

Consequences of Neural Asynchrony: A Case of Auditory Neuropathy

N. KRAUS¹, A.R. BRADLOW², M.A. CHEATHAM³, J. CUNNINGHAM³, C.D. KING³, D.B. KOCH³,
T.G. NICOL³, T.J. MCGEE³, L.K. STEIN³, AND B.A. WRIGHT³

¹*Departments of Communication Sciences; Neurobiology and Physiology; Otolaryngology, Northwestern University, Evanston, IL 60208, USA*

²*Department of Linguistics, Northwestern University, Evanston, IL 60208, USA*

³*Department of Communication Sciences, Northwestern University, Evanston, IL 60208, USA*

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ABSTRACT

The neural representation of sensory events depends upon neural synchrony. Auditory neuropathy, a disorder of stimulus-timing-related neural synchrony, provides a model for studying the role of synchrony in auditory perception. This article presents electrophysiological and behavioral data from a rare case of auditory neuropathy in a woman with normal hearing thresholds, making it possible to separate audibility from neuropathy. The experimental results, which encompass a wide range of auditory perceptual abilities and neurophysiologic responses to sound, provide new information linking neural synchrony with auditory perception. Findings illustrate that optimal eighth nerve and auditory brainstem synchrony do not appear to be essential for understanding speech in quiet listening situations. However, synchrony is critical for understanding speech in the presence of noise.

Keywords: auditory neuropathy, asynchrony, auditory, perception, neural synchrony

INTRODUCTION

Auditory pathway dysfunction can provide insights into the neuroanatomical and physiological processes

that underlie normal hearing. Auditory neuropathy is a hearing disorder in which peripheral hearing appears normal, but the eighth nerve and brainstem are abnormal (Davis and Hirsh 1979; Kraus et al. 1984; Starr et al. 1991). By clinical definition, patients with this disorder have normal otoacoustic emissions (OAEs) and cochlear microphonic (CM) potentials, but exhibit an absent or severely abnormal auditory brainstem response (ABR) (Starr et al. 1996). Because a normal ABR is recorded only when multiple neurons fire synchronously at stimulus onset, patients with auditory neuropathy provide an opportunity to examine the role of synchrony in perception.

The electrophysiological tests for diagnosing auditory neuropathy can be used in very young children, allowing this disorder to be identified early in life. The functional ramifications remain unclear, with reports ranging from functional deafness to relatively intact speech perception in quiet but severely impaired perception in noise (Davis and Hirsh 1979; Worthington and Peters 1980; Lenhardt 1981; Chisin et al. 1979; Kraus et al. 1984, 1993; Starr et al. 1991, 1996, 1998; Sininger et al. 1995; Berlin et al. 1993b, 1994, 1998; Berlin and Hood 1993a; Berlin 1996; Picton et al. 1981; Picton 1986; Stein et al. 1996). Because the preponderance of the reported cases are very young children, there is a paucity of information on the capabilities of adult auditory neuropathy patients. These descriptions are needed in order to (1) understand the effects of neural synchrony on perceptual abilities and central nervous system function, and (2) provide guidelines for treatment and intervention that are based on rea-

Correspondence to: Dr. N. Kraus • Northwestern University • Frances Searle Building • 2299 N. Campus Dr. • Evanston, IL 60208. Telephone: 847 491-3165; fax: 847 491-2325; e-mail: nkraus@nwu.edu

sonable predictions of the hearing deficits that auditory neuropathy patients may experience.

An in-depth understanding of the specific perceptual deficits associated with neural asynchrony requires a comprehensive approach. One case of psychophysical abilities associated with auditory neuropathy was reported by Starr and colleagues (1991). Temporal processing deficits were evident. Gap detection was poor (threshold of 100 ms versus the normal 2 ms) and was much worse for short- than for longer-duration stimuli. Binaural signal processing was impaired as indicated by elevated thresholds for the discrimination of interaural time and intensity differences, and the absence of a binaural masking level difference with the dichotic inversion of phase. Frequency and intensity discrimination of pure tones was also impaired, with the subject requiring 3–15 times the normal frequency change and twice the normal intensity change to discriminate a difference. Despite these deficits, the subject demonstrated relatively normal discrimination of stimulus duration. Unfortunately, Starr and colleagues did not address how these impaired psychoacoustic abilities related to speech perception.

This article describes the auditory capabilities of an adult with auditory neuropathy who has normal hearing sensitivity. Because understanding the perceptual consequences of auditory neuropathy is usually complicated by elevated auditory thresholds, this young woman provides a rare opportunity to examine speech perception, as well as other auditory abilities, in the absence of peripheral hearing loss. Her performance also offers guidance into which measures may yield the most insight into the perceptual deficits or strengths that influence speech perception in natural communication settings. A combined behavioral–neurophysiological, acoustic–phonetic approach is taken to investigate the biological processes involved in the perception of speech sounds (Kraus et al. 1996, 1998, 1999; Koch et al. 1999a; Carrell et al. 1999; Bradlow et al. 1999). This experimental approach, coupled with psychophysical measures involving simple tones and noise bursts, reveals new information about the role of neural synchrony in auditory perception and the perceptual profile that may accompany a neural synchrony disorder.

This investigation is important because neural synchrony is a fundamental neurobiologic process underlying sensory, motor and cognitive events. Although internally generated synchronization of neural discharges has been linked to sensory/motor/cognitive processing and to attentional states that may be independent or loosely coupled to external stimulus events (Riehle et al. 1997; Stopfer et al. 1997; Barinaga et al. 1998; Llinas et al. 1988), it is the neural synchrony, directly elicited by external stimulation, that is considered here. Synchrony related to stimulus timing is

TABLE 1

 Test battery.

Audiometric tests
Pure-tone thresholds
Tympanometry and acoustic reflexes
Otoacoustic emissions
Brainstem-evoked audiometry
Behavioral perception in quiet
Sentence comprehension
Fine-grained speech-sound perception
Behavioral perception in degraded listening conditions
Word identification
Detection of tones in noise
Speech-elicited cortical potentials
Mismatch negativity response
P1/N1/P2 cortical responses

especially important in the auditory system (Eggermont 1990; Phillips 1993; Sinex et al. 1991), where the spectral and temporal complexity of a signal such as speech elicits responses from a broad neural population resulting in patterns of synchronized activity. Eggermont (1990, 1991, 1997) has stressed the importance of neural synchrony across populations of neurons in the signaling of differences between steady-state and dynamic stimuli. In addition, synchronized aggregate neural responses have been shown to reflect perceptually important acoustic features in speech (McGee et al. 1996; Steinschneider et al. 1994).

METHODS AND RESULTS

The skills evaluated range from the perception of speech at the sentence and word levels to the perception of elemental speech sounds and tones. Measures of perception were made in quiet and in noise. Where appropriate, findings were viewed in the context of the sound structure of the signals, and the physiological activity evoked along the auditory pathway. Because of the large number of tests performed (Table I), the methods and results of each measure were combined.

Case history

IT is a 24-year-old woman who speaks both English and Hebrew. Her medical history is largely unremarkable. A neuropsychological evaluation revealed normal intellectual and academic performance. She earned a B.A. in psychology, followed by 2 years in an Outward Bound program. She plans to study public health in graduate school. She is a bright, cooperative adult who has good insight into her condition. IT's consent to participate in this study was obtained according to the declaration of Helsinki and with the

approval of Northwestern University's Institutional Review Board.

IT's parents suspected that something was wrong with their daughter's hearing early in childhood. She was regarded as a "spaced out" child who often ignored obvious acoustic events. For example, she would not realize that the radio was playing only static. She was, however, sensitive to loud sounds, frequently requesting that the volume be lowered. Throughout her childhood, hearing tests indicated normal sensitivity, so her auditory symptoms were dismissed.

As an adult, IT reports that she is deaf in noisy environments. She describes herself as being cut off from sound by an imaginary wall. She cannot carry on a conversation in a car and has been frustrated by attempts to play an instrument or to sing, although she enjoys music. During college, she sat in the front row and had a note-taker because she could not hear the professor if she had to look down to take notes. She found it difficult to learn in large classes, and eventually transferred to a small college where class size was limited. She notices no change in hearing with fever, hot weather, or menstrual cycle. IT's father (and his mother before that) also complained of hearing problems, specifically severe difficulty hearing in noisy environments.

We previously evaluated IT when she was 18 years old (Kraus et al. 1993). That report included conventional audiometric results, electrophysiological recordings, an auditory processing test, and discrimination of selected phonemic contrasts. Magnetic resonance imaging revealed diffuse enlargement of the ventricular system but was otherwise normal. At that time, we were able to tell her that her auditory problems were not imagined and that, based on her ABR, her auditory system was not functioning normally. This information was of considerable comfort to her.

Audiogram, tympanogram, acoustic reflexes, and otoacoustic emissions

Conventional audiometry demonstrated bilaterally symmetric, normal pure-tone thresholds (15, 10, 5, and 5 dB HL at 0.5, 1, 2, and 4 kHz, respectively), normal speech-reception thresholds, and normal speech discrimination in quiet. Tympanometry revealed normal middle-ear function. Acoustic reflexes were absent, possibly contributing to her hyperacusis. Distortion product otoacoustic emissions (DPOAE) were obtained using the ILO92 system. DPOAEs were present in both ears for F2 frequencies between 1.5 to 6.0 kHz (Fig. 1, bottom). Emissions exceeded the noise floor, indicated by the shaded region, by an average of 20 dB.

Auditory brainstem response

Methods. Stimuli were clicks and 10-ms tone bursts of 1, 2, and 4 kHz (2 cycles rise/fall time), presented monaurally at 70 dB nHL at a rate of 31.1/s. Responses were recorded separately to stimuli at starting phases of 0° and 180°. Neural activity was recorded from each ear (Cz–ipsilateral earlobe, forehead ground). Each response (minimum of 4/stimulus condition) reflected an average of 2000 stimulus presentations.

Results. Responses for each ear were bilaterally symmetric. As shown in Figure 1 (top), click-evoked responses revealed an early oscillatory component that reversed phase when the stimulus was inverted. However, response latency did not shift with stimulus intensity or rate, as would be expected if the waves reflected neural responses. With tone-burst stimulation (not shown), the response showed oscillations matched to the stimulus frequency. These response properties are characteristic of hair cell, not neural potentials, and are thus thought to reflect the cochlear microphonic (CM) (Dallos 1973). In other words, the waveforms are dominated by presynaptic responses with the result that no ABR waves are identified.

The ABR of IT's father is also abnormal, although not as impaired as IT's. Despite a normal audiogram, the father's ABR thresholds were at 35 dB HL. Wave I was absent. Although wave III was observed inconsistently, when present, waves III and V displayed poor morphology and were significantly delayed (0.6–0.8 ms).

Behavioral perception in quiet

Speech perception in quiet appeared normal during informal conversation. IT scored 100% on the City University of New York sentence test (Boothroyd et al. 1985) in a quiet auditory-only condition. Perception in quiet was impaired, however, when fine-grained discrimination of synthetic speech stimuli, differing along a single acoustic-phonetic dimension, was assessed.

Fine-grained speech-sound discrimination. *Methods:* A Parameter Estimation by Sequential Tracking (PEST) paradigm (Taylor and Creelman 1967) was used to evaluate just noticeable differences (JNDs) for three synthesized consonant–vowel continua—/ba/ to /wa/, /da/ to /ga/, and /da/ to /ga/—with amplitude enhancement of the formant transitions [see Kraus et al. (1999) and Carrell et al. (1999) for detailed descriptions of stimuli, experimental procedures and normative data]. These continua were created using the Klatt synthesizer (Klatt 1980) and represent changes in either formant transition duration (/ba/ to /wa/) or differences in the third-formant onset frequency (/da/ to /ga/). A four-interval forced-choice procedure was used to prevent response bias.

Response at 1.5 msec is cochlear microphonic.

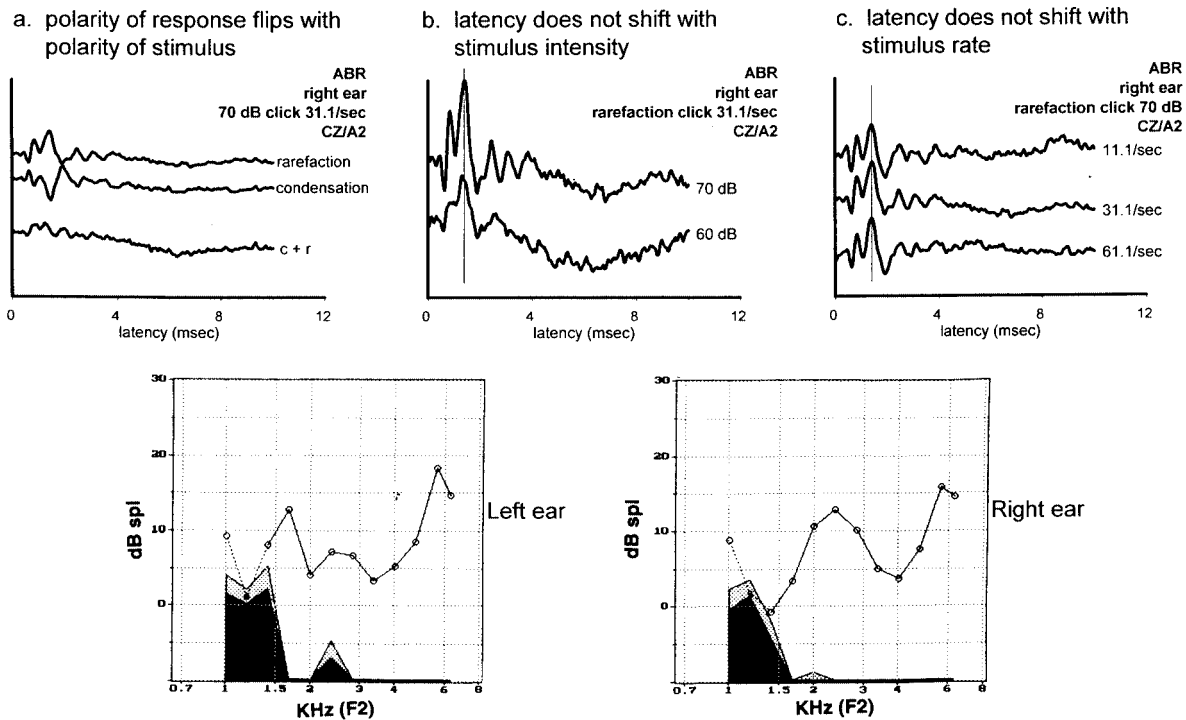


FIG. 1. (Top) The three panels illustrate the absence of ABR waves. The waveforms show only the cochlear microphonic because the polarity of response flips with the polarity of the stimulus (a), latency does not shift with stimulus intensity (b), and latency does not shift with stimulus rate (c). (Bottom) Although only right ear responses are shown, responses were bilaterally symmetric. OAE responses are present in each ear.

In each trial, IT was presented binaurally with two pairs of syllables where one pair was the same and one pair was different. The task was to indicate whether members of the first or the second pair of syllables were different. The order of same and different pairs within trials was randomized. A block ended when IT reached an accuracy level of 69% correct. Three trial blocks were obtained for each stimulus condition.

Results: For the /ba-wa/ continuum, IT had a remarkably good JND compared with normal adult listeners (Fig. 2). On average, normal adults discriminated stimuli in which the formant transition durations differed by at least 6 ms. IT was able to discriminate stimuli in which the formant transition durations differ by just 3 ms. In contrast, her JND for the /da-ga/ continuum was worse than that of normal adult listeners. Whereas normal adults discriminated stimuli in which the third formant onset frequencies differed by approximately 80 Hz, IT required a difference of almost 120 Hz. Moreover, when the /da-ga/ formant transition was enhanced in amplitude relative to the vowel, IT showed even greater difficulty discriminating along this continuum. In contrast, normal listeners had even better JNDs in the enhanced condition. Overall, the data suggest that IT is well able to discriminate synthetic speech stimuli that differ in the temporal domain (duration), but has difficulty

discriminating stimuli that differ spectrally at stimulus onset and are characterized by rapid spectro-temporal changes throughout the formant transition. This pattern of results is similar to the pattern observed in some children with learning problems (see **Discussion**).

Behavioral perception in degraded listening conditions

Fine-grained speech-sound perception in noise. Methods and Results: Discrimination along another synthesized /da-ga/ continuum (stimuli were identical to /da-ga/ described above but contained onset burst frication during the first 10 ms at formants 3, 4, and 5) was tested in continuous Gaussian white noise (SNR +10 dB). IT was unable to discriminate these stimuli at all. Mean JNDs from 10 normal subjects are 140 Hz, SDs 6.

Word identification. Methods: Monosyllabic word recognition was assessed binaurally across signal-to-noise ratios (SNR), across word lists spoken by either a single talker or multiple talkers, and across words that differ in inherent recognition difficulty. By manipulating these three factors—SNR, lexical difficulty, and single vs. multiple talkers—it is possible to investigate the effects on speech perception of multiple sources of

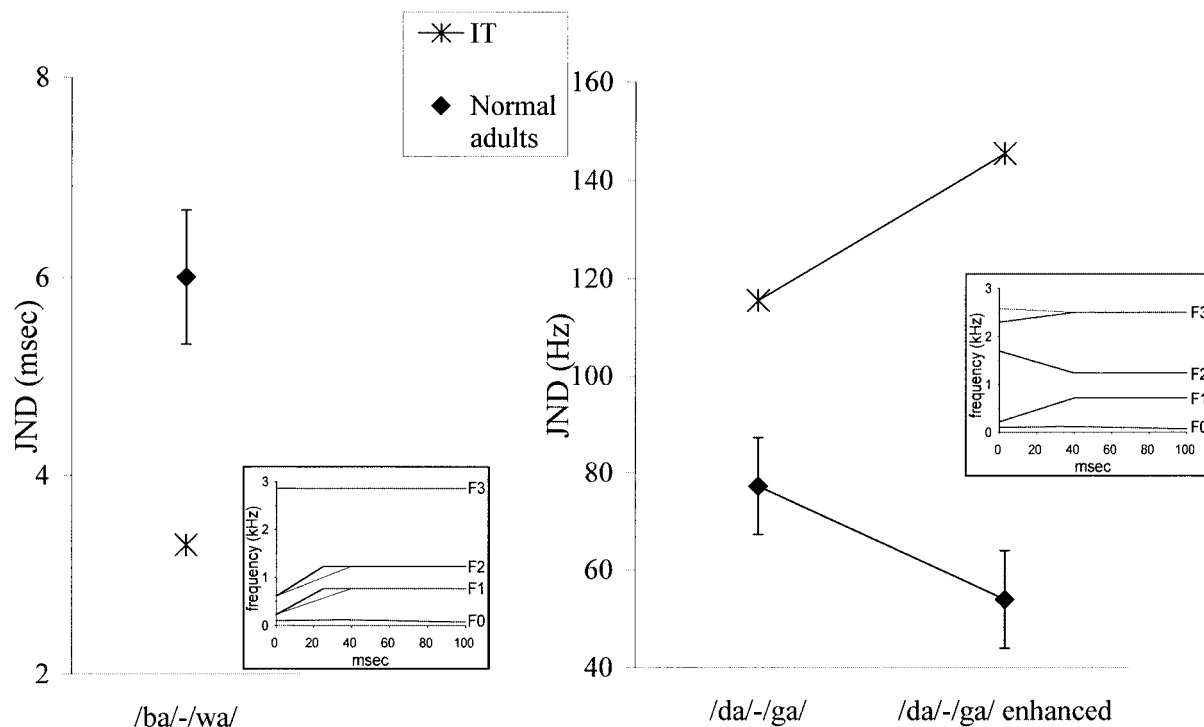


FIG. 2. Just noticeable differences for two synthetic speech continua for normal young adults ($n = 12$, means and standard errors) and IT. Normal adult means and SDs are 6 ms (2), 77 Hz (35) and 55 Hz (19) for /ba-wa/, /da-ga/ and /da-ga-enhanced stimuli, respectively; see also Kraus et al. 1999). The /ba-wa/ continuum varied in the duration of the formant transition. The /da-ga/ continuum varied in

the onset frequency of the third formant with a 40-msec formant transition duration. The /da-ga-enhanced continuum was the same as the /da-ga/ continuum but the amplitude of the formant transition was increased. The inserts show schematic spectrograms of key elements of the prototype phonemes. Thin lines represent /da/ and /wa/ and thick lines represent /ga/ and /ba/, respectively.

variability and signal degradation. These factors introduce precisely the signal variability and degradation encountered in real-world speech perception.

Using a word database developed at Indiana University (Torretta 1996; Bradlow and Pisoni 1999), two lists of 72 words each were created. IT heard each word through a loudspeaker (at 65 dB SPL) in a sound-treated room and then repeated the word, which was written down by the experimenter. Within each list, SNR was progressively decreased across four 18-word sublists from +12 dB to +9 dB to +6 dB, and finally to +3 dB. Words in the first list were spoken by a single female talker, while words in the second list were spoken by nine different talkers (5 males, 4 females). Each list was composed of 36 "easy" words and 36 "hard" words. The words were categorized as easy or hard based on lexical characteristics identified by the Neighborhood Activation Model (NAM) of spoken word recognition (Luce 1986; Luce and Pisoni 1998). According to this model, an easy word is a word that has few similar-sounding "neighbors" with which it can be confused. Furthermore, these few lexical neighbors have a lower frequency of occurrence in the language than the word itself. In contrast, a hard word has many, high-frequency similar-sounding lexical neighbors with which it can be confused. Using a variety of spoken

word recognition tasks, this easy-hard difference has been shown to have dramatic effects on word intelligibility (Pisoni et al. 1985; Luce 1986; Luce et al. 1990; Luce and Pisoni 1998). The intelligibility of the lists were equated, based on word recognition data from a large number of normal hearing subjects collected as part of the database development (Bradlow and Pisoni 1999).

Signal-to-noise ratio Results: Word identification scores across the four SNRs (+12, +9, +6, +3 dB) from a group of 15 normal subjects using the same lists and testing procedures as used for IT (from Koch et al. 1999b) are shown in Figure 3, along with the scores for IT. These scores are averaged across single- and multiple-talker presentation formats, and across easy and hard words. The pattern of decreasing scores with increasing noise was similar for IT and normal adults, although IT showed marked effects of noise at a larger SNR than normals. At the most favorable SNR (+12 dB), IT's performance was similar to that of normals. However, at all other, less favorable SNRs, IT's performance was substantially lower than the normal adults. Most notably, at +3 dB SNR, IT was severely impaired, with only 10% correct word identification in comparison to the normal subjects who scored ~40% correct.

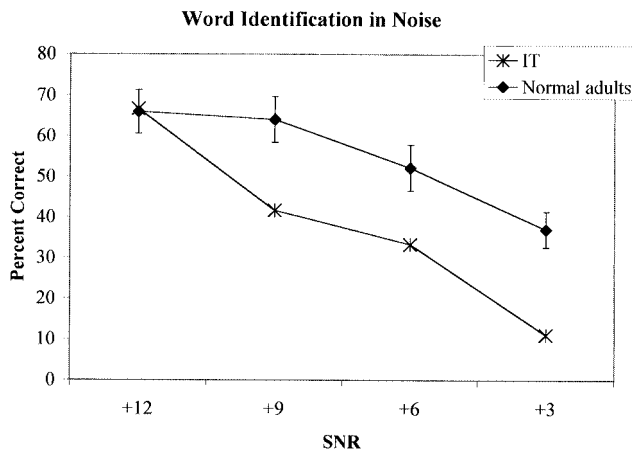


FIG. 3. Percent correct word identification scores are shown for four signal-to-noise ratios (SNR). Means and standard errors are shown for a group of 12 young adults. IT's scores are indicated by asterisks. IT's scores fall within the average at lower SNRs. Her performance is worse than the adult average at decreasing SNRs. Normal adult means and 1 standard deviation are 66 (19), 64 (19), 52(20), and 37 (15) for +12, +9, +6, and +3 dB SNR, respectively.

Talker variability/lexical difficulty Results: Data, averaged across all four SNRs, are summarized in Figure 4. Like normals, IT was able to make use of the signal consistency provided by a single talker compared with the changing talker information in the multiple-talker condition. This suggests that, even in noise, she is sensitive to the nonlinguistic, qualitative aspects of the signal and is able to adapt to a speaking style to the extent that it can assist speech perception ability. The single-talker/multiple-talker effect was most noticeable for the "hard" words, suggesting that IT follows the normal pattern of perceiving words in the context of other words in the English lexicon. Like normal adults, the situation that presents the most difficulty is when the target word has many similar-sounding "competitors" and the surface signal characteristics (talker) change from item to item.

Detection of tones in noise. Methods: Following Wright et al. (1997), threshold was determined for a 20-ms tone of 1000 Hz, presented either before or during a masking noise. Two noise types were employed: a bandpass noise that ranged from 600 to 1400 Hz, and a spectrally notched noise that ranged from 400 to 800 Hz and from 1200 to 1600 Hz. Both noises were 300 ms in duration and had a spectrum level of 40 dB SPL. All stated durations include 10-ms cosine-squared gating envelopes.

The tone and noise were digitally generated in the frequency domain using a digital-signal-processing board (TDT AP2; sampling rate 25 kHz). They were delivered separately through two 16-bit digital-to-analog converters (TDT DD1) followed by separate 8.5-kHz low-pass filters (TDT FLT5), separate programmable attenuators (TDT PA4), and a single sound mixer

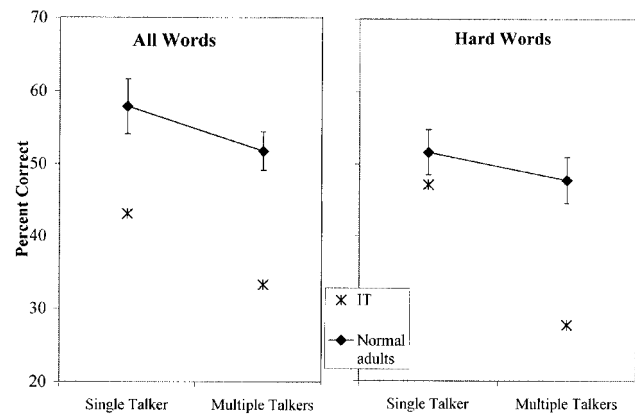


FIG. 4. The effect of single vs. multiple talkers on word identification. Means and standard errors for a group of normal adults are indicated by the filled symbols. IT's word identification scores were consistently better in the single-talker compared with the multiple-talker condition. Her performance was severely affected when acoustic complexity was further increased in the "hard" word condition. IT's scores are indicated by asterisks. Normal mean percent correct scores and standard deviations are 58 (4) and 52 (3) for All Words and 52 (3), 48 (3) for Hard Words, single and multiple talkers, respectively.

(TDT SM3) and headphone driver (TDT HB6). The listener was seated in a sound-treated room and listened monaurally through the left earpiece of Sennheiser HD450 headphones.

Thresholds were measured in three conditions. In the backward-masking condition, the tone ended immediately before the beginning of the bandpass noise. Performance in that condition provides an estimate of how well the listener can separate sounds in time. In two simultaneous-masking conditions, the tone was presented 200 ms after the beginning of either the bandpass or spectrally notched noise. The threshold difference between those two conditions provides an estimate of how well the listener can separate sounds in frequency (Patterson et al. 1982).

The method was two-interval forced-choice with feedback. Observation intervals were separated by 800 ms. Signal level was adjusted adaptively using a maximum-likelihood method, which estimated the tone level required for 94% correct detections after 30 trials (Green 1990). Two threshold estimates were obtained in each condition, but one estimate in the simultaneous-masking condition with the bandpass noise was omitted due to technical problems. Neither IT nor the comparison listeners had any previous experience with the conditions.

Results: Backward masking. IT's threshold in the backward-masking condition was 51 dB SPL. That value is considerably higher than the mean of about 32 dB SPL (SDs 6, range 23–41 dB SPL) for 10 adults with normal hearing tested in the same condition (Hartley et al., in review). Thus, IT is poorer than normal at separating sounds in time.

Results: Simultaneous masking. IT's thresholds in the

simultaneous-masking conditions were 79 dB SPL with the bandpass noise and 75 dB SPL with the spectrally notched noise. This compares to means of about 72 dB SPL (SDs 4, range 65–77 dB SPL) and 54 dB SPL (SDs 7, range 47–70 dB SPL), respectively, for 10 adults with normal hearing tested in the same conditions (Hartley et al., in review). The threshold difference between the bandpass and spectrally notched noise was only 3.5 dB for IT, but was about 18 dB for adults with normal hearing. Thus, IT is much poorer than normal at separating a brief tone from noise components that are remote from the tone in frequency. IT's overall higher thresholds may indicate that she is a less efficient listener than normal adults (Patterson et al. 1982), which is consistent with IT's difficulty hearing in noisy environments.

Speech-elicited cortical potentials

P1/N1/P2 responses to stimuli differing in voice onset time (VOT). *Method:* The stimuli were two synthetic syllables, /ba/ and /pa/, each with a duration of 320 ms. The syllables were composed of five formants. The steady-state values of F1–F5 were 720, 1240, 2500, 3600, and 4500 Hz. For /ba/, there was no burst and the transition duration was 40 ms. The starting frequencies of F1 and F2 were 220 and 900 Hz. For /pa/ a 10-ms burst followed by aspiration began at 5 ms, remained constant until 40 ms, and decreased to zero at 45 ms. Full-amplitude voicing began at 40 ms.

To elicit P1/N1/P2 responses, each syllable was presented 250 times with an interstimulus interval of 1090 ms. Responses were recorded using scalp electrodes placed at Fz (active), on the nose (reference), and on the forehead (ground). For each stimulus, responses were averaged across the 250 presentations.

Results: As shown in Figure 5, IT had robust P1/N1/P2 potentials and her response to /ba/ was similar to that observed in normal subjects. Consistent with the normal pattern, latencies for IT differed for /ba/ and /pa/. However, P1 and N1 responses to /pa/ occurred later than the normal mean for IT. In normal subjects, cortical responses to voiceless stimuli have two peaks, one related to the aspiration/burst (labeled P1' in the figure), the second to the onset of voicing (Sharma and Dorman 1999; Koch et al. 1997). This early peak was absent in IT. Thus, while timing differences were apparent between IT's responses to /ba/ and /pa/, irregularities in the representation of these signals also occurred. Perceptually, IT's fine-grained discrimination of stimuli along a /ba–pa/ continuum was similar to that observed for normal subjects (JND = 1.2; normal adult mean = 2, SDs 1.6; $n = 10$). Unfortunately, information about her perception of these stimuli in noise is not available.

Mismatch response to speech contrasts differing in formant spectrum and duration. *Methods:* The mismatch negativity (MMN) has been purported to be a measure of processes associated with auditory discrimination, because it is the change in acoustic stimulation that triggers the occurrence of the response [Näätänen et al. 1978; see Näätänen (1992) and Kraus et al. (1995a) for reviews]. It is also thought to reflect processes associated with echoic memory (Näätänen et al. 1989). Two speech contrasts used in the behavioral fine-grained speech-sound discrimination experiments—/ba–wa/ and /da–ga/—were presented in an oddball paradigm to the right ear at 75 dB SPL through insert earphones as previously described (Kraus et al. 1996). For each MMN, 3500 stimuli were presented with a rare-stimulus probability of 10–15%. Responses also were obtained to a sequence in which the rare stimulus was presented repetitively for 2000 trials (rare alone). The MMN was calculated as the difference between the responses to a stimulus presented as a rare stimulus in the oddball paradigm and that same stimulus presented alone in a repetitive sequence. Thus, a difference wave is obtained which is not confounded by inherent stimulus differences.

Results: Robust mismatch responses of normal morphology, duration, area, scalp distribution and hemispheric symmetry were obtained to /ba–wa/ contrasts, consistent with IT's excellent behavioral perception of stimuli along a /ba/ to /wa/ continuum. MMN was absent in response to the /da–ga/ contrast (Fig. 6). Thus, processes reflecting discrimination and echoic memory of acoustic stimuli were intact when elicited by stimuli differing in formant duration but not by stimuli differing in formant onset frequency. These responses are consistent with her overall poor perception of sounds along the /da–to–ga/ continuum.

DISCUSSION

Auditory nerve and brainstem synchrony in perception

This case illustrates the extent to which speech perception can be preserved and how it is impaired when auditory pathway synchrony is compromised. In quiet, IT's speech perception was excellent at the sentence and word levels, where contextual and multiple acoustic cues are available. Her speech perception in quiet was abnormal only when the discrimination of fine-grained, stripped-down phonetic elements was required. In noise, IT's speech perception was markedly impaired. She demonstrated poor performance on a variety of speech perception measures including the perception of syllables, words with increasing levels of

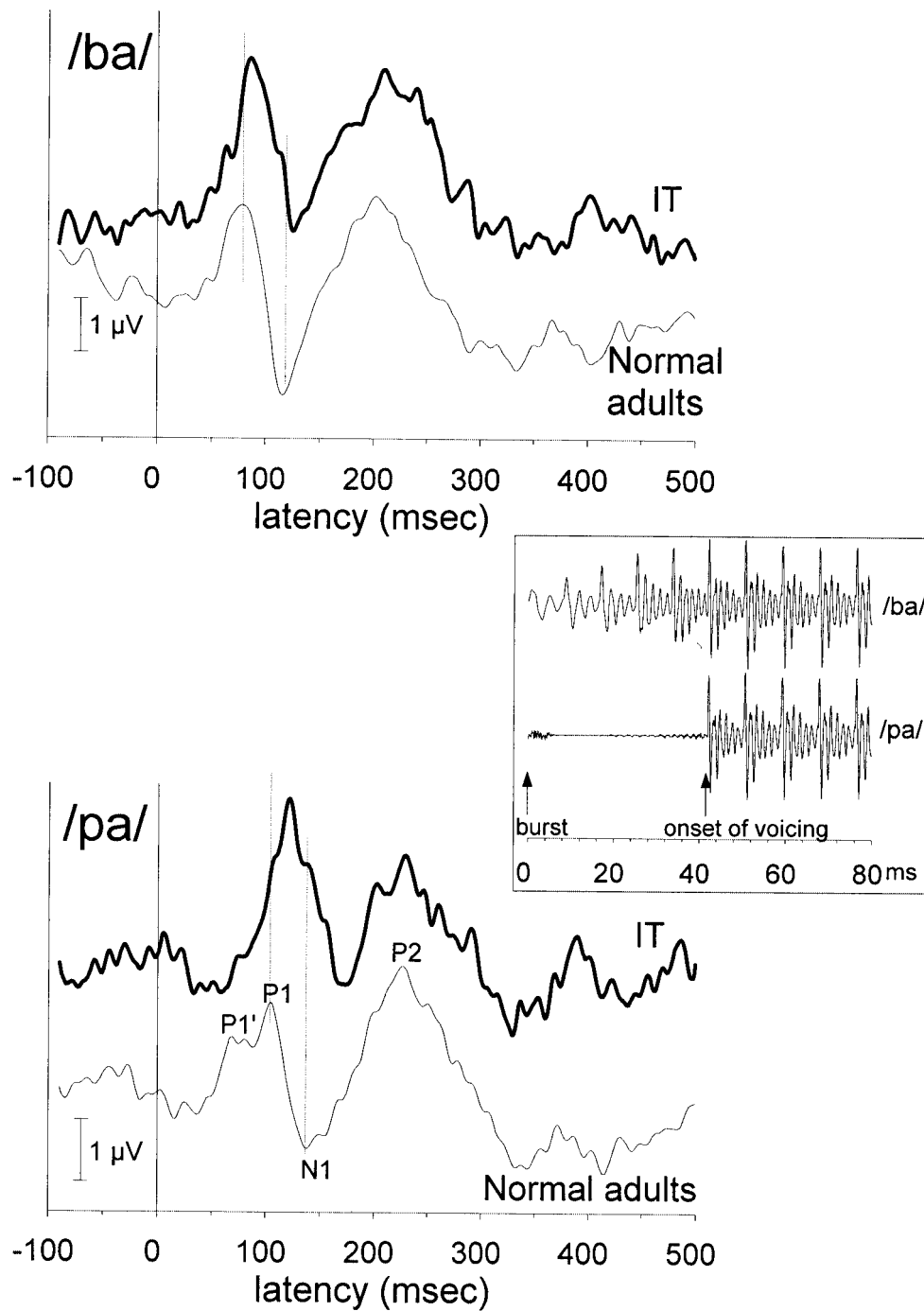


FIG. 5. P1/N1 cortical responses to stimuli differing in voice onset time (/ba/ and /pa/). In each panel, the top thick line is IT's response. The bottom thin line is the grand average response to each stimulus from 11 normal adults. The dashed vertical lines reflect normal mean P1 and N1 response latencies. IT's responses to /ba/ are similar to the normal mean, while P1 and N1 responses to /pa/ occurred later (121 and 174 ms, respectively) than normal mean latencies. In addition, wave P1' was absent for IT. Normal adult means and SDs for /pa/ are 99 (16) and 146 (17) ms for P1 and N1 latencies, respectively. The insert shows the salient acoustic differences between the /ba/ and /pa/ stimuli.

background noise, multiple talkers, and hard words where phonetic confusions are most likely.

IT's difficulties with fine-grained phonetic distinctions and with speech perception in noise are consistent with her problems separating simple sounds in both time and frequency. The psychophysical data suggest a CNS contribution to frequency coding. The abnormal detection thresholds obtained in the simultaneous masking condition demonstrate a deficit in the ability to separate a tone from noise components

that are remote from the tone in frequency. This deficit is unlikely due to abnormal cochlear mechanics (i.e., degraded frequency selectivity of peripheral origin) since otoacoustic emissions were shown to be present in both ears.

This case provides a link between stimulus-timing-related neural synchrony and perception. It illustrates that excellent speech perception is possible in quiet with an absent ABR. Optimal eighth nerve and auditory brainstem synchrony do not appear to be essential

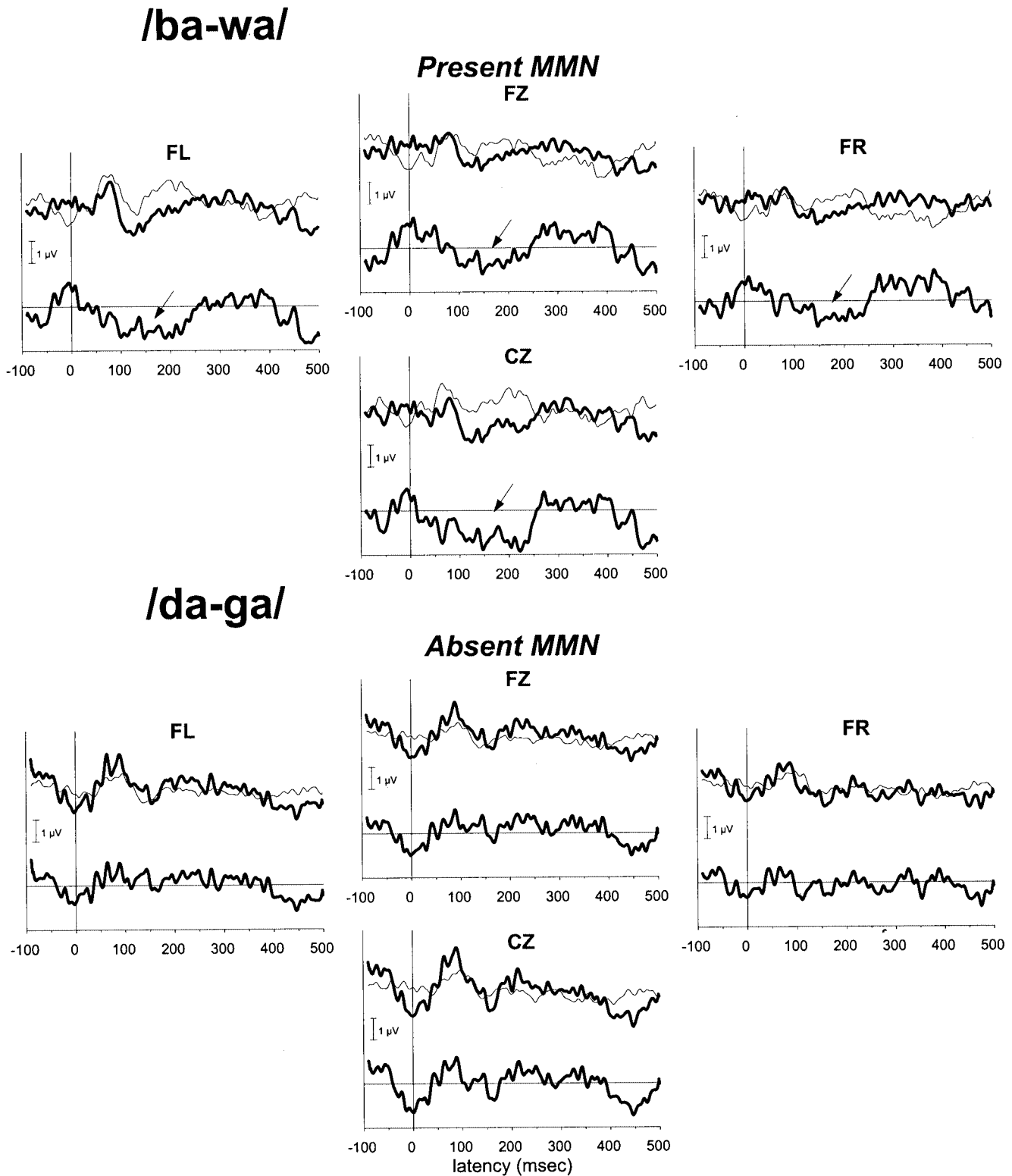


FIG. 6. Grand average MMN responses elicited by a /ba-/wa/ and a /da-/ga/ contrast from central (Fz and Cz) and lateral electrode locations (Fl and Fr). In the four panels at the top of the figure, the top thin line is the response to a /wa/ stimulus when it was presented alone. The top thick line is the response to a /wa/ stimulus when it signaled an acoustic change in a sequence of /ba/ stimuli. In the four panels at the bottom of the figure, the top thin line is the response

to a /da/ stimulus when it was presented alone. The top thick line is the response to a /da/ stimulus when it signaled an acoustic change in a sequence of /ga/ stimuli. In both columns, the MMN is seen in the difference wave (lower thick line) as a deflection below the zero line. Normative data for all MMN parameters (duration, area, amplitude, onset latency) in response to these stimuli are found in Kraus et al. (1999).

for understanding speech in ideal listening situations. Results also indicate that synchrony is critical for understanding speech in the presence of noise, which is what we do most of the time. Nevertheless, it must be noted that the absence of stimulus-timing-related synchrony in IT does not preclude the presence of other forms of synchrony in neural assemblies which exist without precise time-locking to external stimuli or in relation to internally generated cognitive events (Riehle et al. 1997; Barinaga et al. 1998; Stopfer et al. 1997).

Subcortical synchrony and cortical function

Germane to the consideration of neural synchrony is the assumption that evoked responses reflect synchronous activity across a population of neurons. It should be emphasized, however, that cortical potentials reflect neural synchrony differently than the ABR. The ABR peaks reflect synchronous spike discharges generated in nerve tracts, whereas the peaks in cortical responses reflect the summation of excitatory postsynaptic potentials. In other words, the ABR reflects action currents in axons, while the cortical potentials reflect slow dendritic events. These differences are evident in the spectra of these evoked potentials: the dominant peak in the ABR is ~ 1 kHz (Boston and Moller, 1985), whereas the peak for cortical potentials is on the order of tens of hertz (Moller 1994). Because unit contributions to the ABR are biphasic and of short duration, ABR peaks tend to cancel when discharges are separated by fractions of a millisecond. In contrast, for cortical potentials, the waves are so slow that contributions separated by several milliseconds contribute to these later waves. While the ABR reflects highly synchronous discharges with microsecond precision, the synchrony required for cortical potentials is on the order of several milliseconds. These differences demand that the rate of stimulation be slower for cortical than for brainstem responses (e.g., 2/s vs. 30/s, respectively), limiting the precision with which timing information can be represented. Nevertheless, a more rapid rate of stimulus presentation alone cannot account for the absent ABR in IT and in other individuals with auditory neuropathy (Starr et al. 1996). The ABR is absent even when the stimulation rate is as slow as for cortical responses.

For IT, auditory function central to the brainstem, as reflected by cortical-evoked responses, was largely preserved despite abnormal input from lower centers. That is, middle latency responses, P1/N1/P2, MMN, and P300 cortical responses were robust and present in quiet (Kraus et al. 1993). Cortical potentials deviated from normal, however, when elicited by fine-grained, temporal aspects of speech-sound structure. For example (as shown in Fig. 6), IT had absent MMN

to changes in formant onset frequency (/da-ga/). Perhaps the neural representation of these signals depends on the precise neural synchrony known to characterize single neuron activity in auditory cortex in response to the onset of acoustic signals (Phillips 1993; Wang et al. 1995). It is interesting to consider that a similar impairment in perception and neural representation of the spectro-temporal formant changes exemplified by /da-ga/ is seen in children with learning problems (Kraus et al. 1996). Although it has been postulated that impairment of the temporal processing by cortical mechanisms underlies deficits in the ability to discriminate rapid spectro-temporal transitions (Tallal 1981; Nagarajan et al. 1999, Kraus et al. 1996), recent findings also point to a subcortical origin (e.g., brainstem) for these deficits (Cunningham et al. 2000). A high degree of temporal precision is also required to encode rapid formant transitions (Phillips et al. 1989; Phillips and Hall 1990). In the case of IT, subcortical input may not have been sufficiently synchronous to be utilized effectively at more central levels for the perception of the more difficult acoustic discriminations.

Cortical representation of voice onset time (VOT) has been demonstrated in single and aggregate intracranial neuron activity (Eggermont 1995, Steinschneider et al. 1994, McGee et al. 1996). In humans, voiceless stimuli elicit two peaks, one reflecting the initial stimulus burst, and a later one reflecting the onset of voicing (Sharma and Dorman 1999; Koch et al. 1997). Asynchrony of subcortical input may have contributed to IT's atypical cortical representation of VOT as shown in Figure 5. The absence of the early peak (P1') to /pa/ suggests poor representation of transient onset cues which may be related to the stimulus burst. Nevertheless, adequate representation of longer-duration voicing cues, related to harmonic stimulus features, may have contributed to the relative timing differences between her /ba/ and /pa/ responses and her good behavioral perception of stimuli along a VOT continuum.

Finally, a fundamental property of the central nervous system is its inherent plasticity. It is apparent that the central pathways can make use of varied and limited input that can be interpreted as speech by the brain. For example, with deprivation or altered peripheral sensory input, cortical areas which would ordinarily represent input from a peripheral sensory system continue to be active, even though that peripheral system is impaired. In fact, cortical representation reorganizes, and the representation of intact aspects of sensory input is expanded (Irvine and Rajan 1996; Merzenich et al. 1991; Kitzes 1984; Reale et al. 1987; Popelar et al. 1994). Perhaps IT is able to "fill in" missing information based on cortical reorganization resulting from atypical input from auditory brainstem

pathways. It should be noted that IT's cortical potentials were particularly well-formed in amplitude and morphology. Moreover, her perception of fine-grained differences along a /ba-wa/ continuum was extraordinarily good, possibly reflecting neural reorganization and developed compensatory abilities. Future studies, which address cortical reorganization associated with auditory neuropathy, may shed some light on these speculations.

Representation of timing information in speech

Rosen (1992) and Phillips (Phillips et al. 1989; Phillips and Farmer 1990) have provided frameworks for considering speech signals in the time domain. For example, suprasegmental components of speech typically are expressed over hundreds or thousands of milliseconds, periodicity of the fundamental frequency occurs with roughly a 10-ms period, and the fine-structure of speech, characteristic of many consonants, occurs in the tenths-of-millisecond range. This case supports the notion that the synchrony disorder primarily affects the representation of precise timing information occurring at stimulus onset. ABR by definition is a response to stimulus onset and reflects neural information in the tenth-of-millisecond range. In fact, the timing information is so robust that latency delays on the order of 0.2 ms are considered abnormal clinically. However, in addition to affecting responses to stimulus onset, impairment also may extend to other forms of stimulus-timing-related neural synchrony such as the representation of offset responses and phase locking to harmonic and steady-state aspects of the stimulus.

It should be noted that IT had perceptual difficulty in response to sounds containing critical acoustic information at stimulus onset, rather than to stimuli requiring discrimination of durational cues within a syllable. Specifically, discrimination thresholds for synthetic CV syllables revealed that IT had exceptionally good discrimination for speech sounds along a /ba-wa/ continuum but poor discrimination for /da-ga/ contrasts. The difference between /da/ and /ga/ occurs at stimulus onset while the difference between /ba/ and /wa/ occurs within the syllable. Cortical responses to these stimuli revealed a similar pattern of strengths and weakness (to /ba-wa/ and /da-ga/, respectively) in the neural representation of these stimuli. IT's atypical cortical representation of /pa/ further supports the existence of deficits in the representation of transient stimulus cues related to the onset of voiceless syllables, whereas longer-duration harmonic aspects of voicing appeared to be preserved (perhaps via phase locking). Furthermore (as shown in Fig. 2), normal-hearing adults seem to be helped by increasing the amplitude of the formant transition relative to the vowel (enhanced transition), whereas

IT was not. Auditory neurons in cortex increase synchrony and precision of firing with increases in stimulus intensity (Phillips and Hall 1990). Possibly IT cannot profit from this mechanism because, in her case, neural input into auditory cortex lacks onset precision in the first place.

This subject, however, was able to extract speech-sound cues in quiet. She exhibited normal sentence and word identification performance when the listening conditions were favorable (a SNR of at least +12 dB). Moreover, her relatively better perception of words in a single-talker condition, relative to a multiple-talker condition, suggests that she is able to make efficient use of the talker-specific consistencies in the acoustic signal (e.g., voice/source, individual articulatory characteristics that remain relatively stable across items in a list, fundamental frequency) to help her extract important linguistic information.

Overall, the representation of timing information at stimulus onset appeared most vulnerable to disruption, with representation of longer-duration and steady-state timing cues being better preserved. The neural representation and perception of all signals tested, however, was fragile and easily disrupted by noise. It appears that over a wide range of stimuli, IT cannot make use of neural mechanisms (e.g., 8th nerve) that ordinarily represent the temporal structure of the speech signal (Kiang and Moxon 1974; Delgutte and Kiang 1984a, b, c), and that have been shown to be particularly important when speech is presented in noise.

CONCLUSION

IT's profile may provide a "best-case scenario" of how well a person with auditory neuropathy can perform. Although her perceptual deficits and strengths should not be construed as a characterization of all neuropathy patients, they do raise interesting questions and provide clues from which to speculate about the role of neural synchrony in perception. Clearly, a normal audiogram does not indicate normal hearing and an absent ABR does not necessarily indicate elevated behavioral thresholds. Given the alterations in neural activity between the ear and the brain that occur in this case of auditory neuropathy, it is remarkable that hearing and speech perception in quiet are still possible.

The test results reported here imply that the auditory cortex can adjust to the faulty signal representations present at earlier stages along the auditory pathway. In fact, the grossly intact cortical potentials recorded in this case suggest that patients with auditory neuropathy can use varied and limited inputs to perceive complex signals. Further application of the

comprehensive experimental approach used here may help to elucidate the perceptual consequences associated with disorders of neural synchrony, as well as the neurophysiological mechanisms underlying normal and impaired auditory function.

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