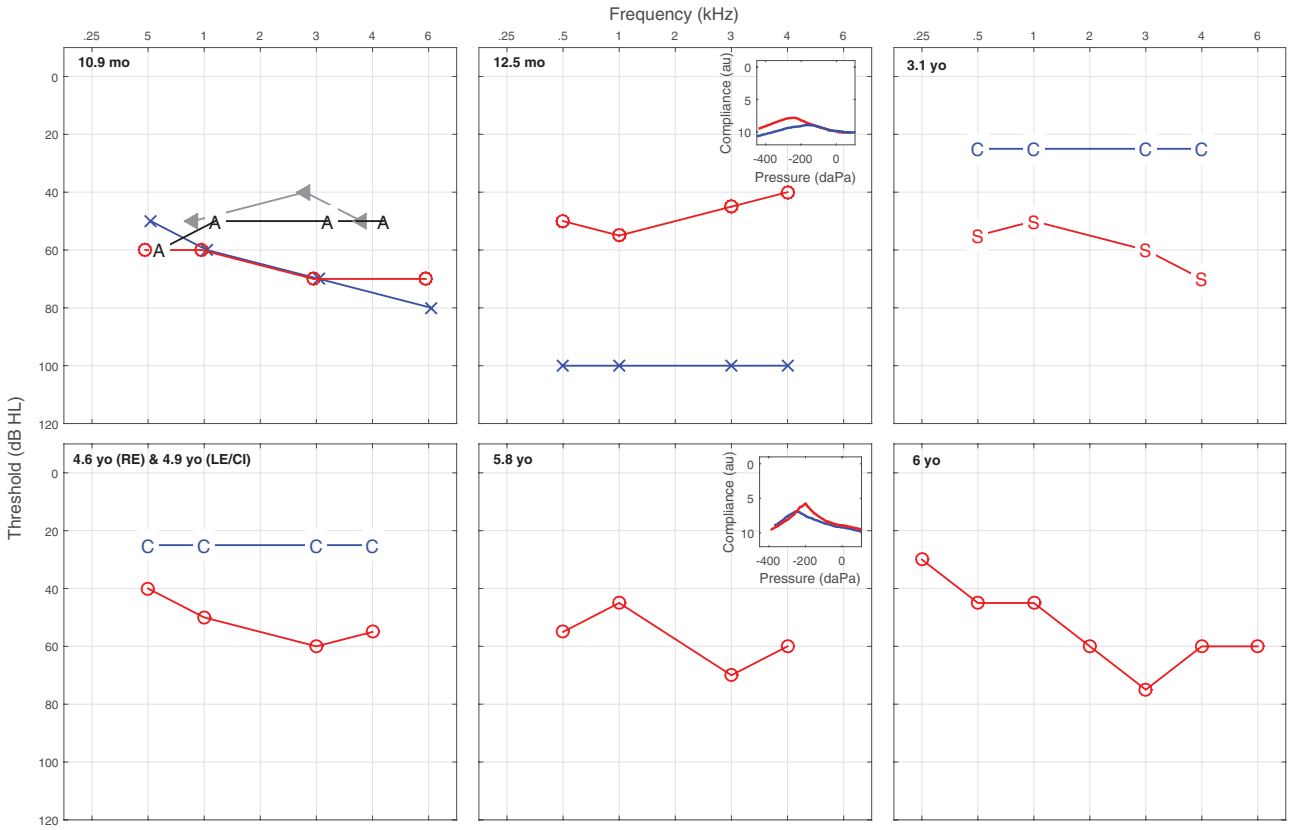


Fig. 2. N.E.'s hearing. A first screening audiogram was attempted at age 10.9 mo, showing poor sensitivity bilaterally but lower bone conduction thresholds. The "A's" show thresholds when N.E. was fitted with a Resound behind-the-ear hearing aid in the left ear. By 12.5 mo, N.E. had no hearing sensitivity in the left ear and received a cochlear implant that improved sensitivity. The right ear continued to be tested over time, showing moderate-to-poor sensitivity. (Insets) On two occasions N.E. had Type C tympanograms bilaterally. C, left-ear cochlear implant; S, right-ear sound field.

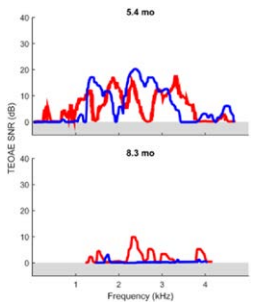
could be elicited. After implantation, N.E. showed good hearing sensitivity in his left ear. We have two records of attempted tympanometry, on which Type C tympanograms were observed bilaterally.

Although records indicate N.E. passed a bilateral OAE screening at birth, subsequent results were equivocal (Table 1). At age 5.4 months, he had robust transient-evoked OAEs (TEOAEs) and DPOAEs bilaterally with good reproducibility. Three months later, however, reliable OAEs could not be elicited in either ear. Although we do not have detailed results, narrative sections of his audiology records suggest N.E.'s OAEs remained absent up until the time he was tested in our laboratory.

N.E. was implanted with a CI in the left ear when he was 1 year old and underwent an eABR study. Consistent with previous reports (Gordon et al. 2003), higher levels elicited earlier and more replicable responses. This eABR study suggests the CI provided relatively normal electric hearing to N.E.'s left ear and is consistent with his good reported outcomes from the implant. Detailed results of the eABR study are reported Figure S1, Supplemental Digital Content 1, http://links.lww.com/

TABLE 1. N.E.'s DPOAEs and TEOAEs

			DPOAEs						TEOAEs
			F2 Frequency						
Age (mo)	Ear	Measure	0.7	1.5	2.2	3.0	3.7	Overall	
5.4	Left	SNR	–5	15	19	17	1	9.2	
		Repro (%)	0	97	98	98	0	90	
	Right	SNR	–5	15	19	17	1	11.4	
		Repro (%)	0	97	98	98	0	88	
8.3	Left	SNR	NR	0	NR	–4	0	NR	
		Repro (%)	0	46	0	0	0	30	
	Right	SNR	–3	8	1	NR	2	3.5	
		Repro (%)	0	87	0	0	0	35	



When tested at 5.4 mo, N.E. had robust DPOAEs (left) and TEOAEs (right) bilaterally with good waveform reproducibility. Three months later, however, neither DPOAEs nor TEOAEs could reliably be measured. The drop in his left-ear emissions is more dramatic, consistent with his audiograms over time. SNR, signal-to-noise ratio, dB; Repro %, waveform reproducibility %; Gray shaded region represents the noise floor. DPOAEs, distortion product otoacoustic emissions; TEOAEs, transient-evoked otoacoustic emissions.

EANDH/A896 and Table S2, Supplemental Digital Content 1, http://links.lww.com/EANDH/A896.

Shortly before visiting our laboratory, N.E.'s candidacy for a second CI was evaluated by an audiology clinic specializing in auditory neuropathy. We have their summary report. Tympanograms were normal bilaterally. Acoustic reflexes and OAEs were absent bilaterally. ABRs were attempted in the right ear and were absent, although they note that the amplitude of the potential decreased, which they interpreted as declining cochlear microphonic consistent with worsening hearing sensitivity. N.E. could not perform a gap detection test (Adaptive Test of Temporal Resolution) in the right ear but could detect a 3.6-ms gap in the implanted ear, similar to normal hearing young adults' performance (Lister et al. 2006), and within the range of CI users' (Shannon 1989) and some neuropathy patients' performance (Zeng et al. 1999), on gap-detection tasks conducted at high sound levels.

Frequency-following Responses

Neither R.C. nor N.E. exhibited FFRs to /d/, whereas every control subject exhibited replicable FFRs. FFRs were attempted in unaided listening conditions through insert earphones. In N.E., FFRs were attempted in his unimplanted ear.

Time-domain waveforms are shown in Figure 3, Panels A (R.C.) and E (N.E.). Below each waveform is the average response from healthy controls (2-year-old boys in Panel C and 6-year-old boys in Panel G; see Figure S2, Supplemental Digital Content 1, http://links.lww.com/EANDH/A896, for data on individual controls). Neither R.C.'s nor N.E.'s waveforms show stereotypes of a reliable response, such as a larger response amplitude than prestimulus region amplitude; a sharp onset response ca. 10 ms; or phaselocked peaks that follow the periodicity of the stimulus, ca. 20 to 50 ms. In contrast, both control groups' waveforms show these hallmarks. The right half of Figure 3 shows spectra for R.C. (Panel B) and N.E. (Panel F). Crucially, these responses show no energy in response to the F0 (ca. 100 Hz), which is the FFR component ascribed to the auditory cortex by neuroimaging (Coffey et al. 2016; Coffey et al. 2017b). In addition, this spectrum suggests a very low level of noise in N.E.'s response. Although we tested N.E.'s unimplanted ear, there might still be a concern about artifact from his CI. The low level of noise in N.E.'s recording suggests such artifact did not interfere with our ability to elicit an FFR.

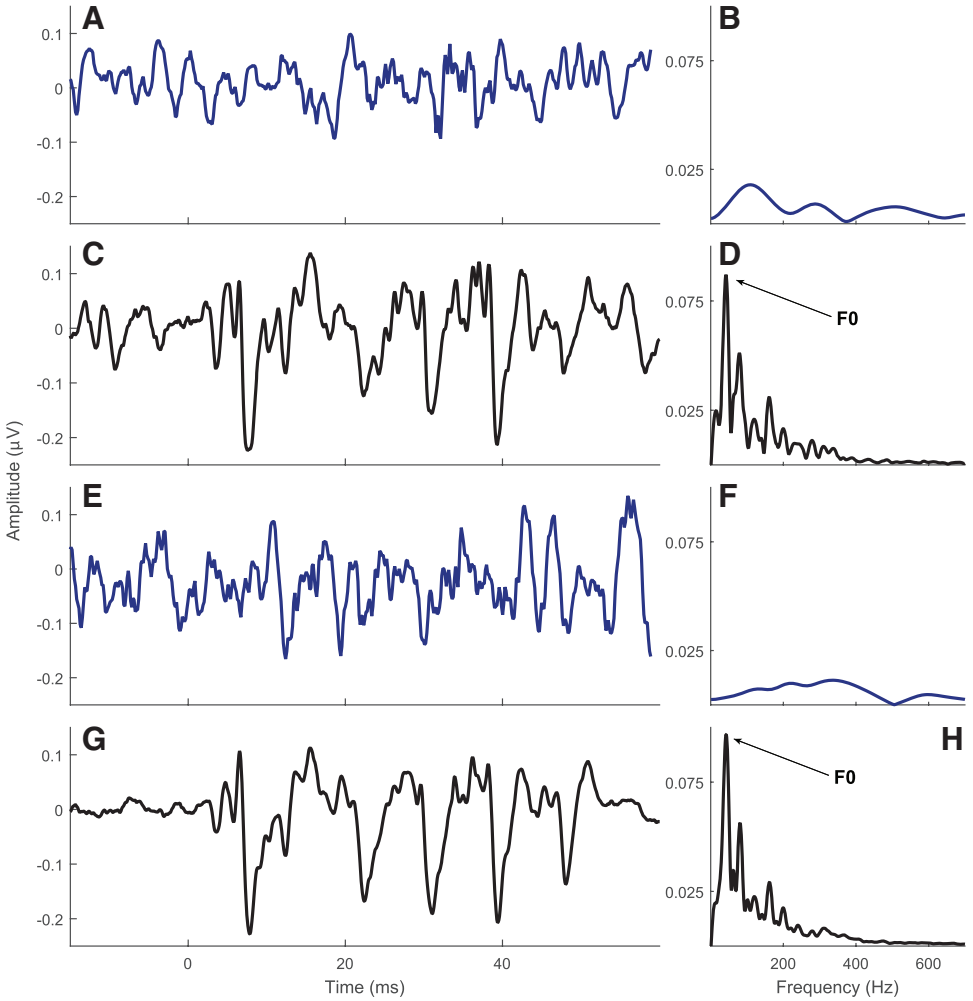


Fig. 3. FFRs are absent in two patients with auditory neuropathy. (A) R.C.'s time-domain waveform shows no response. (B) The spectrum of R.C.'s response is flat, consistent with an absent FFR. (C) Time-domain grand average of 2-year-old controls' FFRs. (D) Spectral-domain grand average of 2-year-old controls' FFRs. (E) N.E.'s time domain waveform shows no response. (F) The spectrum of N.E.'s response is flat, consistent with an absent FFR. (G) Time-domain grand average of 6-year-old controls' FFRs. (H) Spectral-domain grand average of 6-year-old controls' FFRs. FFR, frequency-following response.

Speech Recognition

R.C. • Speech audiometry data are available from some of the evaluations in audiology clinics. Results are shown in Table 2. R.C. had variable speech detection thresholds (SDTs) between the ages of 8.8 and 23.6 months. Listening in sound field and/or with hearing aids did not result in meaningful improvements. SDTs increased over time and were consistent with the sensorineural hearing loss shown in Figure 1.

N.E. • N.E.'s audiologists tested his speech detection and reception thresholds on three occasions. When he was 10.8 months, they measured a 60 dB SDT in the right ear and 50 dB in the left. When he was 12.5 months, they retested the right ear and measured a 50 dB SDT. When he was 4.6 years old, they estimated a 45 to 55 dB speech-reception threshold (SRT) in the right ear. Beginning at this age, they also measured his performance on word and sentence recognition in quiet and noise. Results are shown in Figure 4. At both ages 4.6 and 5.9 years, N.E. had excellent speech perception in quiet, as measured by the Lexical Neighborhood Test and the HINT. In noise, however, N.E.'s performance worsened to <50% of target words, both with his CI alone and when listening with his CI and his right ear. His performance on the Multisyllabic Lexical Neighborhood Test and the Phonetically Balanced Kindergarten (PBK) test was generally good, although poorest when listening in sound field with his CI turned off, suggesting he derives a meaningful listening benefit from his implant.

Results of sentence-in-noise recognition tests conducted in our laboratory are shown in the lower two panels of Figure 4. N.E. performed well on the Clear Speech Test at the easy SNR (−4 dB), although he did not benefit from clear speech at this SNR. He performed slightly, but significantly, worse than normal-hearing children from Bradlow et al. (2003) for both speaking styles (conversational: $t_{34} = -1.89$, $p = 0.03$; clear: $t_{34} = -4.70$, $p < 0.001$). Compared to estimates of adult CI users' performance at these SNRs derived from Liu et al. (2004)‡, N.E. performed better with conversational speech but worse with clear speech, driven by his apparent inability to capitalize on a clear speaking style at the −4 dB SNR. In both the clear and conversational conditions, N.E. performed more poorly at a more challenging SNR (−8 dB), although at this SNR he did benefit from clear speech, recognizing an additional 34% of the target words. He performed worse than control children for the conversational speaking style ($t_{34} = -4.45$, $p < 0.001$) but reached their range of performance for the clear speaking style ($t_{34} = -1.01$, $p = 0.15$). N.E. outperformed adult CI user estimates for both conversational and clear speaking styles. On average, he showed about a 12% boost of clear speech, matching that of normal-hearing children ($t_{34} = 0.51$, $p = 0.69$) but smaller than adult CI users.

On the Style-by-Context test, which was conducted at a more challenging SNR (−24 dB), N.E. performed very poorly, recognizing at most 40% of the target words. His performance was worse than 8 to 12 years olds tested at Northwestern University§ on all four conditions (high context/conversational: $t_{33} = -16.47$, $p < 0.001$; high context/clear: $t_{33} = -26.41$, $p < 0.001$; low context/conversational: $t_{33} = -10.43$, $p < 0.001$; low context/clear: $t_{33} = -10.71$, $p < 0.001$). N.E. also performed more poorly than 5-year-olds from Fallon et al. (2002) for both high and low context conditions (high context: $t_{33} = -39.37$, $p < 0.001$; low context: $t_{33} = -38.50$, $p < 0.001$; n.b. this report did not include the clear speech conditions), suggesting that age effects do not account for his poor performance. N.E.'s performance improved, however, from a high semantic context (10%) and a clear speaking style (17%). His boost from context was similar to 5-year olds' (we do not know the SD) but lower than older children achieved from context ($t_{33} = -5.59$, $p < 0.001$) and style ($t_{33} = -1.94$, $p < 0.03$).

In summary, N.E. had good speech recognition in favorable listening conditions (quiet and moderate to high intensities). However, he exhibited substantial difficulties when listening to noise. These difficulties were somewhat mitigated by presenting target words in high-context situations. N.E. also benefited from clearly spoken speech at challenging SNRs.

TABLE 2. R.C.'s speech detection thresholds under various listening conditions

Age (mo)	Condition	Detection Thresholds (dB HL) Speech	/a/	/i/	/u/	/sh/
8.8	Bone conduction	45	35	45		NR
	Sound field—Unaided	NR				
	Sound field—Aided	NR				
14.5	Unaided*		60+	60+	60+	50
17.7	Sound field—Unaided		50	60		70
23.6	Sound field—Aided	75				

*Thresholds were moderately high, variable, and tended to increase over time. NR, no response. *Record does not indicate if they were with headphones or in sound field).*

EXPERIMENT 2

In this section, we report on a child with a rare missense mutation in the *OPA1* gene that causes progressive auditory neuropathy and optic atrophy. We believe this is the second report of this mutation in the literature (see Santarelli et al. 2015). Clinical data included detailed audiograms, DPOAEs, and speech recognition tests. Our laboratory's testing included FFRs and CAEPs.

Methods

All procedures were approved by the Northwestern University Institutional Review Board in accordance with the Declaration of Helsinki. The patient's parents provided written consent to participate in research.

Subjects

K.B. • K.B. is a 7-year-old girl with optic atrophy (progressive degeneration of the optic nerve) and bilateral auditory neuropathy. Both are attributed to a missense mutation in the *OPA1* gene. Detailed case history, genetic testing results, and audiological data are described in Results section.

‡Liu et al. (2004) measured performance from −10 to 15 dB SNR in 5 dB steps and fit sigmoid functions to describe the incremental gain in speech intelligibility with each dB SNR. We used these fit lines to estimate adult CI users' performance at −4 and −8 dB SNRs. We do not have estimates of CI users' variability at these SNRs so could not compare N.E.'s performance to theirs statistically.

§Note that 8 to 12 years old control children perform more poorly than the 5-year-old children from Fallon et al. (2002). We assume this is due to talker effects because the speech stimuli were re-recorded by the Speech Communication Research Group at Northwestern University. The 5-year-old children perform similarly to 8-to-12-year-old children in the clear speech condition. The difference in performance between conditions (i.e. benefit from context) should control for talker effects.

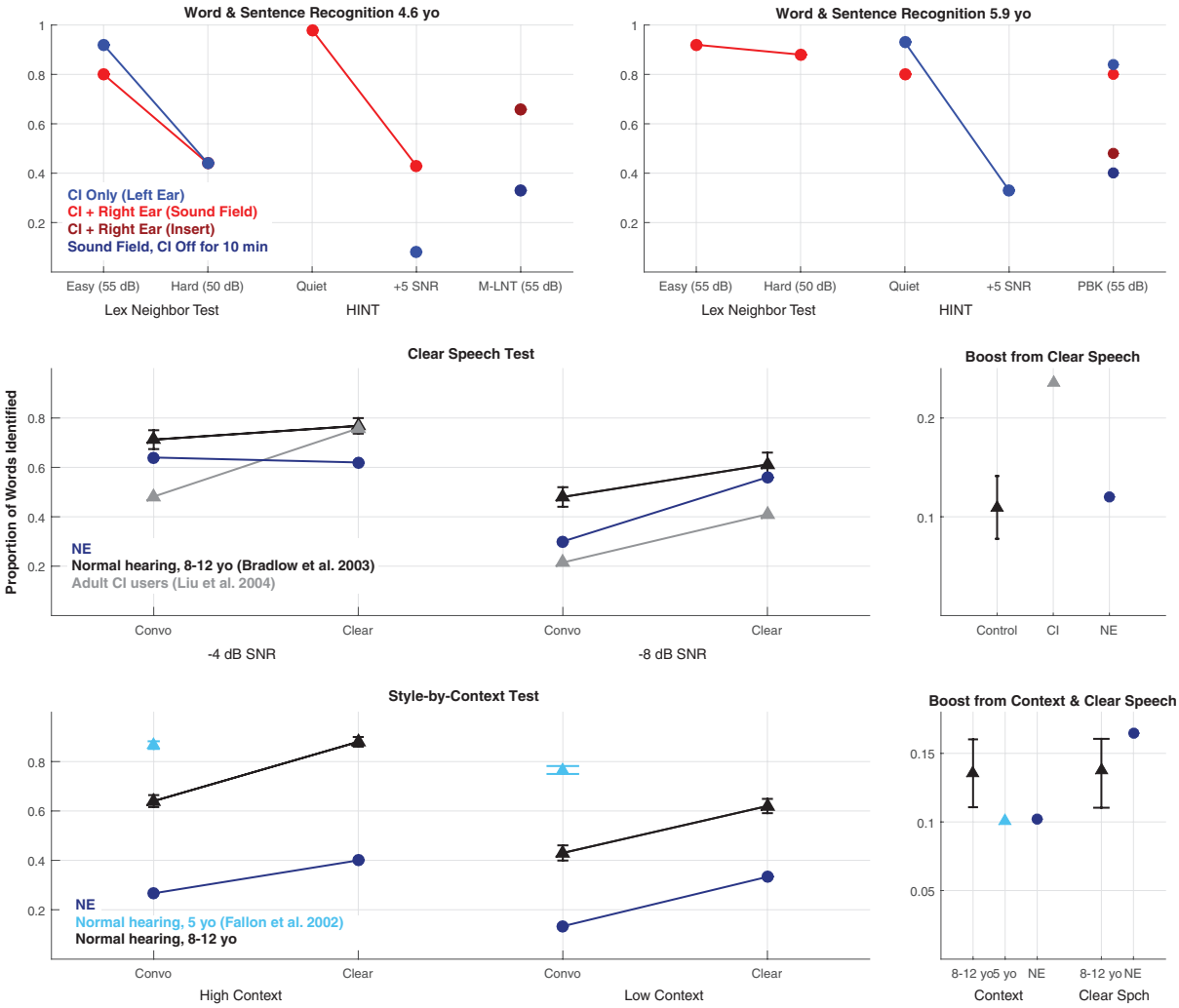


Fig. 4. N.E.'s speech recognition. (Top) Word and sentence recognition measures from audiology records. His audiologists evaluated word and sentences recognition under a variety of listening conditions. His word recognition was good when words and sentences were presented in quiet at moderate to high intensities. In noise he recognized <50% of target words. His speech recognition improved when listening with his CI. (Middle) Results of the Clear Speech Test, showing N.E.'s performance (navy), normal hearing children from Bradlow et al. (2003) (black) and estimates of adult CI users' performance (gray). N.E. performs slightly worse than normal hearing children at the easy SNR and considerably worse at the difficult SNR. (Middle/Right) The boost in performance from clear speech (% $\text{Recognized}_{\text{Clear}}$ – % $\text{Recognized}_{\text{Conversational}}$) is shown for the three groups. N.E. derives roughly the same benefit from clear speech as normal hearing children but considerably less than adult CI users. (Bottom) Results of the Style-by-Context Test. N.E. (navy) performs more poorly than normal hearing 5-yr olds (teal) and normal hearing 8 to 12 years olds (black) at all conditions. (Bottom/Right) The boost in performance from high semantic context and clear speech. N.E. derives a similar benefit from high context as 5 years olds with normal hearing and, at this test's more challenging SNR, a slightly larger benefit from clear speech than older children with normal hearing. SNR, signal to noise ratio; yo, years old.

Controls • The control subjects are age-matched females pulled from the Auditory Neuroscience Laboratory database (Skoe et al. 2015; Krizman et al. 2019). Only females were selected as controls due to sex differences in FFRs. There were 21 7-year-old girls in the database with a mean age of 7.53 years (SD, 0.30 years). Cortical-evoked potentials were available on 14 of the control subjects. All had normal DPOAEs from 0.5 to 4 kHz and reported no history of hearing loss or neurodevelopmental disorder. In addition, all had normal or corrected vision.

Electrophysiology

FFRs and CAEPs were elicited to a 170-ms synthesized /da/; see Supplemental Methods, Supplemental Digital Content 1, http://links.lww.com/EANDH/A896 for details on the stimuli. Stimuli were presented to the right ear through insert earphones. FFRs were measured with a vertical montage (Cz active, A2 reference, and Fpz ground), filtered from 70 to 2000 Hz, and averaged over a 250 ms epoch with a 40 ms prestimulus region. For FFRs, the stimuli were presented at 3.4 Hz. Artifact rejection was set at 35 μV and 4000 sweeps were collected. Responses to alternating polarities were once again added to emphasize FFR_{ENV}. CAEPs were measured with the same montage in response to 500 sweeps, filtered from 0.1 to 40 Hz, and averaged over a 500 ms epoch with a 100 ms prestimulus region. CAEP stimuli were presented at 1 Hz. CAEPs were denoised and eyeblinks were removed per previously published methods (Anderson et al. 2010a). K.B. was tested using a Neuroscan SynAmps system. Stimuli were presented in sound field. She did not wear hearing aids for the FFR. CAEPs were collected with and without her hearing aids. Controls were tested using a BioSEMI Active2 system.

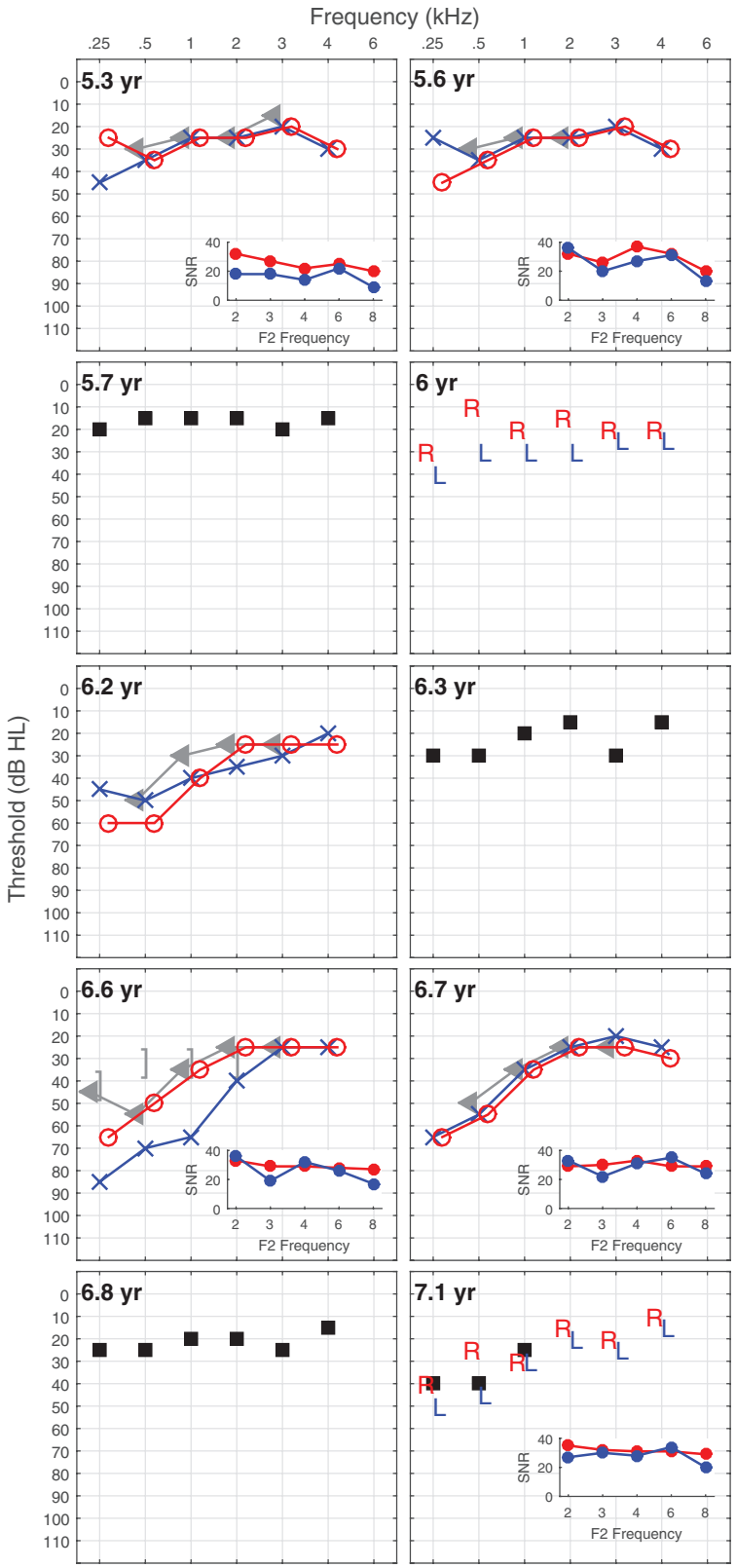


Fig. 5. K.B.'s hearing. Her first audiogram shows a mild bilateral hearing loss. Thresholds increased rapidly as much as 35 dB HL within a year, and as much as 40 dB HL 5 months after, relative to baseline. DPOAEs were consistently large bilaterally (insets) (■, diotic hearing aids; R, right-ear hearing aid; L, left-ear hearing aids). DPOAEs, distortion product otoacoustic emissions.

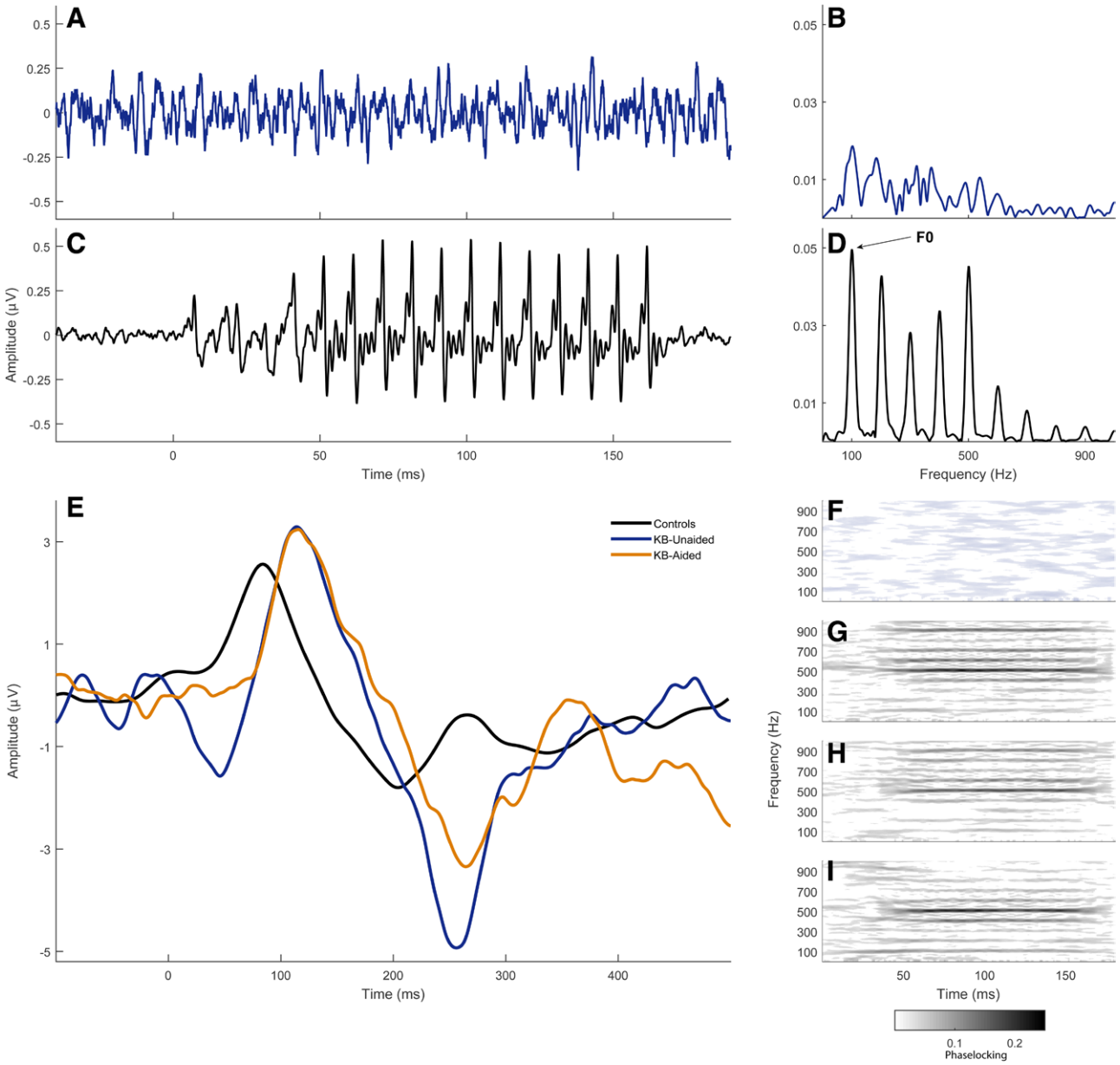


Fig. 6. K.B.'s electrophysiology. (A) FFR to a long (170 ms) /da/ is absent in K.B. shown in the time and (B) frequency domains. (C/D) In contrast, control subjects of the same age have a large and sharp response. Note in K.B.'s response the absence of phaselocked peaks every ~10 ms, which correspond to the periodicity of the stimulus, and that the amplitude of the prestimulus region appears equivalent in amplitude to the response region. (E) Cortical potentials are large and replicable in K.B.. Shown are potentials elicited in sound field when she listened in unaided (blue) and aided (yellow) conditions. The black trace is the control subjects' CAEP to the right ear through inserts. K.B.'s potentials are larger and later than controls'. The aided potential has a smaller N2 amplitude but is otherwise similar, showing that her CAEPs both replicate and differ as a function of listening condition. (F) FFR time–frequency-phase consistency. Any time–frequency bin showing phaselocking reliably above threshold is colored, with deeper colors indicating stronger phaselocking. K.B.'s response shows no reliably or systematic phaselocking corresponding to the stimulus, consistent with her absent FFR. (G–I) In contrast, three representative controls show strong phaselocking to the /da/. CAEP, cortical auditory-evoked potential; FFR, frequency-following response.

RESULTS

Case History and Clinical Presentation

Medical History • K.B. was delivered at 38 weeks gestational age following a normal pregnancy. She was a healthy child, but around age 3.5 years, her mother noticed vision problems. K.B. was later diagnosed with autosomal dominant optic atrophy type 1, a progressive neuropathy of the optic nerve. Her vision deteriorated rapidly over the following 1 to 2 years. Approximately 2 years later, she was first evaluated for hearing difficulties, which revealed a mild loss of hearing sensitivity as measured by audiometry and absent ABRs bilaterally. At the time she was in a school program for the vision impaired 3 days a week and in a mainstream classroom 2 days a week. Within a year, she used hearing aids, an FM system, and was in a hearing loss program in her mainstream first-grade classroom. Neurologic examinations were normal, including MRIs of the brain and cervical and thoracic spine.

Genetic Testing • K.B.'s medical team conducted genetic testing on her and her parents. Screening for autosomal dominant optic atrophy indicated a c.893G>A missense mutation in the *OPA1* gene, located on chromosome 3q28-q29. At the time of testing (2010), this mutation had not been reported, and so was of unknown clinical significance, but was deemed likely pathologic. The mutation was predicted to result in the replacement of serine with asparagine at codon 298 in the OPA1 protein (p.S298B).

Testing also identified three heterozygous variants and one homozygous variant in the *OPA1* gene that are common in the general population so were not considered clinically significant. No mutations in the genes *MTDN1*, *MTDN4*, or *MTDN6* were detected, ruling out Leber hereditary optic neuropathy. No mutations were detected in the *WFS1* gene, ruling out Wolfram syndrome. No mutations in the *OPA1* gene were detected in K.B.'s mother or father.

Hearing Tests • K.B. was followed carefully by a pediatric audiology program from the ages of 5 to 7 years. As shown in Figure 5, during this 2-year period she exhibited a dramatic and rapid decline in hearing sensitivity, as measured by audiometry. At age 5.3 years, her audiogram was consistent with a mild, bilateral sensorineural hearing loss. Within a year, her thresholds below 2 kHz had increased as much as 20 dB HL, with slightly higher thresholds noted in the right year. Less than 6 months later, thresholds had increased another 20 to 60 dB HL from the baseline. At age 5.7 years, she was fitted with bilateral hearing aids (Oticon Safari 900) which she wore with some success.

Yet, DPOAEs were remarkably consistent, showing large bilateral emissions throughout this period. Ipsilateral acoustic reflexes were attempted at age 5.3 years and were absent bilaterally from 0.5 to 2 kHz. These results were replicated at ages 5.6, 6.2, and 6.6 years. Tympanograms were variable. K.B.'s rapid and progressive hearing loss mirrors the rapid, progressive blindness observed in autosomal dominant optic atrophy, albeit with a slightly later onset.

At age 6.2 years, K.B. underwent a full diagnostic ABR study under sedation. No ABRs were observed to either polarity. Air conduction clicks were absent bilaterally up to 90 dB HL. Tone burst ABRs were absent bilaterally up to 105 dB HL

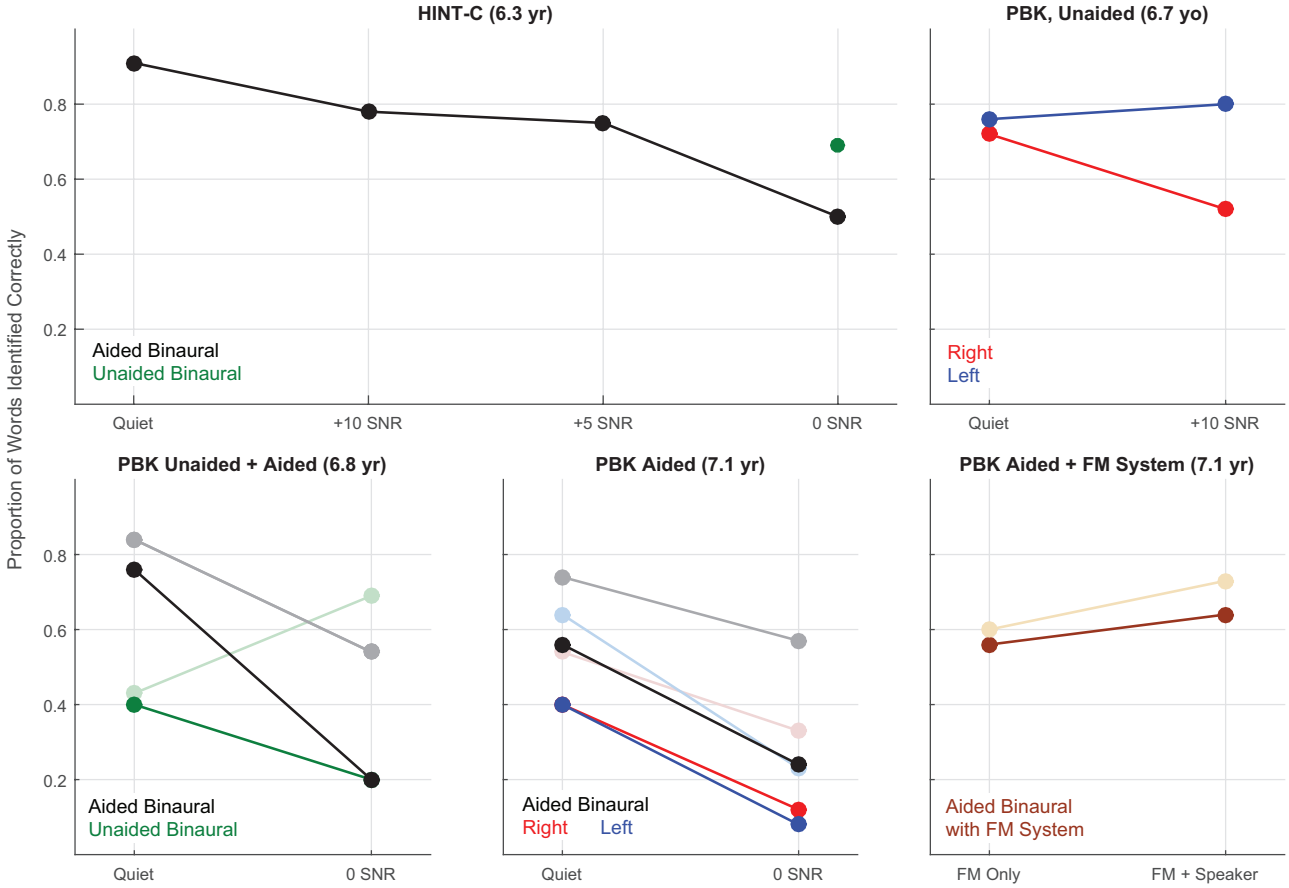


Fig. 7. (Top/Left) Performance on a modified HINT, indicating the proportion of targeted words identified at each SNR. K.B. performed excellently in quiet, and relatively well up to a +5 SNR. At a 0 SNR, however, she recognized <50% of the words. Her performance at this SNR was considerably better when listening *without* her hearing aids, however. (Top/Right) Performance on the PBK at age 6.7 yr when listening without hearing aids. In the right ear her performance worsened in noise. (Bottom/Left) Performance on the PBK about 6 wk later. Black/gray shows performance when listening binaurally through hearing aids and green shows unaided performance. Darker colors show word recognition and lighter colors show phoneme recognition. Phoneme recognition was better than word recognition, and except for the unaided condition K.B.'s performance was dramatically worse in the noise condition. (Bottom/Middle) About 3 mo later her performance overall was worse and was once again poorer in noise. Black/gray shows word and phoneme recognition when listening binaurally with hearing aids, blues show left-ear performance with a hearing aid and reds show right-ear performance listening with hearing aids. Darker colors show word recognition and lighter colors show phoneme recognition. (Bottom/Right) On the same date, K.B. was tested when listening with an FM system through her hearing aids. Performance was dramatically better and improved slightly when cues were also conveyed in sound field. Darker brown shows word recognition and tan shows phoneme recognition.

from 0.5 to 2 kHz. Bone conduction clicks were absent up to the highest levels tested (45 dB HL).

Electrophysiology

FFRs are shown in Figure 6 (see Figure S3, Supplemental Digital Content 1, http://links.lww.com/EANDH/A896, for data on individual controls). K.B. has no FFR. Her response does not show phaselocking to the period of the stimulus and the amplitude of the prestimulus and poststimulus regions appear equivalent to that of the response region. The spectrum of her response (Fig. 6B) confirms the absence of phaselocking. In contrast, control subjects had large and sharp responses with a high signal-to-noise ratio. They also showed strong phaselocking to the F0 and its harmonics.

Unlike the EEG system in Experiment 1, the systems used to test K.B. and the 7-year-old controls saved single-trial data. This allowed us to construct charts that illustrate the consistency of the phase of their responses at specific time–frequency bins. The figures are similar to a spectrogram, with time and frequency on the x and y axes, and the color scale shows the extent to which the phase of the response at that time–frequency point was similar across trials.

Results are shown in Figure 6F for K.B. and Figure 6G–I for representative controls (see Figure S4, Supplemental Digital Content 1, http://links.lww.com/EANDH/A896, for all individual subject data). Any time–frequency bin where the phase was not reliably synchronized is in white. Remaining time–frequency bins are colored, with deeper hues signifying more consistent responses. Controls show bands of phaselocking at the F0 (100 Hz) and its harmonics, in some cases throughout the response and in some cases more strongly in the later period corresponding to the steady state vowel. In contrast, K.B.'s response is disorganized and random, with no discernable horizontal striation. There is no systematic phaselocking in any time region or harmonic.

In contrast with her absent FFRs, K.B. had a large CAEP with a relatively normal gross morphology. K.B.'s response morphology, comprising a P1 and N2 with no evident N1, indicates a less mature CAEP, a morphology present in 6 of the 14 controls (consistent with previous reports in this age range, Cunningham et al. 2000). This morphology replicated for both the unaided and aided listening conditions. CAEPs are shown in Figure 6E. Multiple factors may account for the differences between K.B. and controls, including the EEG systems, stimulus delivery parameters, and K.B.'s sensorineural hearing loss. Still, the pattern of a large and somewhat late CAEP despite an excellent response morphology is consistent with our previous reports in neuropathy (Kraus et al. 1993; Kraus et al. 2000; White-Schwoch et al. 2019). Due to time constraints, we could not undertake a systematic comparison of her aided and unaided CAEPs under multiple listening conclusions, and so it is difficult to draw strong conclusions. For the purposes of this report, our most important conclusion is that K.B. has a replicable CAEP under multiple conditions. It also appears to change slightly as the input changes, confirming that her auditory cortex responds reliably to different inputs (see Supplemental Results, Supplemental Digital Content 1, http://links.lww.com/EANDH/A896 for detailed statistical analysis of K.B.'s CAEPs).

Speech Recognition

K.B. was evaluated on a number of standard speech perception tests by the audiology team that followed her.

When first tested, K.B. had excellent word recognition in quiet (>85%) but it worsened as her sensorineural hearing loss emerged. At age 5.3 years, she was tested on closed-set word recognition (NU-CHIPS) and open-set recognition thereafter (PBK). She had good SRTs bilaterally (20 to 30 dB HL unaided and 10 to 20 dB HL aided) with no sign of decline with advancing hearing loss. K.B.'s results are consistent with previous reports that auditory neuropathy patients have good speech recognition in quiet (Kraus et al. 2000; White-Schwoch et al. 2020), albeit with some variability. See Table S3, Supplemental Digital Content 1, http://links.lww.com/EANDH/A896, for detailed results.

Between the ages of 6 and 7 years K.B. also underwent SIN recognition testing. K.B. could recognize anywhere from 10% to 80% of words in noise across different listening conditions and configurations. Overall, her performance worsened dramatically in noise. She performed better when listening with two ears. She recognized more phonemes accurately than words. She benefited variably from amplification, sometimes recognizing more words when listening with hearing aids and sometimes recognizing fewer.

Detailed results are shown in Figure 7. For each test, we show the proportion of target words K.B. successfully identified. At age 6.3 years she was tested on a modified, nonadaptive form of the HINT-C (Fig. 7 Top/Left). When listening with both hearing aids, her speech recognition was excellent in quiet (91%) but decreased to 50% at a 0 dB SNR. It is interesting that when listening *without* hearing aids at 0 dB she heard nearly 20% more words. Approximately 4 months later, she was tested on the PBK in noise (Fig. 7 Top/Right; the quiet data from this test are the same as in Table S3, Supplemental Digital Content 1, http://links.lww.com/EANDH/A896), which revealed an asymmetry: listening unaided, she identified as many words in noise as in quiet in the left ear, yet identified 20% fewer in the right. Note that her left ear had higher air conduction thresholds than her right ear (see Fig. 5). One month later she was tested again on the PBK, this time listening binaurally (Fig. 7 Bottom/Left and Bottom/Middle). In quiet she heard twice as many words when listening with her hearing aids, but this advantage disappeared in noise. Also shown on this panel in paler colors is her phoneme recognition score for the same listening conditions. She consistently identified more phonemes than she did words under all listening conditions. Approximately 3 months later she was tested again on the PBK, listening with hearing aids. In all conditions she identified fewer words in noise than in quiet. She also performed better listening binaurally than monaurally. And once again across all conditions she had a higher phoneme recognition score than word recognition score. On the same date, she was tested when listening with an FM system (Phonak Zoomlink; Fig. 7 Bottom/Right). Her word recognition improved when speech was presented only through the FM system with 35 dB noise in the background and improved again slightly when speech was presented through both the FM system and in sound field.

DISCUSSION

We used a multiple case study approach to examine the role of subcortical neural synchrony in the FFR and SIN recognition. Consistent with previous reports, three children with auditory neuropathy, despite very different clinical presentations,

had absent FFRs. In contrast, age-matched controls with normal hearing and ABRs had reliable FFRs. The children with auditory neuropathy also had variable speech recognition performance with marked difficulties in noise, also consistent with previous reports (Kraus et al. 2000; Rance 2005; Zeng & Liu 2006; White-Schwoch et al. 2020).

In aggregate, we have failed to elicit FFRs in multiple patients with auditory neuropathy, including (1) hereditary and acquired cases; (2) stable and progressive cases; (3) males and females; (4) repeatedly in the same case; (5) with multiple stimuli at multiple rates and listening conditions; (6) cases with and without elevated hearing thresholds; (7) cases whose access to sound has been augmented by a prosthetic; and (8) despite robust cortical responses to the same stimuli. Together, and in the context of previous reports, these results support the hypothesis that subcortical synchrony is necessary to generate an FFR. We have also shown that several of the same patients exhibit substantial difficulties recognizing SIN, reinforcing the importance of subcortical synchrony for SIN recognition and the connection between the FFR and SIN.

Subcortical Synchrony is Subject to Multiple Sources of Disruption that Consistently Result in an Absent FFR

Multiple etiologies cause the neuropathy phenotype, including presynaptic and postsynaptic insults and acquired and hereditary pathophysiologies (Moser & Starr 2016). Animal models show discrepant phenotypes based on the underlying mechanisms of disruption (Khimich et al. 2005; Roux et al. 2006; Chambers et al. 2016). What is consistent among etiologies is a lack of subcortical synchrony that manifests as an absent ABR.

Here, we show an absent FFR is another consistent aspect of the neuropathy phenotype. In concert with our previous work (White-Schwoch et al. 2019; White-Schwoch et al. 2021), we have shown absent FFRs in four patients with different etiologies of neuropathy and different clinical presentations. Taken together, our work indicates that subcortical synchrony is necessary to generate FFRs, at least when recorded electrophysiologically. Our evidence from listeners with neuropathy is reinforced by lesion studies (Sohmer et al. 1977; Kiren et al. 1994), comparative neurophysiological studies (White-Schwoch et al. 2017), and MEG and EEG source modeling (Zhao & Kuhl 2018; Bidelman 2018).

Our working hypothesis is that subcortical synchrony governs phaselocked potentials later in the auditory neuraxis. This hypothesis motivates a strong prediction: neuropathy patients do *not* exhibit a cortical FFR if recorded using MEG or intracranial electrodes. It is important to note that this dyssynchrony does not vitiate CAEPs, which operate one to orders of magnitude slower than FFRs. Our view may seem in tension with evidence that FFRs can ostensibly be recorded from auditory cortex. Such signals have been reported in healthy listeners using MEG (Coffey et al. 2016), scalp EEG (Mai & Howell 2020), and intracranial EEG (Guo et al. 2021). Our results predict these signals would be absent in listeners with neuropathy.

Subcortical Synchrony is Critical When Listening in Noise

The two older children, N.E. and K.B. completed SIN testing. Although they had excellent speech perception in quiet, both exhibited substantial difficulties in noise. This is consistent with previous studies documenting SIN difficulties in neuropathy patients (Kraus et al. 2000; Zeng & Liu 2006; Rance et al. 2007; White-Schwoch et al. 2020).

We also had the opportunity to explore factors that might boost SIN abilities. Clinical testing on K.B.'s word and phoneme recognition showed that she tended to benefit from listening with two ears, consistent with previous reports on neuropathy patients (Rance et al. 2012; White-Schwoch et al. 2020). She performed best when listening with an FM system with room acoustic cues available. However, she exhibited equivocal benefits from amplification.

We were able to conduct the most extensive SIN testing on N.E., which revealed several factors that affected his performance. First, N.E. benefited from clear speech, particularly at challenging SNRs. His benefit from clear speech was smaller however, than that estimated in adult CI users (Liu et al. 2004). In addition, he performed more poorly overall than CI users, suggesting that listening through a CI cannot explain all of his SIN difficulties. N.E.'s clear-speech benefit was also smaller than that Zeng and Liu (2006) reported in adults with neuropathy, including those using CIs (≈20 to 30% more words vs. ≈10% more in N.E.). N.E. also exhibited a boost in intelligibility from presenting target words in a high semantic context.

It appears that, in most noisy conditions, listeners with neuropathy exhibit significant difficulties with SIN recognition. Still, their performance changes in predictable directions as factors influencing healthy listeners' performance are introduced. These include the talker's speaking style, the SNR of the target, and listening diotically. Overall, this suggests subcortical synchrony is a bottleneck to SIN recognition. A lack of synchrony squelches listeners' performance on SIN tasks, but their performance can still be improved by factors known to improve performance in healthy listeners—albeit to a smaller magnitude.

These results motivate the use of sentence-in-noise testing under a variety of listening scenarios as a component of clinical evaluations, particularly when evaluating candidacy for hearing aids or CIs in older children and adults. Very little is known about neuropathy patients' long-term outcomes, and neuropathy patients with relatively normal hearing in childhood may require additional listening interventions as they age (Berlin et al. 2010; White-Schwoch et al. 2020). Holistic SIN testing can help guide counseling and interventions. We also note other sources of adversity to speech recognition should be considered in neuropathy patients, such as accented talkers and reverberation.

Listeners With Neuropathy Respond Variably to Auditory Input

A hallmark of neuropathy is variable response to sound. This variability manifests physiologically and behaviorally. Animal models show synapses at afferent terminals fire out of phase (Roux et al. 2006), causing the dyssynchrony that ablates ABRs and FFRs (Starr et al. 2003). This dyssynchrony also appears to cause variable performance on behavioral auditory tasks. Indeed, all three listeners performed variably on speech recognition tasks, with unpredictable benefits from accommodations such as amplification or clear speech. This is consistent with several perceptual studies where neuropathy patients perform both more poorly *and* more variably than controls—even a casual glance at the figures shows the neuropathy group nearly

always has larger error bars (Zeng et al. 1999; Rance et al. 2002; Rance et al. 2004; Zeng et al. 2005; Rance et al. 2012). This variability may represent a mix of cognitive factors, such as difficulty marshalling attention for long periods of time, and direct consequences of the dyssynchrony itself.

OPA1 Plays a Critical Role in Hearing

K.B.'s neuropathy was attributed to a missense mutation in the *OPA1* gene. To the best of our knowledge, this is the second report of this mutation (Santarelli et al. 2015). Other mutations in the *OPA1* gene are associated with progressive hearing loss and abnormal ABRs (Payne et al. 2004; Amati-Bonneau et al. 2005; Li et al. 2005; Leruez et al. 2013). *OPA1* is involved in mitochondrial inner membrane structure (Delettre et al. 2000; Olichon et al. 2003) and ATP production (Amini et al. 2018). Mutations causing optic atrophy are associated with a rapid and progressive degeneration of retinal ganglion cells that typically begins in early childhood. A similar phenomenon may cause deafness, albeit with a slightly later age of onset. K.B.'s hearing loss emerged around age 5 years and her thresholds increased rapidly. Progressive degeneration of spiral ganglion cells is consistent with an absent ABR and both ABR and electrocochleographic abnormalities previously have been documented in optic atrophy patients (Huang et al. 2009; Santarelli et al. 2015).

Audiograms and OAEs Indicate Discrepant Levels of Hearing Sensitivity in Listeners With Neuropathy

In all three cases, audiograms and OAEs indicated very different levels of hearing sensitivity. The most striking discrepancy was in K.B., who had a rapidly progressing hearing loss indicated by the audiogram, yet large and stable DPOAEs. There have been several observations of larger-than-expected OAE amplitudes in neuropathy patients (Abdala et al. 2000; Berlin et al. 2010; White-Schwoch et al. 2020). A lack of synchrony may eliminate efferent inhibition, even at rest (Terreros & Delano 2015). Such a lack of inhibition is consistent with absent acoustic reflexes and also means the ears' protective mechanisms in noise would not function. This may account for the progressive loss of hearing sensitivity sometimes noted in neuropathy patients (Berlin et al. 2010; White-Schwoch et al. 2020). These discrepancies emphasize the importance of a detailed analysis of cochlear function, particularly when contemplating prostheses. More broadly, these clinical profiles reinforce that the presence of DPOAEs does not guarantee normal cochlear function (Cheatham et al. 2014), as is often assumed in models of acquired neuropathies (Kujawa & Liberman 2009).

Limitations and Future Directions

Although our work on neuropathy, SIN recognition, and the FFR has yielded a consistent picture, it has relied on case studies that may not generalize. Here, we evaluated listeners with neuropathy despite other factors that may affect hearing, including medical histories, hearing loss, and use of auditory prostheses. We think this heterogeneity is an important strength of this study, because it reflects the heterogeneity of the neuropathy population in general. Still, this potential confound should be considered in interpreting our results.

We had limited time with each patient and had to rely on the medical records they could obtain and share. Similarly, we do not always have ideal control groups for comparisons, such as hearing loss-matched children. It should be noted, however, that reliable FFRs have successfully been collected in listeners with similar levels of hearing loss as the cases presented here (Anderson et al. 2013a; Anderson et al. 2013b; Ananthakrishnan et al. 2016; Jenkins et al. 2018). As always, it will be important to replicate these findings in larger and more diverse populations. Overall, though, our results make strong predictions about FFRs and SIN performance in listeners with neuropathy and animal models thereof.

CONCLUSION

Three children with auditory neuropathy underwent extensive audiological, electrophysiological, and perceptual evaluations. Despite different etiologies and very different clinical presentations, all had absent FFRs. The two children old enough to complete extensive speech recognition testing had excellent speech perception in quiet but exhibited substantial difficulties in noise. Together, these results support the hypothesis that subcortical synchrony underlies FFR and SIN recognition. By extension, the FFR may be sensitive to milder disruptions to subcortical synchrony that impair SIN abilities in the general population.

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The authors have no conflicts of interest to disclose.

Address for correspondence: Nina Kraus, Auditory Neuroscience Laboratory (www.brainvolts.northwestern.edu), Northwestern University, 2240 Campus Dr., Evanston, IL 60201, USA. E-mail: nkraus@northwestern.edu.

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