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Authors

Zeng, Fan-Gang

Kong, Ying-Yee

Michalewski, Henry J

et al.

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Perceptual Consequences of Disrupted Auditory Nerve Activity

Fan-Gang Zeng,^{1,2,3,5} Ying-Yee Kong,^{3,5} Henry J. Michalewski,⁴ and Arnold Starr^{3,4}

¹Departments of Anatomy and Neurobiology, ²Biomedical Engineering, ³Cognitive Sciences, ⁴Neurology, and ⁵Otolaryngology–Head and Neck Surgery, University of California, Irvine, California

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Zeng, Fan-Gang, Ying-Yee Kong, Henry J. Michalewski, and Arnold Starr. Perceptual consequences of disrupted auditory nerve activity. *J Neurophysiol* 93: 3050–3063, 2005. First published December 22, 2004; doi:10.1152/jn.00985.2004. Perceptual consequences of disrupted auditory nerve activity were systematically studied in 21 subjects who had been clinically diagnosed with auditory neuropathy (AN), a recently defined disorder characterized by normal outer hair cell function but disrupted auditory nerve function. Neurological and electrophysical evidence suggests that disrupted auditory nerve activity is due to desynchronized or reduced neural activity or both. Psychophysical measures showed that the disrupted neural activity has minimal effects on intensity-related perception, such as loudness discrimination, pitch discrimination at high frequencies, and sound localization using interaural level differences. In contrast, the disrupted neural activity significantly impairs timing related perception, such as pitch discrimination at low frequencies, temporal integration, gap detection, temporal modulation detection, backward and forward masking, signal detection in noise, binaural beats, and sound localization using interaural time differences. These perceptual consequences are the opposite of what is typically observed in cochlear-impaired subjects who have impaired intensity perception but relatively normal temporal processing after taking their impaired intensity perception into account. These differences in perceptual consequences between auditory neuropathy and cochlear damage suggest the use of different neural codes in auditory perception: a suboptimal spike count code for intensity processing, a synchronized spike code for temporal processing, and a duplex code for frequency processing. We also proposed two underlying physiological models based on desynchronized and reduced discharge in the auditory nerve to successfully account for the observed neurological and behavioral data. These methods and measures cannot differentiate between these two AN models, but future studies using electric stimulation of the auditory nerve via a cochlear implant might. These results not only show the unique contribution of neural synchrony to sensory perception but also provide guidance for translational research in terms of better diagnosis and management of human communication disorders.

INTRODUCTION

Perception is a delicate chain of events including conversion of a sensory stimulus into electrical signals at the receptor level, transmission of the electrical signals via the peripheral nerve, and processing and interpretation of the electrical signal in the CNS. Any breakdown in the process could have significant consequences in perception. In audition, perceptual consequences of both peripheral and central auditory disorders have been studied extensively. For example, peripheral damage

in the inner ear and the auditory nerve leads to threshold elevation, abnormal loudness, pitch, and temporal processing (Buss et al. 1998; Formby 1986; Moore 1996; Moore and Oxenham 1998; Nienhuys and Clark 1978; Oxenham and Bacon 2003; Prosen et al. 1981; Ryan and Dallos 1975); central disorders and degeneration produce complex processing deficits in speech and sound object recognition (Cacace and McFarland 1998; Gordon-Salant and Fitzgibbons 1999; Levine et al. 1993; Wright et al. 1997); and electric stimulation of the auditory nerve via a cochlear implant in deaf persons results in fundamental changes in the brain affecting behaviors ranging from basic psychophysics to language development (Giraud et al. 2001; Simmons et al. 1965; Svirsky et al. 2000; Zeng and Shannon 1994). Examination of the above-mentioned studies shows that detailed documentation of behavioral changes coupled with a clearly defined pathology can make significant contributions in two important ways. Clinically, these studies often lead to better diagnosis and management of a particular disease. Theoretically, these studies shed light on the relative contribution of different neural codes to perception at a mechanism level.

Here we focus on perceptual consequences of a recently defined hearing disorder that preserves the outer hair cell function but apparently disrupts auditory nerve activity. This hearing disorder was first described in one single subject and considered to involve a dysfunction of the auditory nerve (Starr et al. 1991). Subsequently, 10 subjects with similar symptoms were identified. Since eight of them had accompanying peripheral neuropathy, the term “auditory neuropathy” (AN) was coined (Starr et al. 1991, 1996). The clinical diagnosis of AN has been typically characterized by the presence of otoacoustic emission and/or cochlear microphonics and the concurrent absence of the averaged auditory brain stem responses. The presence of otoacoustic emission and/or cochlear microphonics is indicative of normal cochlear outer hair cell activity, whereas the absence of the auditory brain stem responses is indicative of disrupted auditory nerve activity. Despite absent auditory brain stem responses, it is evident that sound information must have been transmitted, because individuals with AN can hear sound, have normal brain imaging, and identifiable, although usually delayed, cortical potentials (Rance et al. 2002; Starr et al. 2003; Zeng et al. 1999).

Address for reprint requests and other correspondence: F.-G. Zeng, 364 Med Surge II, Univ. of California, Irvine, CA 92697-1275 (E-mail: fzeg@uci.edu).

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The distorted auditory nerve activity has been suggested in the form of either desynchronized or reduced discharge in the auditory nerve because both could lead to absent or abnormal brain stem responses and present but delayed cortical responses (Berlin et al. 2003b; Starr et al. 1996, 2003). Desynchronized neural discharge can occur due to demyelination and ion channel dysfunction in the auditory nerve (Starr et al. 1998; Waxman 1977) and/or dysfunctional synaptic transmission between the inner hair cells and the auditory nerve (Fuchs et al. 2003; Glowatzki and Fuchs 2002). Loss of the neural input to the brain can occur due to inner hair cell loss (Harrison 1998; Salvi et al. 1999; Sawada et al. 2001) and/or auditory nerve loss (Hallpike et al. 1980; Spoendlin 1974; Starr et al. 2003). Although the term AN has been widely accepted clinically as a diagnosis, alternative terms such as “auditory dys-synchrony” have been suggested to reflect the common phenomenon that likely has several underlying pathologies (Berlin et al. 2003a; Rapin and Gravel 2003). We note that the auditory nerve loss model received strong support as a recent temporal bone study in a 77-year-old AN subject showed a 95% reduction of the ganglion cells but essentially normal number and morphology of the inner and outer hair cells except for a 30% reduction of the outer hair cells in just the apical turn (Starr et al. 2003).

The etiologies for AN are multiple, ranging from genetic, including mutations in several genes (*MPZ*, *NDRG1*, and *PMP22*) that are critical for peripheral nerve myelination and axonal survival (Chapon et al. 1999; De Jonghe et al. 1999; Kalaydjieva et al. 2000; Maier et al. 2003), to infectious (measles, mumps), metabolic (diabetes, hypoxia), congenital (atresia), and neoplastic (tumors) (Starr et al. 1996). The prevalence of AN has been estimated to be as high as 10% of the children identified as having hearing loss (Berlin et al. 2003a; Rance et al. 1999). Because AN patients typically do not derive benefits from conventional hearing aids, treatment options are limited, with only recent success being reported with cochlear implantation (Berlin et al. 1996; Buss et al. 2002; Mason et al. 2003; Miyamoto et al. 1999; Peterson et al. 2003; Shallop et al. 2001; Trautwein et al. 2000).

Limited behavioral data have been reported on the perceptual consequences of auditory neuropathy (Kraus et al. 2000; Rance et al. 2004; Starr et al. 1991; Zeng et al. 1999). Starr et al. (1991) and Kraus et al. (2000) each presented a case study in which the subject's audiological, behavioral, and electrophysiological performance was systematically documented. Kraus et al. noted in their case study that the AN subject had a nearly normal audiogram but significant difficulty in speech perception in noise. Zeng et al. (1999) found significant temporal processing impairment in eight AN subjects and were able to correlate the degrees of their temporal processing impairment with the degrees of their speech perception deficits. Rance et al. (2004) found additional frequency discrimination deficits in some of their 14 AN subjects, who also had concurrent temporal processing impairment.

This study systematically examined perceptual consequences of disrupted auditory nerve activity in 21 subjects who have been clinically diagnosed with AN. Psychophysical data will be reported in basic auditory processing of intensity, frequency, and time, as well as complex processing of nonsimultaneous masking, simultaneous masking, and binaural hearing. Temporal processing from 8 of these 21 subjects was

previously reported (Zeng et al. 1999) and will be combined into the present data. Intensity discrimination from five AN subjects, frequency discrimination from three subjects, and detection of a tone in noise from two subjects were also previously reported in non-peer-reviewed book chapters or conference proceedings (Zeng 2000, 2001a,b). Although the group difference between the AN and normal-hearing control subjects is emphasized here, interesting individual cases will be presented to highlight the perceptual consequences of disrupted auditory nerve activity.

METHODS

Subjects

A total of 21 previously diagnosed AN subjects participated in this study. Table 1 summarizes their personal and audiological information, identified only by a code name. Subjects AN1-8 were identical to those who participated in an earlier study on temporal and speech perception (Zeng et al. 1999). The subjects included 13 females and 8 males, and were from 6 to 53 yr old, with a mean age of 21 yr. Their degree of hearing loss varied from nearly normal hearing with a pure-tone average threshold (PTA at all tested frequencies from 125 to 8,000 Hz) in the 20 dB HL range to severe hearing loss, with a PTA in the 70 dB HL range. Figure 1 shows the mean audiogram from the 21 AN subjects. Clinical diagnosis of AN relied on the presence of otoacoustic emission (16 of 19 tested subjects) and/or cochlear microphonics (19 of 20 tested subjects), as well as concurrent absence or severe abnormalities of auditory brain stem responses beyond that expected for the degree of pure-tone hearing loss (all 21 subjects) and absence of middle ear reflex (all 17 tested subjects). Cortical potentials were generally present but in a distorted and/or delayed form (15 of 17 tested subjects). Brain imaging was also performed in 13 of the 21 tested subjects with high-resolution CT, PET, or MRI, showing no discernible sign of an abnormal CNS. Finally, neurological exams were conducted to identify peripheral neuropathy in 7 of the 21 tested subjects, including 5 of 7 subjects having biopsies of sural nerve confirming the presence of peripheral neuropathy.

A total of 34 normal-hearing subjects also participated in this study to serve as the control. To the extent possible, age-matched subjects or unaffected family members served as the control. Tests were usually performed on the same day for both the AN and control subjects. This strategy was particularly useful when the test involved child subjects who apparently liked the alternative test sessions during which the unaffected siblings took turns performing the test. Informed consent was obtained for adult subjects; a special child's assent form with parental consent was obtained for child subjects whose age was ≤ 17 yr. Local Institutional Review Board approval was obtained for these assent and consent forms, as well as the experimental procedures. No adverse incidents occurred during and/or after the test.

Stimuli

All stimuli were generated digitally using TDT System II equipment (Tucker-Davis Technologies, Gainesville, FL). A 16-bit D/A converter was used with a 44,100-Hz sampling rate. A 2.5-ms ramp was applied to all stimuli to avoid spectral splatter. The full digital range was used to generate a 1,000-Hz calibration tone that reached a maximal level of 100 dB SPL in Sennheiser HDA200 headphones (Wedemark, Germany), measured by a B&K Type 2260 sound level meter in a Zwislocki real-ear simulator (Brüel and Kjær Sound and Vibration Measurement, Nærum, Denmark). The corresponding voltage (132 mV) was measured daily, whereas the sound pressure level was measured periodically for equipment calibration and maintenance. The subject performed all tasks in a double-walled, sound attenuating booth (Industrial Acoustics, Bronx, NY).

TABLE 1. Subject information

Subject	Age	Gender	PTA	Speech	OAE	CM	Reflex	ABR	Cortical	Imaging	PN
AN1	50	F	28	56	Yes	Yes	No	Abnormal	DNT	DNT	Yes
AN2	53	F	43	DNT	Yes	Yes	DNT	Abnormal	Yes	DNT	Yes
AN3	19	F	66	12	Yes	DNT	No	Absent	Yes	MRI	Yes
AN4	23	F	43	0	Yes	Yes	No	Absent	No	MRI	No
AN5	17	F	64	0	No	Yes	No	Absent	Yes	CT	No
AN6	37	M	51	CNT	Yes	No	No	Absent	No	MRI	Yes
AN7	27	M	42	40	Yes	Yes	No	Abnormal	Yes	DNT	No
AN8	10	M	73	0	Yes	Yes	DNT	Abnormal	DNT	DNT	No
AN9	11	M	53	CNT	Yes	Yes	No	Absent	DNT	MRI	No
AN10	26	M	25	90	Yes	Yes	DNT	Abnormal	Yes	MRI	No
AN11	9	F	45	84	Yes	Yes	No	Absent	Yes	CT/PET	No
AN12	6	F	68	70	Yes	Yes	No	Absent	Yes	CT	No
AN13	30	F	31	60	Yes	Yes	No	Absent	Yes	DNT	Yes
AN14	13	M	58	CNT	DNT	Yes	DNT	Absent	Yes	CT	Yes
AN15	7	F	38	40	Yes	Yes	No	Absent	Yes	CT	No
AN16	18	F	29	16	Yes	Yes	No	Absent	Yes	DNT	No
AN17	18	F	51	44	Yes	Yes	No	Abnormal	Yes	CT	No
AN18	19	M	44	20	No	Yes	No	Absent	Yes	DNT	Yes
AN19	12	F	68	68	No	Yes	No	Absent	Yes	CT	No
AN20	35	F	65	0	Yes	Yes	No	Absent	Yes	CT	No
AN21	9	M	71	56	DNT	Yes	No	Absent	DNT	DNT	No
Average	21	13F	50	39	16/19	19/20	0/17	0/21	15/17	13/13	7/21

PTA, pure-tone average threshold; OAE, oto-acoustic emission; CM, cochlear microphonics; ABR, auditory brain stem responses; PN, peripheral neuropathy.

Three sets of experiments were conducted to characterize fundamental detection and discrimination abilities in AN subjects. First, intensity discrimination was measured as a function of level from near threshold to the maximal comfortable loudness for a 200-ms, 1,000-Hz tone. Second, frequency discrimination was measured as a function of frequency from 250 to 8,000 Hz in octave steps. These tones were presented at the maximal comfortable loudness and all had a 200-ms duration. Third, temporal processing measures were obtained for temporal integration, gap detection, and temporal modulation detection with a broadband (20–14,000 Hz) white noise. Temporal integration was measured as a function of duration from 5 to 500 ms. Gap detection was measured as a function of presentation level from 5 to 50 dB sensation levels (SL). A temporal gap was produced as a silent interval in the center of the noise. Temporal modulation was measured as a function of modulation frequency from 2 to 2,000 Hz with the stimuli being presented at the most comfortable loudness level. The level of the modulated signal was dynamically adjusted

according to the modulation level to achieve the same root-mean-square level as the unmodulated stimulus. To quantify the temporal modulation detection, a first-order Butterworth low-pass filter was fitted to produce peak sensitivity and 3-dB cut-off frequency measures

$$y = -10 \log \left(\frac{x_0}{1 + (f/f_c)^2} \right) \quad (1)$$

where y is modulation index (m) in dB ($-10 \log m$), f is the modulation frequency in hertz, $-10 \log(x_0)$ is the peak sensitivity or gain in dB, and f_c is the 3-dB cut-off frequency or bandwidth in hertz.

Three additional sets of experiments were conducted to measure complex processing in nonsimultaneous masking, simultaneous masking, and binaural hearing. The total number of subjects who participated in these experiments ranged from 3 to 10 because they were required to have either normal thresholds or mild hearing loss. Four AN subjects (AN4, 9, 10, and 14) participated in the backward and forward masking experiment. Backward masking refers to a condition where the detection of a signal is affected by a masker occurring after the signal, whereas forward masking refers to a condition where the detection of a signal is affected by a masker occurring before the signal. The masker was a 100-ms, 1,000-Hz tone, whereas the signal was a 9-ms, 1,000-Hz tone. Signal delay, defined as the offset of the signal and the onset of the masker in backward masking and the reverse in forward masking, was varied from 1 to 500 ms. To account for the individual difference in absolute threshold, the masked threshold was normalized by the following equation

$$\text{Normalized threshold} = 100 \times (TH - TH_Q) / (TH_{1ms} - TH_Q) \quad (2)$$

where TH is the threshold in dB SPL at any delay, TH_{1ms} is the threshold at the 1-ms delay, and TH_Q is the threshold in quiet.

Ten AN subjects participated in the simultaneous masking experiment (AN2, 7, 10, 11, 12, 13, 15, 16, 18, and 19). The noise masker was white noise that had a 20- to 14,000-Hz bandwidth and a 500-ms duration. The signal was either a 200-ms tone that was temporally centered on the noise or a 9-ms tone that was presented with either a 3- or 300-ms delay from the onset of the noise. Signal frequency varied from 250, 500, 1,000, 2,000, to 4,000 Hz depending on the subject's threshold (<30 dB HL). Detection of a long tone in noise has been traditionally used to measure spectral resolution (Fletcher 1938) and pathology related to "dead regions" in the cochlea (Moore

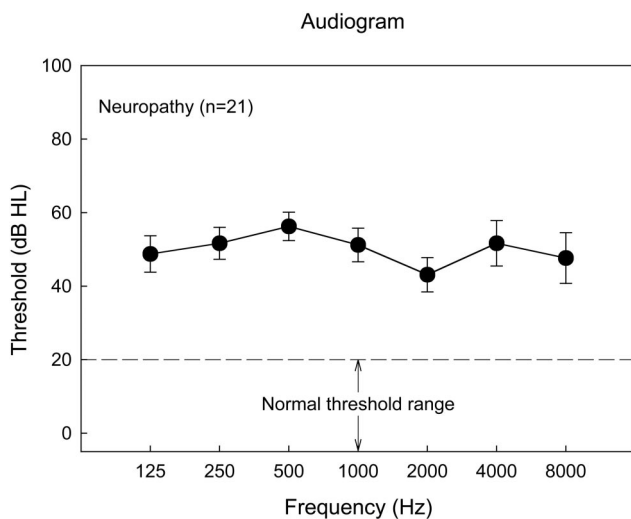


FIG. 1. Pure-tone detection threshold as a function of frequency (audiogram) from 21 auditory neuropathy (AN) subjects. ●, mean values; error bars, \pm SE. Threshold values <20 dB HL (dashed line) are considered normal hearing.

2004). On the other hand, threshold difference detection of a brief tone in noise between onset and steady-state conditions has been termed "overshoot" and used to measure pathology related to outer hair cell and olivocochlear bundle functions (Bacon and Takahashi 1992; Carlyon and Sloan 1987; McFadden and Champlin 1990; Zeng et al. 2000).

Three AN subjects (AN10, 17, and 18) with mild-to-moderate hearing loss participated in the following binaural hearing tests, including sound localization using the interaural level time difference (ILD) and interaural time difference (ITD) cues, as well as monaural and binaural beats. In the ILD experiment, 500-ms pure tones were presented with either 0-dB ILD (90 dB SPL at both left and right ears) or 10-dB ILD (95 dB SPL at left and 85 dB SPL at right ear). The tone frequency varied from 250 to 8,000 Hz in octave steps. In the ITD experiment, a pair of 500-ms, 500-Hz tones was presented to two ears with ITD varying 0, 30, 60, and 90° in phase, corresponding to 0-, 167-, 333-, and 500- μ s lead time in the right ear. Monaural and binaural beats were measured by presenting two 1,000-ms tones with a 3-Hz difference to either the same ear (monaural beats) or the first tone to one ear and the second tone to the other ear (binaural beats). In the monaural beat experiment, the frequency was 500, 1,000, 2,000, 4,000, or 8,000 Hz for the first tone and 3 Hz higher, respectively, for the second tone. In the binaural beat experiment, the frequency was 500 Hz for the first tone and 503 Hz for the second tone.

Psychophysical procedure

An adaptive, three-interval, three-alternative, forced-choice, two-down and one-up procedure was employed to track the 70.7% percent correct response criterion (Levitt 1971). This procedure was used in all objective measures, including temporal integration, intensity, and frequency discrimination, backward and forward masking, simultaneous masking, and monaural beat detection. During each trial, the subject heard three sounds that were visually marked by three intervals on a computer screen. One of the three intervals contained the signal, whereas the other two contained the standard. The order of the signal and standard sounds was randomized (3-alternative). The subject had to choose the signal (forced-choice) and was given a visual feedback regarding the correct response. The initial difference between the signal and the standard was large so it was easy for the subject to tell which interval contained the signal. The difference was reduced after two consecutive correct responses and increased after one incorrect response (2-down, 1-up). A reversal was recorded when the subject made an incorrect response from two or more consecutive correct responses or vice versa. A large step size was used for the first three or four reversals, and a small step size was used for the remaining reversals (adaptive step size). Each run had a total of 12 reversals. The reported data were averaged from the last eight reversals.

An additional seven-alternative, forced-choice procedure was employed for sound localization measurement. The seven alternatives are represented by integers from -3 to 3, corresponding to the leftmost and the rightmost position (with the center position being represented by 0). The seven numbers were labeled with seven boxes that were geometrically arranged to form a semicircle on a computer screen. The subject had to choose a number corresponding to his or her perceived sound position. If the sounds from two ears could not be fused, two separate images might be perceived. In this case, the subject was instructed to report the separate images without having to choose any alternative. However, this situation was not encountered in this study.

Finally, a subjective report and counting procedure was employed to measure the presence of monaural and binaural beats. The subject was instructed to pay attention to loudness fluctuation and report the number of beats heard. In the monaural beat experiment, the modulation threshold was measured using the same three-interval, two-up and one-down, adaptive procedure as described above.

Statistical analysis

A between-subjects ANOVA with uneven sample sizes was used to test whether there was a significant difference in performance between the AN and normal-hearing subjects. Should the overall difference reach the significance level ($P < 0.05$), posthoc tests were usually conducted to examine the conditions under which the difference was significant. ANOVA was conducted with SPSS for Windows (version 11.0 2002, SPSS, Chicago, IL).

RESULTS

Intensity discrimination

Figure 2 shows intensity discrimination as a function of sensation level (dB above the individual subject's threshold) in eight AN subjects (●) and eight normal controls (▽). Both groups showed the typical pattern that had been termed as "the near-miss to Weber's law," in which the difference limen decreased slightly as a function of the stimulus level (McGill and Goldberg 1968). Although the AN subjects showed slightly larger difference limens at low levels than the normal controls, no significant main effect was observed between groups [$F(1,69) = 3.17$; $P > 0.05$]. This result indicates that AN subjects encounter no significant difficulty in performing pure-tone intensity discrimination.

Frequency discrimination

Figure 3 shows frequency discrimination as a function of standard frequency in 12 AN subjects (●) and 4 normal controls (▽). A significant difference in performance was observed between the AN subjects and the normal controls [$F(1,86) = 5.53$; $P < 0.05$]. The normal controls required < 10 Hz to discriminate a pitch difference for frequencies $\leq 1,000$ Hz, but the AN subjects required a difference that was about two orders of magnitude higher than the normal difference limen. Interestingly, the difference between the two groups reduced with frequency and was not significant at 8,000 Hz ($P > 0.10$). This result suggests that AN subjects have pro-

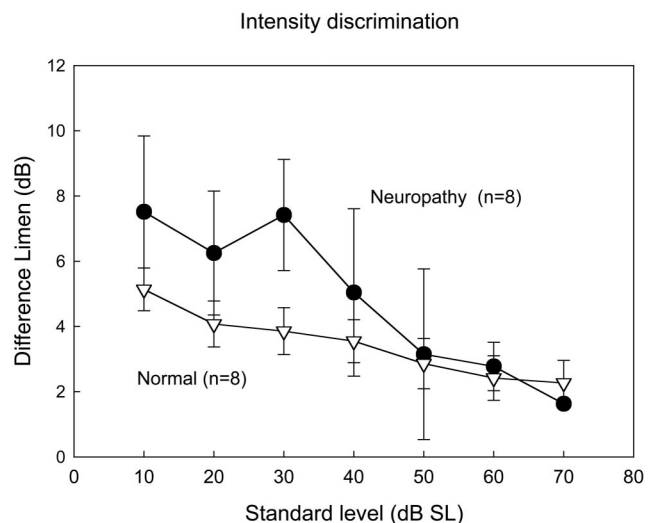


FIG. 2. Intensity discrimination in 8 AN (●) and 8 normal-hearing (▽) subjects. Difference limen of a 1,000-Hz pure tone (dB) is plotted as a function of standard level (dB SPL). Error bars, \pm SE.

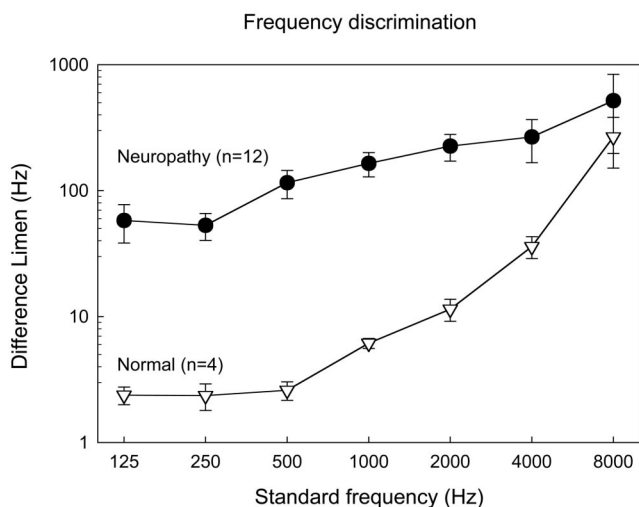


FIG. 3. Frequency discrimination in 12 AN (●) and 4 normal-hearing (▽) subjects. Difference limen (Hz) is plotted as a function of standard frequency (Hz). Error bars, \pm SE.

found impairment in pitch discrimination at low frequencies (<4,000 Hz) but not at high frequencies (>4,000 Hz).

Temporal processing

Figure 4 shows temporal integration as a function of duration in 16 AN subjects (●) and 4 normal controls (▽). Both AN and normal-hearing subjects showed a 100- to 200-ms course of temporal integration, but the slope of the temporal integration function was slightly elevated in the AN subjects (-3.9 dB per doubling duration) compared with the normal-hearing subjects (-3.0 dB per doubling duration). A between-subjects ANOVA revealed a significant group effect between the AN and normal-hearing subjects [$F(1,99) = 5.81$; $P = 0.05$], but a posthoc *t*-test revealed a significant difference only for the 5- and 10-ms sounds ($P < 0.05$). This result indicates that AN subjects have difficulty detecting short sounds but not long sounds.

Figure 5 shows gap detection as a function of sensation level in 20 AN subjects (●) and 7 normal controls (▽). There was a

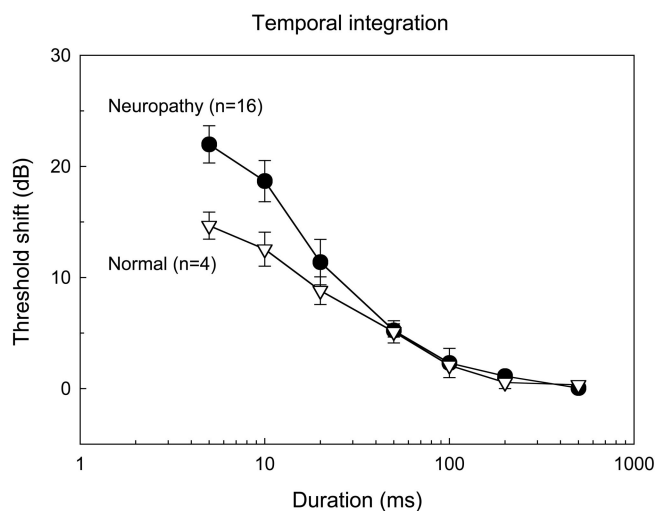


FIG. 4. Temporal integration in 16 AN (●) and 4 normal-hearing (▽) subjects. Threshold shift (dB re: threshold with a 500-ms noise) is plotted as a function of stimulus duration (ms). Error bars, \pm SE.

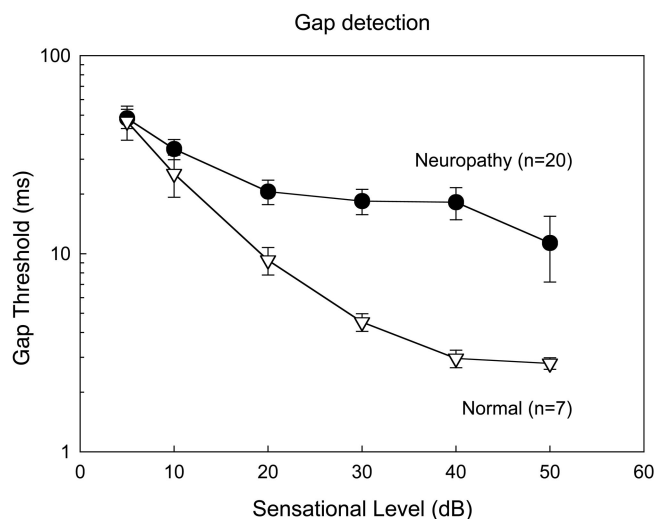


FIG. 5. Gap detection in 20 AN (●) and 7 normal-hearing (▽) subjects. Gap threshold (ms) is plotted as a function of stimulus level (dB SL). Error bars, \pm SE.

significant group effect between the AN and the control subjects [$F(1,107) = 14.88$; $P < 0.001$]. The normal controls required about a 50-ms silent interval to detect a gap at 5-dB low sensation (very soft sound) but improved to 3 ms at high sensation levels (40 and 50 dB). The AN subjects performed similarly to the normal controls at low sensation levels (5 and 10 dB) but required significantly longer gaps (15–20 ms) than the normal-hearing subjects at higher sensation levels (postdoc *t*-test, $P < 0.05$). This result suggests that the AN subjects have difficulty in gap detection even at comfortable loudness levels.

Figure 6 shows modulation detection as a function of modulation frequency in 16 AN subjects (●) and 4 normal controls (▽). There was a significant difference between the two groups [$F(1,70) = 111.10$; $P < 0.001$] but no significant interactions between groups and modulation frequency. The normal controls showed a typical low-pass pattern, with peak sensitivity of -19.9 dB (10% modulation) and 3-dB cut-off frequency of 258.1 Hz ($r = 0.96$). The AN subjects showed a lower peak

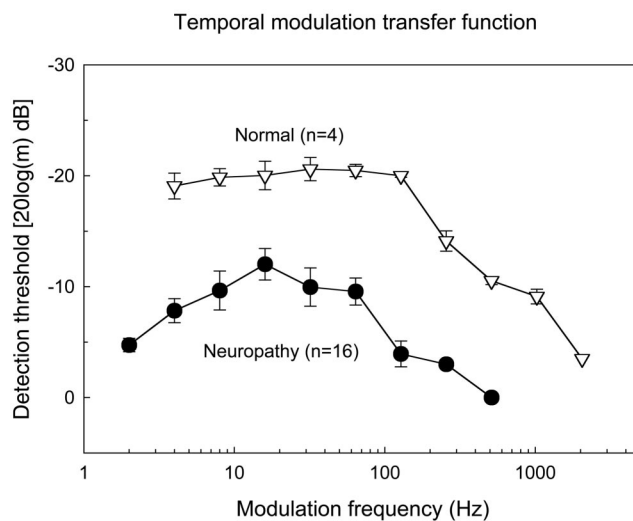


FIG. 6. Temporal modulation transfer function in 16 AN (●) and 4 normal-hearing (▽) subjects. Detection threshold (dB re: 100% modulation) is plotted as a function of modulation frequency (Hz). Error bars, \pm SE.

sensitivity of -8.7 dB (37% modulation) and a lower cut-off frequency of 17.0 Hz ($r = 0.81$). The relatively poor fit in AN subjects was due to the band-pass characteristic in the data. This result suggests that AN subjects have difficulty in detecting both slow and fast temporal modulations.

Backward and forward masking

Figure 7 shows backward (*left*) and forward (*right*) masking as a function of signal delay in four AN subjects (●) and four normal controls (▽). Both masking conditions produced a significant group effect between the AN and normal-hearing subjects [$F(1,33) = 52.39$; $P < 0.001$ for backward masking and $F(1,36) = 10.43$; $P < 0.05$ for forward masking]. In backward masking, the normal controls showed $\leq 15\%$ masking when the masker and the signal was separated by 20 ms or longer, whereas the AN subjects still showed 60% masking even at 100-ms signal delay. In forward masking, both the normal and AN subjects showed a 100- to 200-ms recovery time, with the AN subjects having significantly more masking than the normal controls between 5- and 50-ms delays. Note also the clear asymmetrical pattern between backward and forward masking in the normal controls and the relatively symmetrical masking patterns in the AN subjects. This result suggests that AN subjects cannot effectively separate sounds occurring successively.

Simultaneous masking: long tones

Figure 8 shows detection of a 200-ms, 1,000-Hz pure-tone signal in noise as a function of noise level in seven AN subjects (●) and five normal controls (▽). The dotted line represents the predicted detection threshold using the equivalent rectangular bandwidth (ERB) of the presumed auditory filter at 1,000 Hz (Moore and Glasberg 1987). The normal controls showed essentially the same amount of masking as predicted by the ERB model, whereas the AN subjects showed significant excessive masking of about 20 dB [$F(1,38) = 71.10$; $P < 0.001$]. This result shows that AN subjects have difficulty in detecting signals in noise.

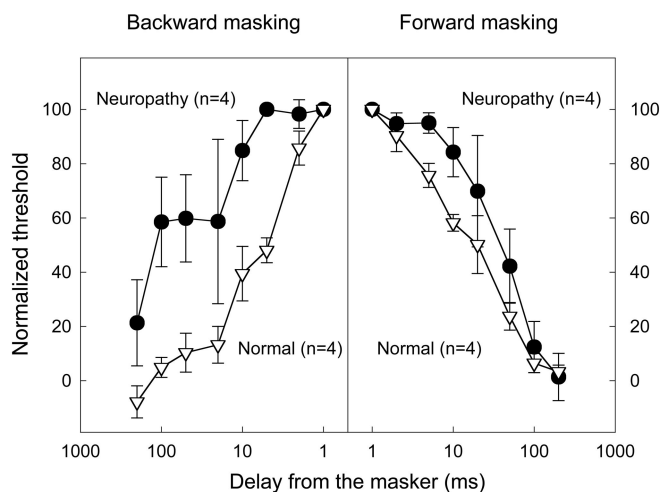


FIG. 7. Backward masking (*left*) and forward masking (*right*) in 4 AN (●) and 4 normal-hearing (▽) subjects. Normalized threshold (see Eq. 2) is plotted as a function of signal delay from the masker (ms). Error bars, \pm SE.

Simultaneous masking of long-duration tones

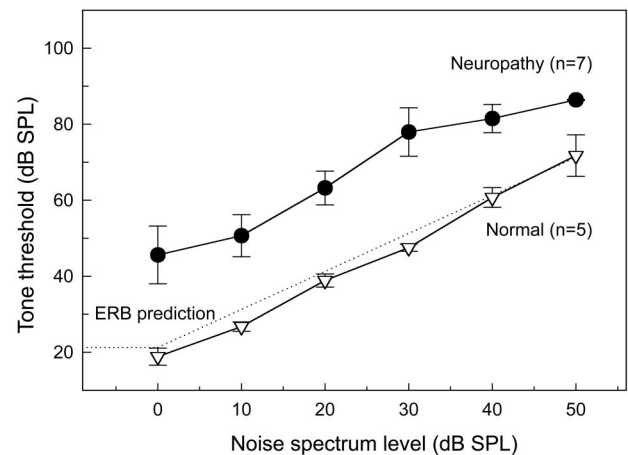


FIG. 8. Simultaneous masking of long-duration tones in noise in 7 AN (●) and 5 normal-hearing (▽) subjects. Detection threshold (dB SPL) is plotted as a function of noise spectrum level (dB SPL). Error bars, \pm SE. Dotted line represents prediction of normal detection threshold based on equivalent rectangular bands (ERBs).

Figure 9 presents six individual cases to show both unique and common features in simultaneous masking by AN subjects. First, excessive masking was also observed at frequencies other than 1,000 Hz, including 250 Hz (AN10), 2 kHz (AN12 and AN14), and 4 kHz (AN7, AN10, and AN16). Second, excessive masking was observed independently of the threshold at the test frequency, which could be normal (AN7 and AN10 at 4 kHz) or elevated (all the remaining conditions). Third, the slope of the masking function varied between subjects, including 1) a relatively normal slope, namely, a 1-dB increase in noise level produced a 1-dB increase in the signal detection threshold (AN7 at 4 kHz, AN10 at 4 kHz, AN14, and AN16), 2) an abnormally steeper slope, in which a 1-dB increase in noise level produced a 2-dB increase in signal detection threshold (AN12 and AN13), and 3) an abnormally shallower slope, in which a 2- or 3-dB increase in noise level produced a 1-dB increase in signal detection threshold (AN7 at 1 kHz and AN10 at 250 Hz). Fourth, excessive masking could be produced by extremely low-level noise (AN10 at 4 kHz with -20 dB noise level, AN12 with 10 dB noise level, and AN16 with -20 dB noise level). Finally, excessive masking may be observed in both adult and children subjects. At the time of testing, AN12 was 7 yr old, with her 10-yr-old sister serving as a control; AN14 was 13 yr old, with his 14-yr-old brother serving as a control; and AN16 was 17 yr old, with her 14-yr-old sister serving as a control.

Simultaneous masking: short tones

Figure 10 presents individual cases to examine the masking effect on short-duration signals from six AN subjects who had ≥ 30 dB HL hearing at tested frequencies and five normal controls who were either age-matched (AN10) or unaffected family members of the tested AN subject. First, recall that the AN subjects required 6- to 9-dB higher levels than the normal control to detect short signals in quiet (Fig. 4). This difficulty of detecting short-duration signals was clearly increased in noise, requiring an average 22.6 ± 9.2 (SD) dB higher signal

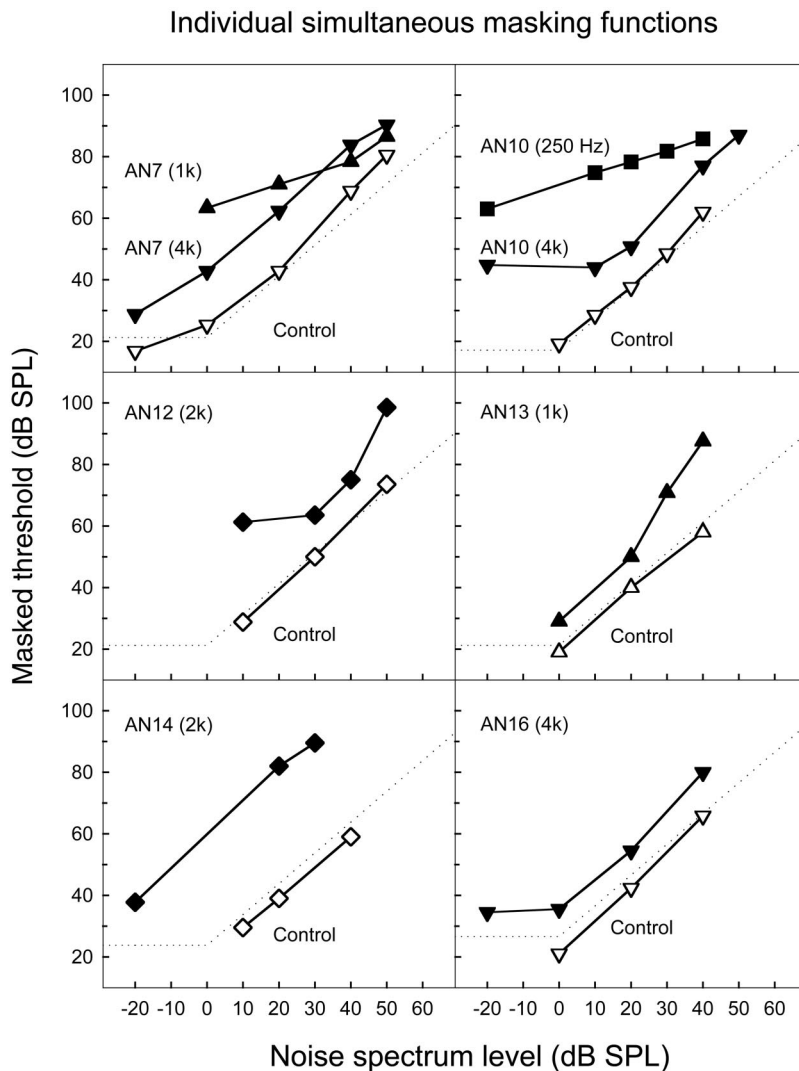


FIG. 9. Simultaneous masking of long-duration tones in noise in 6 individual AN subjects (filled symbols) and their corresponding normal-hearing controls (open symbols). Squares represent tones at 250 Hz, triangles at 1,000 Hz, diamonds at 2,000 Hz, and inverted triangles at 4,000 Hz. Dotted line represents prediction of normal detection threshold based on ERBs.

level than the normal control to detect the signal in noise. The average difference was 21.4 dB for the 3-ms delay condition and 23.5 dB for the 300-ms delay condition, with no significant difference between the conditions (t -test, $P = 0.58$).

Second, note the apparent overshoot effect, the greater threshold at 3-ms delay than 300-ms delay in the four normal controls (AN7, AN10, AN13, and AN16), particularly at intermediate noise levels between 10 and 30 dB SPL. The overshoot effect was also present in the six AN subjects, with the largest effect of 25.3 dB for AN13 at 10-dB noise level and the smallest effect of 2.0 dB for AN18. Taking all noise levels into account, the AN and control groups have an average overshoot effect of 3.2 ± 6.8 and 5.6 ± 6.5 dB, respectively. Taking only the noise level at which the largest overshoot was observed into account, the AN and control groups have an average overshoot effect of 11.0 ± 8.5 and 12.6 ± 6.7 dB, respectively. There were no group differences ($P > 0.30$) for the overshoot effect (averaged or maximal measures). These results suggest that AN subjects generally have significant difficulty in detection of brief signals in noise in general, but they do not seem to have any additional difficulty in detecting a signal at the onset of the noise than in the steady state of the noise.

Binaural processing: interaural level difference

Figure 11 shows sound localization using interaural level differences (ILD) as a function of signal frequency from three AN subjects (circles and squares) and three normal controls (inverted and regular triangles). Except for producing a sound image that was lateralized to the right (about 2), a 0-dB ILD produced essentially a center position (0) for both the AN and control groups [$F(1,23) = 0.74$; $P = 0.40$]. On the other hand, a -10-dB ILD produced a sound image that was essentially lateralized to the left for both AN and control groups [$F(1,23) = 1.70$; $P = 0.21$]. This result indicates that AN subjects can use the interaural level difference cue to localize sound.

Binaural processing: interaural time difference

Figure 12 shows sound localization using ITDs as a function of phase difference for a 500-Hz sinusoidal sound in three AN subjects (●) and three normal controls (▽). As the phase difference (with right ear leading) was increased, the normal control group reported a sound image from the center position (0) to the rightmost position (3), whereas the AN subjects reported no changes in the perceived sound position

Individual temporal masking functions (Overshoot)

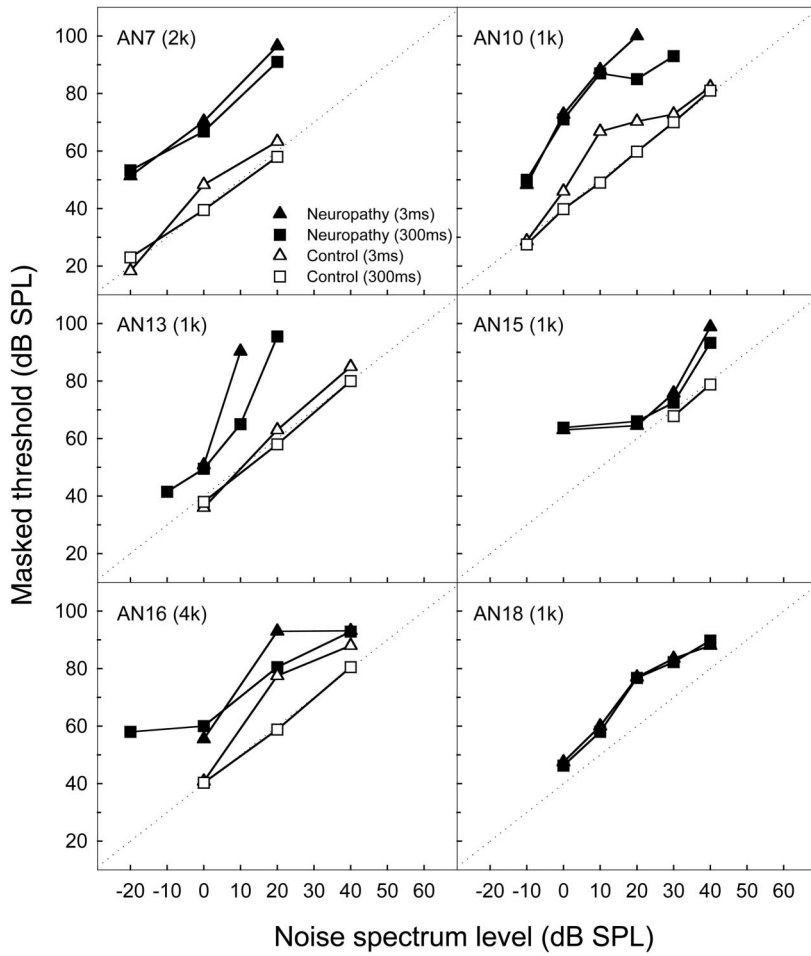


FIG. 10. Simultaneous masking of short-duration tones in noise in 6 individual AN subjects (filled symbols) and their corresponding normal-hearing controls (open symbols). Triangles represent the onset condition in which the tone is presented only 3 ms after the onset of the noise, whereas squares represent the steady-state condition in which the tone is presented about 300 ms after the onset of the noise. Difference in detection threshold between the onset and the steady-state condition is referred to as the overshoot.

Lateralization using interaural level differences

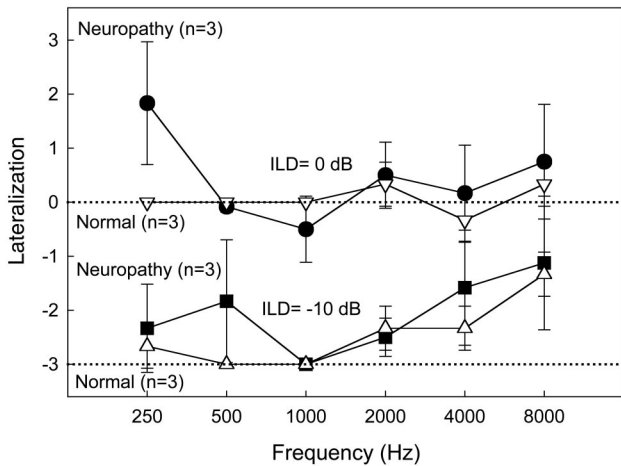


FIG. 11. Sound localization using the interaural level difference (ILD) cue in 3 AN (filled symbols) and 3 normal-hearing (open symbols) subjects. Lateralization (-3 representing the left position, 0 the center position, and 3 the right position) is plotted as a function of test frequency (Hz). The 0-dB ILD condition is represented by either circles in AN subjects or inverted triangles in normal controls. The -10-dB ILD condition is represented by either squares in AN subjects or triangles in normal controls. Error bars, \pm SE.

Lateralization using interaural time differences

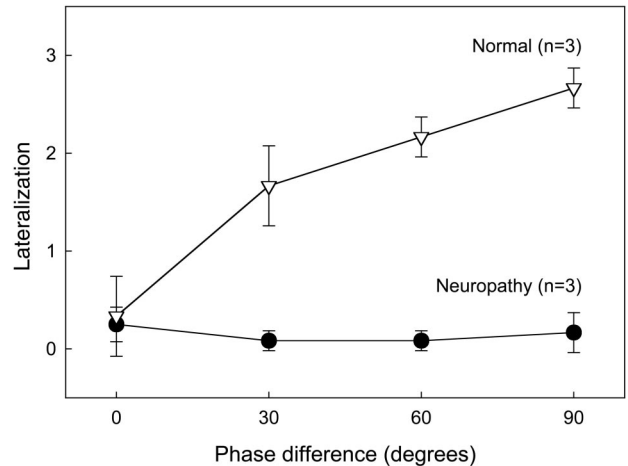


FIG. 12. Sound localization using the interaural time difference (ITD) cue in 3 AN (●) and 3 normal-hearing (▽) subjects. Lateralization (0 representing the center position and 3 the right position) is plotted as a function of interaural phase difference between a pair of 500-Hz pure tones (0, 30, 60, and 90° corresponding to 0-, 167-, 333-, and 500- μ s lead time in the right ear). Error bars, \pm SE.

[$F(1,16) = 114.8$; $P < 0.0001$]. This result indicates that AN subjects cannot use the interaural time difference cue to localize sound.

Binaural processing: beats and fusion

Both the AN and normal control subjects could perceive the monaural beats and reported the correct number of beats in the stimulus. Figure 13 shows the modulation threshold for monaural beat detection from three AN subjects (●) and three normal controls (▽). The AN subjects could detect about 10% modulation (−20 dB), whereas the normal control subjects could detect about 4% modulation (−28 dB). However, this difference was not significant [$F(1,18) = 3.0$; $P = 0.10$] due to both the relatively small sample size ($n = 3$) and the large individual variability in this task.

After performing the monaural beat experiment, verifying that the AN subjects could perceive reliably monaural beat sensation, the binaural beat experiment was performed with a 500-Hz tone being presented to the left ear and a 503-Hz tone being presented to the right ear. Both the AN and normal control reported a fused auditory image, with no beat sensation reported by the AN subjects, but a clearly audible and reliable beat sensation reported by the normal control. Because detection of monaural beats requires only spike synchrony to the 3-Hz modulation in the waveform envelope, whereas detection of binaural beats requires spike synchrony to the rapidly varying carrier frequency (500 Hz in 1 ear and 503 Hz in the other), these results suggest that AN subjects can follow slow temporal fluctuation (3 Hz) to perceive monaural beats but cannot follow fast fluctuation (500 and 503 Hz) to perceive binaural beats.

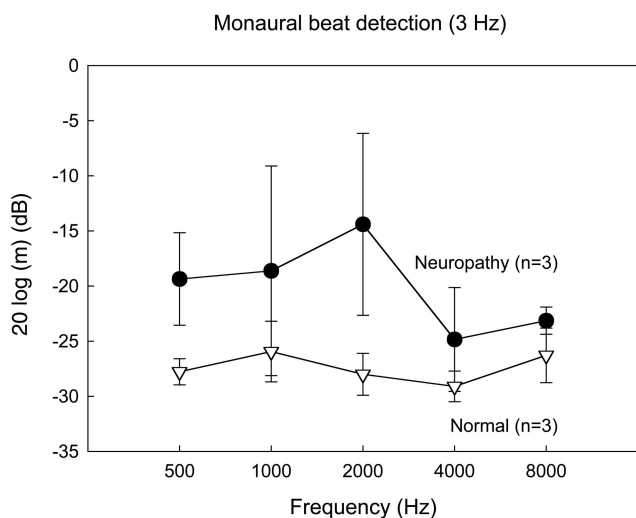


FIG. 13. Detection of 3-Hz monaural beats in 3 AN (●) and 3 normal-hearing (▽) subjects. Detection threshold (dB re: 100% modulation) is plotted as a function of standard frequency (Hz). Error bars, \pm SE.

DISCUSSION

We systematically studied perceptual consequences of disrupted auditory nerve activity in 21 subjects who had been diagnosed with AN. We found in these subjects that auditory perception related to intensity processing is relatively normal, including intensity discrimination, pitch discrimination at high frequencies (>4,000 Hz), monaural beats, and localization

using interaural level differences. On the other hand, auditory perception related to temporal processing is significantly impaired, including pitch discrimination at low frequencies (<4,000 Hz), temporal integration, gap detection, temporal modulation detection, signal detection in noise, binaural beats, and localization using interaural time differences. We will discuss differences and similarities in the perceptual consequences between AN and cochlear damage. In addition, we will discuss possible neural mechanisms underlying AN, as well as translational research potentials for better diagnosis and treatment of AN.

Comparison with other hearing disorders

The most common type of hearing disorder is of the cochlear origin, which is usually caused by noise trauma and/or ototoxic drugs, resulting in damaged inner and outer hair cells (Lieberman and Dodds 1984). Perceptual consequences of cochlear damage have been extensively studied (Moore 1996). Here we highlight the differences as well as the similarities in perceptual consequences between AN and cochlear damage.

First, cochlear damage changes intensity related perception. Cochlear damage produces steeper than normal loudness growth (loudness recruitment) and better than normal intensity discrimination at equal sensation levels (Fowler 1936; Turner et al. 1989). AN produces no significant effect on intensity discrimination, and if anything at all, slightly worsens performance at low sensation levels (Fig. 2). We also measured loudness growth function in two AN subjects and found no sign of loudness recruitment (Zeng et al. 2001a).

Second, cochlear damage impairs frequency discrimination uniformly across all frequencies but generally does not increase the difference limen by more than one order of magnitude of the normal values (Freyman and Nelson 1991). In contrast, AN impairs frequency discrimination selectively, increasing the difference limen by almost two orders of magnitude at low frequencies but producing no significant effect on the difference limen at high frequencies (Fig. 3). The only similarity is the lack of significant correlation between the value of difference limen and the amount of hearing loss at the test frequency in both AN and cochlear damage.

Third, after taking reduced audibility and nonlinear compression into account (Oxenham and Bacon 2003), cochlear damage usually does not impair temporal processing, such as temporal integration function (Florentine et al. 1988), gap detection (Florentine and Buus 1984; Nelson and Thomas 1997), temporal modulation detection (Bacon and Gleitman 1992; Moore et al. 1992), and forward and backward masking (Nelson and Freyman 1987). However, these data show significantly impaired temporal processing in AN as measured by the same tasks, including detection of short sounds (Fig. 5), gap detection (Fig. 5), temporal modulation detection (Fig. 6), and forward and backward masking (Fig. 7). We would like to reaffirm that neither audibility nor cochlear compression is likely a confounding factor, because many of the AN subjects tested here have only mild-to-moderate hearing and all of them have preserved outer hair cell functions as evidenced by the presence of otoacoustic emission and/or cochlear microphonics. We also note that the impaired temporal processing in AN is similar to that in other hearing disorders that have

confirmed neurological origins such as the presence of tumors in the auditory nerve (Formby 1986).

Although cochlear damage widens the auditory filter, it generally will not increase the detection threshold for long-duration tones in noise beyond several decibels if the damage involves only the outer hair cells (Moore et al. 1993). As a matter of fact, one would expect to only have a 3-dB increase in the threshold even if the auditory filter's bandwidth is doubled. The slope of the growth of the masking function is typically 1 in both normal-hearing and cochlear-impaired subjects, implicating that a 1-dB increase in noise level will produce a 1-dB masking effect on detection of the tone (Stelmachowicz et al. 1987). However, the average detection threshold of tones in noise is increased by 20 dB (Fig. 8) or more for short tones (Fig. 10), and the slope of the growth of masking is often >1 (Fig. 9) in AN. This excessive masking has also been observed in listeners with dead regions or inner hair cell loss but rarely in listeners with outer hair cell loss (Moore 2004). The presence of the overshoot effect in AN (Fig. 10) is also in contrast to the greatly reduced overshoot associated with cochlear damage (Bacon and Takahashi 1992), even when the damage is temporary and reversible, such as that induced by taking aspirin (McFadden and Champlin 1990).

Finally, after taking audibility and asymmetric hearing loss into account, cochlear damage typically has little or no effect on binaural tasks, such as sound localization using interaural level and timing differences (Hall et al. 1984; Hausler et al. 1983; Hawkins and Wightman 1980; Smoski and Trahiotis 1986). Similar to cochlear damage, AN subjects can use the interaural level difference to localize sound (Fig. 11). Different from cochlear damage, AN subjects cannot use the interaural timing difference at all (Fig. 12).

In summary, these findings show that perceptual consequences of disrupted auditory nerve activity are significantly different from those of hearing loss of cochlear origin. On the one hand, perception related to intensity is usually normal in AN but severely affected with cochlear damage. On the other hand, perception related to timing is significantly affected in AN but relatively normal with cochlear damage. These differences suggest that different physiological mechanisms are likely to be involved in AN and cochlear damage.

Physiological mechanisms

The term AN was coined because many of the subjects initially studied had some form of peripheral neuropathy based on neurological examination (Starr et al. 1996). Many more patients with AN have since been identified, but the underlying physiological mechanisms remain unclear and have been a major source of debate (Berlin et al. 2003a; Rapin and Gravel 2003; Starr et al. 2000). The sites of lesion include all possible combinations of the inner hair cell, the synapse between the inner hair cell and the auditory nerve, and the auditory nerve itself (Hallpike et al. 1980; Harrison 1998; Salvi et al. 1999; Sawada et al. 2001; Spondlin 1974; Starr et al. 2003, 2004). Lesion on these sites can lead to two neurophysiological manifestations, including 1) desynchronized spikes due to either demyelination in the auditory nerve (Waxman 1977) or dysfunctional synaptic transmission between the inner hair cells and the auditory nerve (Glowatzki and Fuchs 2002) and 2)

reduced spike count due to either receptor loss (Harrison 1998; Salvi et al. 1999) or axonal loss (Starr et al. 2003).

There is ample physiological evidence for the importance of synchronized auditory nerve discharge in the central auditory system. Using a novel technique (shuffled autocorrelograms), Louage et al. (2004) were able to quantify spike timing between different stimuli and across different auditory nerve fibers. They found, in cats, that auditory nerve fibers of high characteristic frequency produce highly synchronized spikes (<1 ms). Temporal dispersion in AN subjects is likely >1 ms as evidenced by the absence or significant delays (1–3 ms) of wave V in the auditory brain stem responses in AN subjects (Starr et al. 2001, 2003). The desynchronized auditory nerve activity is likely to produce abnormal response in brain stem neurons that detect coincident firing of auditory nerve fibers (Carney 1990; Carr 2004; Golding et al. 1995; Joris 1996; Joris et al. 1998; Oertel et al. 2000). These physiological mechanisms may underlie the observed perceptual changes in AN subjects.

Figure 14 uses the gap detection task as an example to show two phenomenological models of AN to account for a wide range of observed neurological and behavioral data. Figure 14A shows the normal auditory pathway with synchronized neural conduction in three auditory nerve fibers. The bottom trace represents the gap stimulus, while the "average" trace represents the central neuron's output in response to the three auditory nerve fibers' synchronized discharges (within 0.5 ms). Note that neural synchrony preserves the gap in terms of the temporal discharges relative to background spontaneous or random activity. Figure 14B shows the first AN model based on desynchronized nerve conduction in three demyelinated nerve fibers, which have differentially delayed neural representations of the gap (~ 1.5 ms) and therefore produce a smeared central representation of the gap at the output. Figure 14C shows the second AN model based on reduced nerve conduction with only one nerve fiber able to transmit the gap information. Note that both desynchronized (Fig. 14B) and reduced (Fig. 14C) nerve conditions produced an averaged discharge pattern that is difficult to distinguish from the background spontaneous activity. In most cases of AN, both desynchronized and reduced spikes may co-exist to exaggerate the perceptual consequences of neural synchrony.

Both models can explain the key signatures in evoked potentials and perceptual consequences of AN. For example, there has been a large body of neurophysiological data and models showing that intensity perception is not critically dependent on phase locking information or optimal combination of information from a large group of nerve fibers (Carlyon and Moore 1984; Prosen et al. 1981; Viemeister 1983 1988; Winter and Palmer 1991; Zeng and Turner 1991). Consistent with this finding, neither the desynchronized nor the reduced neural activity should affect intensity related perception. On the other hand, animal lesion studies and computational models have shown that frequency discrimination, particularly at low frequencies, is critically dependent on the presence of inner hair cells (Nienhuys and Clark 1978) and requires both phase locking and combinatorial information from many nerve fibers (Heinz et al. 2001a,b).

While it is apparent that desynchronized neural activity impairs temporal processing, it is less apparent how reduced

Models of AN

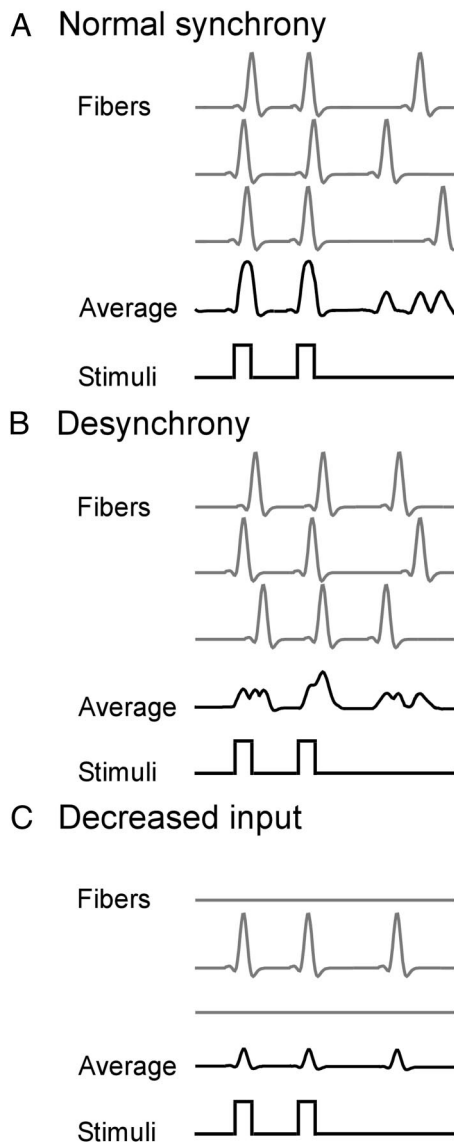


FIG. 14. Phenomenological models of AN. A: normal auditory pathway converting the “gap” stimuli (bottom trace) via 3 synchronized nerve fibers (<0.5 ms; top 3 traces) into an undistorted central representation of the gap at the output (4th trace). B: 1 AN model with desynchronized nerve conduction, in which the central representation of the gap is distorted due to different delays (~ 1.5 ms). C: another AN model with reduced nerve conduction, in which the central representation of the gap is also difficult to detect because of its similarity to the background spontaneous activity.

spike count can also impair temporal processing. Referring back to the gap detection data (Fig. 5), we note clearly that both the normal-hearing and the AN subjects performed poorly at low sensation levels, producing about a 50-ms gap detection threshold at 5 dB SL. At low levels, a sound would likely activate a small number of nerve fibers in both normal and neuropathy cases. However, as the level is increased, the sound would recruit and activate more nerve fibers in normal-hearing subjects but not in AN subjects due to the reduced number of receptors, nerve fibers, or both. Therefore the gap detection improves with level in normal-hearing subjects but not in AN subjects.

Finally, both the desynchronized spike model and the receptor/neuron loss model can explain the increased threshold for detection of tones in noise. In the desynchronized spike model, the detection threshold can be significantly increased because the more sensitive phase-locking cue is absent; the less sensitive overall rate cue has to be used (Colburn et al. 2003). In the receptor/neuron loss model, the detection threshold can be significantly increased because there is essentially a hole or dead region in the cochlea, forcing the subject to use a less sensitive “off-frequency” cue (Moore 2004).

At present, no neurophysiological or psychoacoustic tests can reliably differentiate between these two models. For example, statistical analysis found no significant differences in intensity, frequency, and temporal processing between the 7 AN subjects who had confirmed peripheral neuropathy and the remaining 14 subjects who did not. Since many of the AN subjects are expected to receive a cochlear implant, future studies using electric stimulation of the auditory nerve might help differentiate the site of lesion in AN. Should the damage be mostly restricted to the inner hair cell loss, cochlear implants would be able to effectively stimulate the residual neurons, restoring evoked brain stem potentials. Indeed, electric stimulation has been reported to restore electrically evoked brain stem potentials in several AN subjects who have received a cochlear implant (Shallop et al. 2001; Starr et al. 2004).

Translational research

In addition to its apparent theoretical implications on the relationship between neural coding and sensory perception, this study sheds light into better diagnosis and treatment options for persons with AN. An effective and efficient means of screening for AN is the gap detection task at high sensation levels. We have developed a web-based gap detection program that can be used (http://www.ucihs.uci.edu/hesp/webtest/gap-detection/ie_gap.html). We have successfully used this JAVA-based program to study a large family with inherited deafness likely affecting the inner hair cells and the peripheral process of the auditory nerve fibers (Starr et al. 2004). An enhanced off-line version of this program is available for nonprofit use by writing to the corresponding author of this study.

At present, conventional hearing aids provide no or minimal benefits to alleviate the unique difficulty associated with AN, particularly in speech recognition with noise (Berlin et al. 2003a,b). These perceptual data suggest several innovative signal processing algorithms that may lead to improved performance in AN (Zeng 2000; Zeng and Liu 2005). One idea is to eliminate low-frequency components but to preserve, or perhaps emphasize, high-frequency components in speech sounds. This idea is based on the present observation that many AN subjects have extremely poor frequency discrimination at low frequencies but nearly normal discrimination at high frequencies. The low-frequency sound could cause undesirable masking and might be better off filtered out. Another idea is to accentuate the temporal waveform modulation in speech sounds to compensate for the impaired temporal processing in AN. These features are not available in today’s hearing aid devices but may provide significant benefits to persons with AN.

Yet another treatment option is cochlear implant action. Some affected persons have already received a cochlear im-

plant or will receive an auditory brain stem implant should the brain stem implant performance justify the risk (Brackmann et al. 1993). The present data and models can potentially provide guidance to these treatment options. For example, a presurgical promontory stimulation may determine the extent to which electric stimulation may restore neural synchrony in cochlear implant candidates (Kileny et al. 1994). While the absence of electrically evoked potentials may not be a good indicator of the postsurgical performance (Nikolopoulos et al. 2000), its presence would certainly increase the likelihood of success in restoring neural synchrony via a cochlear implant in persons with AN. Another example is appropriate programming of the cochlear implant in persons with AN. Fast rate of stimulation to improve temporal encoding is a current trend in cochlear implant programming (Rubinstein et al. 1999). Should demyelination and axonal loss be a significant factor in AN, high-rate electric stimulation may produce adverse effects such as neural fatigue or even nonresponse (Stephanova and Daskalova 2004). Given this consideration, high-rate stimulation may provide less benefit than low-rate stimulation in persons with AN.

In summary, a systematic and comprehensive report is presented on perceptual consequences of disrupted auditory nerve activity in 21 persons who were clinically diagnosed with AN. The result shows that, in AN subjects, intensity-related perception is nearly normal, but temporal processing is impaired. A particularly interesting finding was that frequency discrimination is severely impaired at low frequencies but normal at high frequencies, reinforcing the duplex encoding of pitch using the phase-locking cue at low frequencies and the place cue at high frequencies. These perceptual consequences are significantly different from those caused by the more commonly observed hearing loss of cochlear damage, which has typically impaired intensity perception but relatively normal frequency and temporal processing once the impaired intensity perception is taken into account. These results strongly suggest the use of different neural codes in auditory perception: a suboptimal spike count code for intensity perception, a synchronized spike code for temporal processing, and a duplex code for frequency processing. Two AN models based on desynchronized discharge and neuronal loss are proposed to account for the presently observed perceptual consequences. Although current psychoacoustic and electrophysiological methods cannot differentiate between these two AN models, electric stimulation of the auditory nerve via a cochlear implant may allow us to differentiate between them. Nevertheless, these results suggest several translational research ideas that can potentially improve the diagnosis and treatment of AN.

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Present address of Y.-Y. Kong: MRC Cognition and Brain Sciences Unit, Cambridge, UK.

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REFERENCES

- Bacon SP and Gleitman RM.** Modulation detection in subjects with relatively flat hearing losses. *J Speech Hear Res* 35: 642–653, 1992.
- Bacon SP and Takahashi GA.** Overshoot in normal-hearing and hearing-impaired subjects. *J Acoust Soc Am* 91: 2865–2871, 1992.
- Berlin CI, Hood L, Hurley L, and Wen H.** Hearing aids: only for hearing-impaired patients with abnormal otoacoustic emissions. In: *Hair Cells and Hearing Aids*, edited by Berlin CI. San Diego, CA: Singular Press, 1996, p. 99–111.
- Berlin CI, Hood L, Morlet T, Rose K, and Brashears S.** Auditory neuropathy/dys-synchrony: diagnosis and management. *Ment Retard Dev Disabil Res Rev* 9: 225–231, 2003a.
- Berlin CI, Morlet T, and Hood LJ.** Auditory neuropathy/dyssynchrony: its diagnosis and management. *Pediatr Clin North Am* 50: 331–340, 2003b.
- Brackmann DE, Hittselberger WE, Nelson RA, Moore J, Waring MD, Portillo F, Shannon RV, and Telischi FF.** Auditory brainstem implant: I. Issues in surgical implantation. *Otolaryngol Head Neck Surg* 108: 624–633, 1993.
- Buss E, Hall JW III, Grose JH, and Hatch DR.** Perceptual consequences of peripheral hearing loss: do edge effects exist for abrupt cochlear lesions? *Hear Res* 125: 98–108, 1998.
- Buss E, Labadie RF, Brown CJ, Gross AJ, Grose JH, and Pillsbury HC.** Outcome of cochlear implantation in pediatric auditory neuropathy. *Otol Neurotol* 23: 328–332, 2002.
- Cacace AT and McFarland DJ.** Central auditory processing disorder in school-aged children: a critical review. *J Speech Lang Hear Res* 41: 355–373, 1998.
- Carlyon RP and Moore BC.** Intensity discrimination: a severe departure from Weber's law. *J Acoust Soc Am* 76: 1369–1376, 1984.
- Carlyon RP and Sloan EP.** The "overshoot" effect and sensory hearing impairment. *J Acoust Soc Am* 82: 1078–1081, 1987.
- Carney LH.** Sensitivities of cells in anteroventral cochlear nucleus of cat to spatiotemporal discharge patterns across primary afferents. *J Neurophysiol* 64: 437–456, 1990.
- Carr CE.** Timing is everything: organization of timing circuits in auditory and simulated sensory systems. *J Comp Neurol* 472: 131–133, 2004.
- Chapon F, Latour P, Diraison P, Schaeffer S, and Vandenberghe A.** Axonal phenotype of Charcot-Marie-Tooth disease associated with a mutation in the myelin protein zero gene. *J Neurol Neurosurg Psychiatry* 66: 779–782, 1999.
- Colburn HS, Carney LH, and Heinz MG.** Quantifying the information in auditory-nerve responses for level discrimination. *J Assoc Res Otolaryngol* 4: 294–311, 2003.
- De Jonghe P, Timmerman V, Ceuterick C, Nelis E, De Vriendt E, Lofgren A, Vercrussen A, Verellen C, Van Maldergem L, Martin JJ, and Van Broeckhoven C.** The Thr124Met mutation in the peripheral myelin protein zero (MPZ) gene is associated with a clinically distinct Charcot-Marie-Tooth phenotype. *Brain* 122: 281–290, 1999.
- Fletcher H.** The mechanism of hearing as revealed through experiments on the masking effect of thermal noise. *Proc Natl Acad Sci USA* 24: 265–274, 1938.
- Florentine M and Buus S.** Temporal gap detection in sensorineural and simulated hearing impairments. *J Speech Hear Res* 27: 449–455, 1984.
- Florentine M, Fastl H, and Buus S.** Temporal integration in normal hearing, cochlear impairment, and impairment simulated by masking. *J Acoust Soc Am* 84: 195–203, 1988.
- Formby C.** Modulation detection by patients with eighth-nerve tumors. *J Speech Hear Res* 29: 413–419, 1986.
- Fowler LP.** A method for early detection of otosclerosis. *Arch Otolaryngol* 24: 731–741, 1936.
- Freyman RL and Nelson DA.** Frequency discrimination as a function of signal frequency and level in normal-hearing and hearing-impaired listeners. *J Speech Hear Res* 34: 1371–1386, 1991.
- Fuchs PA, Glowatzki E, and Moser T.** The afferent synapse of cochlear hair cells. *Curr Opin Neurobiol* 13: 452–458, 2003.
- Giraud AL, Price CJ, Graham JM, Truy E, and Frackowiak RS.** Cross-modal plasticity underpins language recovery after cochlear implantation. *Neuron* 30: 657–663, 2001.
- Glowatzki E and Fuchs PA.** Transmitter release at the hair cell ribbon synapse. *Nat Neurosci* 5: 147–154, 2002.
- Golding NL, Robertson D, and Oertel D.** Recordings from slices indicate that octopus cells of the cochlear nucleus detect coincident firing of auditory nerve fibers with temporal precision. *J Neurosci* 15: 3138–3153, 1995.

- Gordon-Salant S, and Fitzgibbons PJ.** Profile of auditory temporal processing in older listeners. *J Speech Lang Hear Res* 42: 300–311, 1999.
- Hall JW, Tyler RS, and Fernandes MA.** Factors influencing the masking level difference in cochlear hearing-impaired and normal-hearing listeners. *J Speech Hear Res* 27: 145–154, 1984.
- Hallpike CS, Harriman DG, and Wells CE.** A case of afferent neuropathy and deafness. *J Laryngol Otol* 94: 945–964, 1980.
- Harrison RV.** An animal model of auditory neuropathy. *Ear Hear* 19: 355–361, 1998.
- Hausler R, Colburn S, and Marr E.** Sound localization in subjects with impaired hearing. Spatial-discrimination and interaural-discrimination tests. *Acta Otolaryngol Suppl* 400: 1–62, 1983.
- Hawkins DB and Wightman FL.** Interaural time discrimination ability of listeners with sensorineural hearing loss. *Audiology* 19: 495–507, 1980.
- Heinz MG, Colburn HS, and Carney LH.** Evaluating auditory performance limits: I. One-parameter discrimination using a computational model for the auditory nerve. *Neural Comput* 13: 2273–2316, 2001a.
- Heinz MG, Colburn HS, and Carney LH.** Evaluating auditory performance limits: II. One-parameter discrimination with random-level variation. *Neural Comput* 13: 2317–2338, 2001b.
- Joris PX.** Envelope coding in the lateral superior olive. II. Characteristic delays and comparison with responses in the medial superior olive. *J Neurophysiol* 76: 2137–2156, 1996.
- Joris PX, Smith PH, and Yin TC.** Coincidence detection in the auditory system: 50 years after Jeffress. *Neuron* 21: 1235–1238, 1998.
- Kalaydjieva L, Gresham D, Gooding R, Heather L, Baas F, de Jonge R, Blechschmidt K, Angelicheva D, Chandler D, Worsley P, Rosenthal A, King RH, and Thomas PK.** N-myc downstream-regulated gene 1 is mutated in hereditary motor and sensory neuropathy-Lom. *Am J Hum Genet* 67: 47–58, 2000.
- Kileny PR, Zwolan TA, Zimmerman-Phillips S, and Telian SA.** Electrically evoked auditory brain-stem response in pediatric patients with cochlear implants. *Arch Otolaryngol Head Neck Surg* 120: 1083–1090, 1994.
- Kraus N, Bradlow AR, Cheatham MA, Cunningham J, King CD, Koch DB, Nicol TG, McGee TJ, Stein LK, and Wright BA.** Consequences of neural asynchrony: a case of auditory neuropathy. *J Assoc Res Otolaryngol* 1: 33–45, 2000.
- Levine RA, Gardner JC, Fullerton BC, Stufflebeam SM, Carlisle EW, Furst M, Rosen BR, and Kiang NY.** Effects of multiple sclerosis brainstem lesions on sound lateralization and brainstem auditory evoked potentials. *Hear Res* 68: 73–88, 1993.
- Levitt H.** Transformed up-down methods in psychoacoustics. *J Acoust Soc Am* 49: 467–477, 1971.
- Lieberman MC and Dodds LW.** Single-neuron labeling and chronic cochlear pathology. III. Stereocilia damage and alterations of threshold tuning curves. *Hear Res* 16: 55–74, 1984.
- Louage DH, van der Heijden M, and Joris PX.** Temporal properties of responses to broadband noise in the auditory nerve. *J Neurophysiol* 91: 2051–2065, 2004.
- Maier M, Castagner F, Berger P, and Suter U.** Distinct elements of the peripheral myelin protein 22 (PMP22) promoter regulate expression in Schwann cells and sensory neurons. *Mol Cell Neurosci* 24: 803–817, 2003.
- Mason JC, De Michele A, Stevens C, Ruth RA, and Hashisaki GT.** Cochlear implantation in patients with auditory neuropathy of varied etiologies. *Laryngoscope* 113: 45–49, 2003.
- McFadden D, and Champlin CA.** Reductions in overshoot during aspirin use. *J Acoust Soc Am* 87: 2634–2642, 1990.
- McGill WJ, and Goldberg J.** A study of the near-miss involving Weber's law and pure-tone intensity discrimination. *Percept Psychophys* 4: 105–109, 1968.
- Miyamoto RT, Kirk KI, Renshaw J, and Hussain D.** Cochlear implantation in auditory neuropathy. *Laryngoscope* 109: 181–185, 1999.
- Moore BC.** Perceptual consequences of cochlear hearing loss and their implications for the design of hearing aids. *Ear Hear* 17: 133–161, 1996.
- Moore BC.** Dead regions in the cochlea: conceptual foundations, diagnosis, and clinical applications. *Ear Hear* 25: 98–116, 2004.
- Moore BC and Glasberg BR.** Formulae describing frequency selectivity as a function of frequency and level, and their use in calculating excitation patterns. *Hear Res* 28: 209–225, 1987.
- Moore BC and Oxenham AJ.** Psychoacoustic consequences of compression in the peripheral auditory system. *Psychol Rev* 105: 108–124, 1998.
- Moore BC, Shailer MJ, Hall JW III, and Schooneveldt GP.** Comodulation masking release in subjects with unilateral and bilateral hearing impairment. *J Acoust Soc Am* 93: 435–451, 1993.
- Moore BC, Shailer MJ, and Schooneveldt GP.** Temporal modulation transfer functions for band-limited noise in subjects with cochlear hearing loss. *Br J Audiol* 26: 229–237, 1992.
- Nelson DA and Freyman RL.** Temporal resolution in sensorineural hearing-impaired listeners. *J Acoust Soc Am* 81: 709–720, 1987.
- Nelson PB and Thomas SD.** Gap detection as a function of stimulus loudness for listeners with and without hearing loss. *J Speech Lang Hear Res* 40: 1387–1394, 1997.
- Nienhuys TG and Clark GM.** Frequency discrimination following the selective destruction of cochlear inner and outer hair cells. *Science* 199: 1356–1357, 1978.
- Nikolopoulos TP, Mason SM, Gibbin KP, and O'Donoghue GM.** The prognostic value of promontory electric auditory brain stem response in pediatric cochlear implantation. *Ear Hear* 21: 236–241, 2000.
- Oertel D, Bal R, Gardner SM, Smith PH, and Joris PX.** Detection of synchrony in the activity of auditory nerve fibers by octopus cells of the mammalian cochlear nucleus. *Proc Natl Acad Sci USA* 97: 11773–11779, 2000.
- Oxenham AJ and Bacon SP.** Cochlear compression: perceptual measures and implications for normal and impaired hearing. *Ear Hear* 24: 352–366, 2003.
- Peterson A, Shallop J, Driscoll C, Breneman A, Babb J, Stoessel R, and Fabry L.** Outcomes of cochlear implantation in children with auditory neuropathy. *J Am Acad Audiol* 14: 188–201, 2003.
- Prosen CA, Moody DB, Stebbins WC, and Hawkins JE Jr.** Auditory intensity discrimination after selective loss of cochlear outer hair cells. *Science* 212: 1286–1288, 1981.
- Rance G, Beer DE, Cone-Wesson B, Shepherd RK, Dowell RC, King AM, Rickards FW, and Clark GM.** Clinical findings for a group of infants and young children with auditory neuropathy. *Ear Hear* 20: 238–252, 1999.
- Rance G, Cone-Wesson B, Wunderlich J, and Dowell R.** Speech perception and cortical event related potentials in children with auditory neuropathy. *Ear Hear* 23: 239–253, 2002.
- Rance G, McKay C, and Grayden D.** Perceptual characterization of children with auditory neuropathy. *Ear Hear* 25: 34–46, 2004.
- Rapin I and Gravel J.** "Auditory neuropathy": physiologic and pathologic evidence calls for more diagnostic specificity. *Int J Pediatr Otorhinolaryngol* 67: 707–728, 2003.
- Rubinstein JT, Wilson BS, Finley CC, and Abbas PJ.** Pseudospontaneous activity: stochastic independence of auditory nerve fibers with electrical stimulation. *Hear Res* 127: 108–118, 1999.
- Ryan A and Dallos P.** Effect of absence of cochlear outer hair cells on behavioural auditory threshold. *Nature* 253: 44–46, 1975.
- Salvi RJ, Wang J, Ding D, Stecker N, and Arnold S.** Auditory deprivation of the central auditory system resulting from selective inner hair cell loss: animal model of auditory neuropathy. *Scand Audiol Suppl* 51: 1–12, 1999.
- Sawada S, Mori N, Mount RJ, and Harrison RV.** Differential vulnerability of inner and outer hair cell systems to chronic mild hypoxia and glutamate ototoxicity: insights into the cause of auditory neuropathy. *J Otolaryngol* 30: 106–114, 2001.
- Shallop JK, Peterson A, Facer GW, Fabry LB, and Driscoll CL.** Cochlear implants in five cases of auditory neuropathy: postoperative findings and progress. *Laryngoscope* 111: 555–562, 2001.
- Simmons FB, Epley JM, Lummis RC, Guttman N, Frishkopf LS, Harmon LD, and Zwicker E.** Auditory nerve: electrical stimulation in man. *Science* 148: 104–106, 1965.
- Smoski WJ and Trahiotis C.** Discrimination of interaural temporal disparities by normal-hearing listeners and listeners with high-frequency sensorineural hearing loss. *J Acoust Soc Am* 79: 1541–1547, 1986.
- Spoendlin H.** Optic cochleovestibular degenerations in hereditary ataxias. II. Temporal bone pathology in two cases of Friedreich's ataxia with vestibulo-cochlear disorders. *Brain* 97: 41–48, 1974.
- Starr A, Isaacson B, Michalewski HJ, Zeng FG, Kong YY, Beal P, Paulson GW, Keats BJ, and Lesperance MM.** A dominantly inherited progressive deafness affecting distal auditory nerve and hair cells. *J Assoc Res Otolaryng* 5: 411–426, 2004.
- Starr A, McPherson D, Patterson J, Don M, Luxford W, Shannon R, Sininger Y, Tonakawa L, and Waring M.** Absence of both auditory evoked potentials and auditory percepts dependent on timing cues. *Brain* 114: 1157–1180, 1991.
- Starr A, Michalewski HJ, Zeng FG, Fujikawa-Brooks S, Linthicum F, Kim CS, Winnier D, and Keats B.** Pathology and physiology of auditory neuropathy with a novel mutation in the MPZ gene (Tyr145->Ser). *Brain* 126: 1604–1619, 2003.

- Starr A, Picton TW, Sininger Y, Hood LJ, and Berlin CI.** Auditory neuropathy. *Brain* 119: 741–753, 1996.
- Starr A, Sininger Y, Nguyen T, Michalewski HJ, Oba S, and Abdala C.** Cochlear receptor (microphonic and summing potentials, otoacoustic emissions) and auditory pathway (auditory brain stem potentials) activity in auditory neuropathy. *Ear Hear* 22: 91–99, 2001.
- Starr A, Sininger Y, and Pratt H.** The varieties of auditory neuropathy. *J Basic Clin Physiol Pharmacol* 11: 215–230, 2000.
- Starr A, Sininger Y, Winter M, Derebery MJ, Oba S, and Michalewski HJ.** Transient deafness due to temperature-sensitive auditory neuropathy. *Ear Hear* 19: 169–179, 1998.
- Stelmachowicz PG, Lewis DE, Larson LL, and Jesteadt W.** Growth of masking as a measure of response growth in hearing-impaired listeners. *J Acoust Soc Am* 81: 1881–1887, 1987.
- Stephanova DI and Daskalova M.** Excitability properties of normal and demyelinated human motor nerve axons. *Electromyogr Clin Neurophysiol* 44: 147–152, 2004.
- Svirsky MA, Robbins AM, Kirk KI, Pisoni DB, and Miyamoto RT.** Language development in profoundly deaf children with cochlear implants. *Psychol Sci* 11: 153–158, 2000.
- Trautwein PG, Sininger YS, and Nelson R.** Cochlear implantation of auditory neuropathy. *J Am Acad Audiol* 11: 309–315, 2000.
- Turner CW, Zwislocki JJ, and Fillion PR.** Intensity discrimination determined with two paradigms in normal and hearing-impaired subjects. *J Acoust Soc Am* 86: 109–115, 1989.
- Viemeister NF.** Auditory intensity discrimination at high frequencies in the presence of noise. *Science* 221: 1206–1208, 1983.
- Viemeister NF.** Intensity coding and the dynamic range problem. *Hear Res* 34: 267–274, 1988.
- Waxman SG.** Conduction in myelinated, unmyelinated, and demyelinated fibers. *Arch Neurol* 34: 585–589, 1977.
- Winter IM and Palmer AR.** Intensity coding in low-frequency auditory-nerve fibers of the guinea pig. *J Acoust Soc Am* 90: 1958–1967, 1991.
- Wright BA, Lombardino LJ, King WM, Puranik CS, Leonard CM, and Merzenich MM.** Deficits in auditory temporal and spectral resolution in language-impaired children. *Nature* 387: 176–178, 1997.
- Zeng FG.** Auditory neuropathy: why some hearing-impaired listeners can hear but do not understand and how can DSP technology help them? IEEE Signal Processing Society, Ninth DSP (DSP 2000) Workshop, Hunt, TX, Oct. 15–18, 2000.
- Zeng FG and Liu S.** Clear speech perception in auditory neuropathy subjects. *J Speech Lang Hear Res* In press.
- Zeng FG, Martino KM, Linthicum FH, and Soli SD.** Auditory perception in vestibular neurectomy subjects. *Hear Res* 142: 102–112, 2000.
- Zeng FG, Oba S, Garde S, Sininger Y, and Starr A.** Psychoacoustics and speech perception in auditory neuropathy. In: *Auditory Neuropathy: A New Perspective on Hearing Disorders*, edited by Sininger Y and Starr A. San Diego, CA: Singular Press, 2001a, p. 141–164.
- Zeng FG, Oba S, Garde S, Sininger Y, and Starr A.** Temporal and speech processing deficits in auditory neuropathy. *Neuroreport* 10: 3429–3435, 1999.
- Zeng FG, Oba S, and Starr A.** Suprathreshold processing deficits due to desynchronous neural activities in auditory neuropathy. In: *Physiological and Psychophysical Bases of Auditory Function*, edited by Breebaart DJ, Houtma AJM, Kohlrausch A, Prijs VF, and Schoonhoven R. Maastricht, Netherlands: Shaker Publishing, 2001b, p. 365–372.
- Zeng FG and Shannon RV.** Loudness-coding mechanisms inferred from electric stimulation of the human auditory system. *Science* 264: 564–566, 1994.
- Zeng FG and Turner CW.** Binaural loudness matches in unilaterally impaired listeners. *Q J Exp Psychol A* 43: 565–583, 1991.