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Authors
Starr, A
McPherson, D
Patterson, J
et al.

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ABSENCE OF BOTH AUDITORY EVOKED POTENTIALS AND AUDITORY PERCEPTS DEPENDENT ON TIMING CUES

by A. STARR,[1] D. McPHERSON,[1] J. PATTERSON,[1] M. DON,[2] W. LUXFORD,[2] R. SHANNON,[2] Y. SININGER,[2] L. TONAKAWA[2] *and* M. WARING[2]

(*From the* [1]*University of California, Irvine, and the* [2]*House Ear Institute, Los Angeles, California, USA*)

SUMMARY

An 11-yr-old girl had an absence of sensory components of auditory evoked potentials (brainstem, middle and long-latency) to click and tone burst stimuli that she could clearly hear. Psychoacoustic tests revealed a marked impairment of those auditory perceptions dependent on temporal cues, that is, lateralization of binaural clicks, change of binaural masked threshold with changes in signal phase, binaural beats, detection of paired monaural clicks, monaural detection of a silent gap in a sound, and monaural threshold elevation for short duration tones. In contrast, auditory functions reflecting intensity or frequency discriminations (difference limens) were only minimally impaired. Pure tone audiometry showed a moderate (50 dB) bilateral hearing loss with a disproportionate severe loss of word intelligibility. Those auditory evoked potentials that were preserved included (1) cochlear microphonics reflecting hair cell activity; (2) cortical sustained potentials reflecting processing of slowly changing signals; and (3) long-latency cognitive components (P300, processing negativity) reflecting endogenous auditory cognitive processes. Both the evoked potential and perceptual deficits are attributed to changes in temporal encoding of acoustic signals perhaps occurring at the synapse between hair cell and eighth nerve dendrites. The results from this patient are discussed in relation to previously published cases with absent auditory evoked potentials and preserved hearing.

INTRODUCTION

Auditory evoked potentials provide objective measures of auditory function particularly in children and neonates to allow appropriate intervention if auditory sensitivity is impaired (Hecox and Galambos, 1974; Galambos and Despland, 1980). Auditory evoked potentials also test the integrity of central auditory pathways and can assist in the diagnosis and treatment of a variety of neurological conditions (Starr and Achor, 1975; Starr, 1986). However, there are several paradoxical findings accompanying the use of auditory evoked potentials that are difficult to resolve. For example, even though auditory brainstem evoked potentials reflect the activity of auditory brainstem and peripheral structures (Buchwald and Huang, 1975; Starr and Hamilton, 1976; Møller *et al.*, 1981), some patients can lack components of auditory brainstem potentials and be without subjective, or even objective, alterations of auditory function (Cacace *et al.*, 1983; Jabbari *et al.*, 1983). Even more disconcerting is the rare patient in whom brainstem and even middle-latency auditory evoked potentials are completely absent although the stimuli

Correspondence to: Dr Arnold Starr, Department of Neurology, California College of Medicine, University of California, Irvine, Irvine, CA 92717, USA.

are perceptible (Worthington and Peters, 1980; Bernard and Soulier, 1983; Satya-Murti *et al.*, 1983; Kraus *et al.*, 1984; Hildesheimer *et al.*, 1985; C. Berlin, personal communication; J. Jerger, personal communication). We have had the opportunity to analyse this latter inconsistency in detail in a patient in whom those auditory evoked potentials used for clinical assessment of auditory functions (brainstem, middle and long-latency) were absent yet who heard the click and tones used in these tests. We examined in detail both the patient's perceptual capabilities and physiological functions of the auditory system to help understand these findings.

The results showed the patient to have a marked impairment in using temporal features of acoustic stimuli for perception with a corresponding absence of those auditory evoked potentials that are sensitive to temporal cues. Other auditory evoked potentials not sensitive to temporal cues were preserved. The data are interpreted as being compatible with a deficit in the region of the hair cells and eighth nerve dendrites affecting the precision of timing of eighth nerve discharges. The results from both the present study and the previous case reports suggest that these patients may comprise a new type of auditory disorder affecting temporal auditory feature analysis.

METHODS

Clinical history

The subject of study is an 11-yr-old girl with progressive hearing loss of 4 yrs duration who had not been helped by hearing aids. The family history is negative for hearing disorders. She had particular difficulties in understanding speech and had become proficient in lip-reading. She volunteered that speakers sounded 'weird, like spacemen'. She had no tinnitus but occasionally had persisting auditory experiences lasting several seconds following exposure to loud sounds like a passing truck. We could not elicit this experience with any of the signals we used in these studies. There were no symptoms of vestibular, motor, cognitive or other sensory dysfunction. Both the general physical and neurological examinations were normal. Routine haematological and biochemical tests as well as MRI of the brain, brainstem, and eighth nerves were normal. Caloric stimulation of the labyrinths while recording eye movements revealed absent responsiveness from the right ear and reduced responsiveness from the left ear.

Clinical measures of auditory function in 1984 and 1985 (Table 1) showed a bilateral mild pure tone loss (20−40 dB) extending across all frequencies. Air conduction thresholds increased gradually with a conductive component (air-bone gap) first appearing in the left ear in 1986 and in the right ear in 1989. The air-bone gap became particularly marked in the left ear in 1989 and 1990 and tympanograms at those times demonstrated negative pressures (−250 to −450 mm H_2O). Tuning fork tests of the left ear at the 1990 examination showed that bone conduction thresholds were lower than air conduction thresholds. There was a progressive bilateral decrease in word intelligibility scores between 1984 and 1990, and performance worsened if stimulus levels were raised. In 1990, using sound fields at 70 dB SPL, the patient had difficulty distinguishing between consonant-vowel-consonant monosyllabic words differing only by their vowels, for example, 'goat, got, get or gate' (57% correct with chance performance being 25%), and was only slightly better (74% correct) when the distinguishing acoustic feature was the consonants, for example, 'tip, zip, pip or chip'. However, she always correctly identified the high frequency consonants 'ch, s, t, wh, sh'.

The patient underwent a myringotomy on the left ear in January 1990 for placement of a ventilation tube in an effort to correct the conductive deficit. At the time the middle ear was explored, no fluid was found and the ossicles were entirely mobile. The finding of a normal middle ear was surprising in light of the immediately preceding clinical audiological measures. We used the opportunity to try to assess the excitability of the eighth nerve by placing a stimulating ball electrode, insulated except for the tip, in the round window niche. Electrically stimulating between this electrode and another placed on the contralateral side of the head (100 μs/phase biphasic current pulses at 0.7 mA) did not evoke any reproducible short-latency potentials. The round window electrode was maintained in place while the tympanic membrane flap was

TABLE I. AUDIOMETRIC TEST RESULTS (BONE CONDUCTION/AIR CONDUCTION)

Right ear *Frequency (Hz)*	*Dates of audiological examinations*						
	9/84	*11/85*	*6/86*	*8/87*	*2/88*	*2/89*	*1/90*
	Threshold (dB HL)						
250	NT/40	NT/10	10/20	20/30	30/35	30/45	25/55
500	NT/65	5/10	20/20	25/25	35/40	45/55	70/70
1000	NT/55	20/20	20/40	40/45	45/45	45/70	45/50
2000	NT/20	0/0	10/20	20/20	30/35	30/55	40/45
4000	NT/35	5/25	25/25	60/60	60/60	50/75	45/60
8000	NT	15	20	40	50	45	45
Speech							
SRT/SAT (dB HL)	NT	15/NT	35/NT	30/NT	50/25	45/NT	NT/55
WDS (%)	NT	NT	88	56	36	12	16
Acoustic reflex	NT	NT	Abs	Abs	NT	NT	Abs
Tympanometry (mm H_2O)	NT	NT	−250	NL	NT	−100	NL

Left ear *Frequency (Hz)*	*Dates of audiological examinations*						
	9/84	*11/85*	*6/86*	*8/87*	*2/88*	*2/89*	*1/90*
	Threshold (dB HL)						
250	NT/35	15/25	10/25	35/45	30/50	40/60	40/80
500	NT/35	30/40	50/50	60/80	55/55	55/105	NR/95
1000	NT/35	35/35	50/70	55/60	45/50	NR/95	60/90
2000	NT/20	20/20	15/25	30/35	20/25	NR/100	40/45
4000	NT/35	25/30	35/40	70/70	40/40	65/75	60/80
8000	NT	25	30	85	65	85	85
Speech							
SRT/SAT (dB HL)	NT	35/NT	50/35	NT/55	40/35	NT/60	NT/80
WDS (%)	NT	NT	54	NT	0	NT	8(12/89)
Acoustic reflex	NT	NT	Abs	Abs	NT	NT	Abs
Tympanometry (mm H_2O)	NT	NT	−250	−300	NT	−450	−400

NT = not tested; Abs = absent; NR = no response; NL = normal; SRT = speech reception threshold; SAT = speech awareness threshold; WDS = word intelligibility score.

replaced and the insulated electrode lead packed in the ear canal. Stimulating later that day after the patient had awoken resulted in the patient experiencing discomfort in the 'ear' or on the 'tongue' at the highest current levels without having any auditory sensations. No short-latency potentials could be recorded to these stimuli. We cannot ascertain whether the failure to evoke short-latency potentials or to elicit auditory sensations on stimulating the cochlea reflected a loss of sensitivity of the eighth nerve to electrical currents or whether the electrode had moved postoperatively from its original position in the round window niche to a position relatively remote from the cochlea.

Auditory brainstem potential testing performed by several laboratories showed either an absence of reproducible components, or only a few waves of atypical form and latencies not corresponding to normal records. On our tests, visual evoked potentials to checkerboard pattern reversal stimulation and somatosensory evoked potentials to both median and posterior tibial nerve stimulation were within normal limits.

We recorded a variety of auditory evoked potentials (*see* Table 2 for test details) on 3 occasions: March 1988, June 1988, and February 1989. The former 2 were completed before the definition of the

TABLE 2. AUDITORY EVOKED POTENTIAL RECORDING PARAMETERS

Auditory evoked potential component	*Electrode site*	*Filter window*	*Stimulus type*	*Rate of stimulation*
Cochlear microphonic	Canal-Cz	100–5000 Hz	Click or 4 kHz tone	11/s 1/s
Brainstem evoked potentials	Cz-Cvii Cz-M ipsi Cz-M contra	100–3000 Hz	Click	11/s
Frequency following response	Cz-M contra	30–3000 Hz	400 Hz	1/s
Middle-latency auditory evoked potentials	Cz-Cvii	30–500 Hz	200, 1000 and 4000 Hz tone	5/s
Long-latency auditory evoked potentials	Cz-Cvii	0.03–30 Hz	200, 1000 and 4000 Hz tone	0.5/s
Sustained DC potential	Cz-M ipsi	0.03–30 Hz	1000 Hz tone	0.4/s
Cognitive evoked potentials 1. Target detection 2. Omitted stimulus 3. Processing negativity	Fz-M linked Cz-M linked Pz-M linked Eye: above and below	0.03–17 Hz	Musical notes (middle C and high D)	0.5/s

Ipsi = ipsilateral to ear of stimulation; contra = contralateral to ear of stimulation; M = mastoid; Cvii = seventh cervical vertebra (all other electrode notations are in reference to the 10–20 system of placement).

air-bone gap in the left ear. The tests included: (1) auditory brainstem potentials (3 occasions); (2) auditory middle-latency potentials (3 occasions); (3) auditory long-latency potentials (3 occasions); (4) cochlear microphonic potentials (2/89); (5) frequency following responses (2/89); (6) sustained 'DC' cortical potentials (2/89); and (7) cognitive event-related potentials to both auditory and visual stimuli (P300 and processing negativity, 6/88, 2/89).

For cognitive evoked potentials in the auditory modality, 2 notes, middle C (fundamental of 256 Hz) and D one octave higher (fundamental of 576 Hz) comprising both the fundamental and its harmonics, were generated by a computer and presented once every 2 s via headphones for a total of 300 trials. The duration of the notes was 100 ms. The higher target note had a probability of 0.2 and was randomly intermixed with the frequent nontarget stimulus. Their intensity was 60 dB nHL, a level that was 'clear' for the patient. For the visual modality, 2 letters, 'X' (the nontarget) or 'O' (the target) were presented on a video monitor once every 2 s also for 300 trials. The subjects (2 controls with normal hearing aged 11 and 12 yrs and the patient) pressed a response button whenever the target appeared and reaction times (RT) and accuracy were measured. Evoked potentials both to the targets and nontargets not contaminated by eye movements were averaged 5 times for the patient, twice for one control, and 4 times for the second control. In the auditory modality, potentials were also recorded in a 'no task' condition using only one of the notes with the subject instructed 'not to pay attention to the stimuli and to remain awake'. For the patient and one of the controls evoked potentials were also averaged to auditory targets and nontargets during a 'visual attention' condition requiring that she read a story and later answer questions about its content. The potentials evoked to the nontargets in both the 'no task' and the 'visual attention' task were subtracted from the potentials evoked by the same stimuli during classification of the notes to provide a measure of brain potentials accompanying focused auditory attention (Näätänen, 1982). The subjects were also tested during a variant of the target detection task in which only nontarget notes were presented once every 2 s except for occasional ($P = 0.2$) and unpredictable omissions. The subject pressed a response button with each omission and averages of the brain events were made commencing at the time when the stimulus would have appeared. Potentials evoked by the absence of a stimulus are certainly cognitive in origin.

Control subjects

Up to 5 young (aged 11–17 yrs) subjects with normal hearing, 1 of whom was the patient's sister, were used in those tests for which we did not have appropriate normative data. Audiometry was normal both in the sister and the controls.

Psychophysical assessment

Psychophysical assessments of auditory function were performed on 3 occasions (3/88, 2/89, 12/89). The tests quantified perception of acoustic signals based on frequency, intensity and temporal cues. The dates of the tests are indicated below for comparison with the audiometric results.

For temporal discrimination we measured: (1) lateralization of binaural clicks as a function of interaural time and intensity disparities (3/88); (2) threshold to mask low frequency signals (masking level difference or MLD) when the binaural signals were in-phase and 180° out-of-phase (3/88); (3) perception of binaural beats and monaural physical beats with low frequency signals that differed slightly in frequency, that is, 300 and 303 Hz (3/88); (4) monaural resolution of paired clicks as a function of temporal separation (3/88); (5) resolution of paired electrical stimulation to the median nerve and to the volar surface of the middle digit (2/89); (6) monaural just noticeable differences (JNDs) for the duration of a 1000 Hz tone at 40 dB SL (2/89); (7) the relation between tone duration and monaural threshold, right ear only (12/89); and (8) monaural detection of a silent period in a tone burst as a function of the duration of the tone burst, right ear only (12/89). Those tests requiring binaural processes were carried out in 3/88 when the air conduction thresholds of the ears were comparable.

For frequency discrimination we tested monaural JNDs at 200, 500, 1000, 2000, 4000 and 8000 Hz (2/89) and for intensity discrimination monaural JNDs for tones at 20 and 40 dB SL (2/89).

Test procedures

Temporal discrimination

Binaural lateralization. TDH 49 earphones were activated with 100 μs pulses, approximately 30 dB above monaural thresholds, at a 1/s rate. Large interaural differences in intensity were first used so that the subject would experience an image that was easily lateralized to the right or the left side of the head. A systematic measure of intracranial lateralization was then made as a function of interaural time and intensity differences.

Masking level differences (MLDs). Binaural thresholds were defined to equal intensity continuous 300 Hz signals in the presence of masking noise; the latter was derived from a single generator and presented binaurally at 30 dB SL. Binaural thresholds for the low frequency tone when in-phase and when 180° out-of-phase were determined.

Binaural beats. Two low frequency tones differing slightly in frequency (e.g., 300 and 303–350 Hz) were presented one to each ear. Their intensities were the same and were not quantified beyond their being suprathreshold and of 'comfortable loudness'. The subject was first trained to appreciate the quality of this auditory percept monaurally by mixing the 2 frequencies to produce an amplitude modulated signal, that is, a physical beat, that changed in intensity at a rate equal to the frequency difference (3–50 Hz) between the 2 tones.

Monaural temporal resolution. Pairs of clicks were presented monaurally at 85 dB nHL with the temporal separation between the two clicks varying in 1 ms increments. The subject reported the signals as 'one click' or 'two clicks'. Occasional catch trials containing only a single stimulus were presented. The time separation at which the paired signals were consistently identified as 'two clicks' was the measure of monaural temporal resolution.

Somatosensory temporal resolution. Pairs of electrical pulses from a constant current stimulator were delivered to a pair of skin electrodes, 1 inch apart, placed near the median nerve at the wrist or to the volar surface of the middle finger. The pulses were 0.1 ms in duration. The intensity of the pulses to the digit was raised above sensory threshold to a level that was tolerable while the current strength for median nerve stimulation was just below that evoking contraction of the hand muscles. The stimuli were applied once every 3–4 s and the subject reported whether there were 'one' or 'two' stimuli. Initially large interstimulus intervals were employed; subsequently the interstimulus interval was reduced in 10 ms increments. Occasional catch trials having only a single stimulus were used.

Monaural stimulus duration. Pairs of 1000 Hz tones (10 ms rise and fall time, 40 dB SL) separated from each other by 500 ms were presented every 5–10 s. Two tone durations were tested: 50 and 500 ms. For the 50 ms duration tones, the duration of the second tone of the pair was varied in 5 ms increments and 50 ms for the 500 ms duration tones. The subject reported the signals as being either 'same' or 'different' in duration.

Monaural threshold as a function of signal duration. The threshold of 1000 Hz tone bursts, presented 1/s, was defined as a function of the signal's duration. Only the right ear was tested. Tonal durations between 200 and 5 ms were used. Threshold was measured using the method of limits: the average of an ascending and descending signal series that was varied in 2 dB steps.

Monaural gap detection. Pairs of 1000 Hz tones were presented at 117 dB nHL, a level which was reported as 'comfortably loud' by the patient. Only the right ear was tested. In the middle of one of the tone pairs, a silent interval was introduced on a random schedule. One of the tone pairs never contained a silent period. The tone pairs were separated by 500 ms. The patient was instructed to press one of two response buttons after each of the stimulus pairs; one button indicated that the gap was in the first tone and the other button indicated that the gap was in the second tone. For each duration of the tone bursts (5, 10, 20, 50, 55, 60, 80 and 200 ms) the length of the silent period was varied adaptively to achieve a 79% correct performance.

Frequency discrimination

Monaural JNDs at 200, 500, 1000, 2000 and 4000 Hz were defined. At each of these frequencies pairs of tone bursts (500 ms duration, 10 ms rise and fall times, 30 dB SL) separated by 400 ms were presented once every 5–10 s. The initial tone was the 'standard' and the second tone's frequency was varied. Occasional catch trials were inserted in which the 2 tone bursts were of the same frequency. The subject was asked whether the 2 tones were the 'same' or 'different' in pitch. The just noticeable difference was defined at the 100% confidence limits.

Intensity discrimination

Monaural JNDs for a 1000 Hz tone at 20 and 40 dB SL were defined. The paired stimuli were presented as for frequency JNDs and the intensity of the second stimulus varied in 1 dB increments. The subject was asked whether the 2 tones were the 'same' or 'different' in loudness.

RESULTS

Evoked potentials

Cochlear potentials

Potentials recorded from an electrode in the external ear canal referenced to the vertex revealed a series of components extending for up to 5 ms (fig. 1A) in response to clicks of 87 dB nHL, approximately 35 dB above the patient's threshold to clicks at this recording session. The potentials reversed polarity when the click was changed from condensation to rarefaction. The potentials were not obtained when the air tube coupling the transducer to the ear canal was clamped, indicating that the recordings were not artefacts of the electrical voltages applied to the transducer. The latency of these potentials did not change as signal intensity was reduced (fig. 1B) in contrast to neural components which lengthen in latency. The microphonic, rather than neural, character of these potentials was further suggested by their persistence in the presence of noise (fig. 1C) sufficient to mask the perception of the clicks (Coats and Dickey, 1970). We were surprised by the duration of the cochlear microphonic accompanying the presentation of the transient click stimulus. However, the waveform of the acoustic signal measured in a 3 cc coupler showed there to be an initial high amplitude transient followed by low amplitude acoustic energy for 5 ms, approximately the same duration as the cochlear

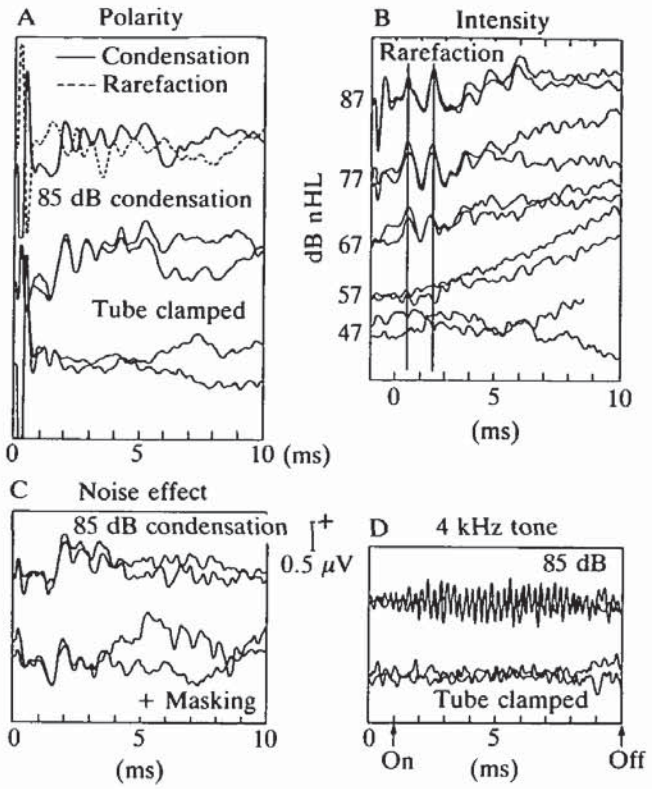

FIG. 1. Cochlear microphonic recordings (2/89) obtained from the patient between an electrode in the right ear canal referenced to the vertex. A, the early latency components reverse polarity with a change of click polarity from condensation to rarefaction. These components are not artefacts of the voltages applied to the transducer since they are lost when the air tube transmitting the acoustic energy from the transducer to the ear canal was clamped. B, these potentials persist over a 30 dB intensity range, becoming smaller as intensity is reduced, without a change of latency (*see* vertical lines alignment on peaks). C, these potentials persist in the presence of a noise sufficient to mask the perception of the click. D, cochlear microphonic potentials recorded over a longer time base to a 4 kHz tone with and without masking noise.

microphonic components recorded from the ear canal electrode. Cochlear microphonics were also detected to a long duration 4 kHz tone of 87 dB nHL (fig. 1D).

Auditory brainstem potentials

Auditory brainstem evoked potentials had no identifiable components at 65 and 75 dB nHL. At both 85 and 95 dB nHL reproducible waves were recorded from only 1 of the 3 recording montages: vertex to the mastoid ipsilateral to the ear being stimulated. Reproducible waves were not obtained from the vertex to mastoid contralateral to the ear being stimulated or from the vertex to a noncephalic reference (fig. 2, 'ABR'). Right ear stimulation at 95 dB nHL showed latencies for vertex positive components at 1.1, 1.8, 2.0 and 3.2 ms. Left ear stimulation showed latencies at 1.8 and 2.6 ms. The components occurred at the same latency though at a reduced amplitude when the click intensity was reduced to 85 dB nHL. Measurement of cochlear potentials clarified that these atypical ABR components did not represent artefacts of the voltages applied to the earphones, but were reflections of cochlear microphonics detected by the electrode placed close to the stimulated ear.

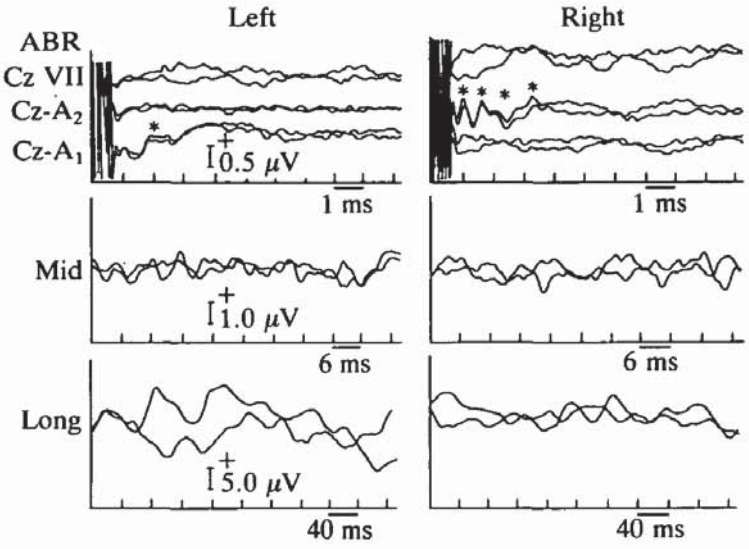

FIG. 2. Auditory brainstem (ABR), middle (mid), and long-latency (long) auditory evoked potentials recorded (3/88) from the patient to left and right ear stimulation. An asterisk is placed above reproducible components. Note that for the ABR these components were only detected in the recordings between the vertex and the ear receiving the stimulus (Cz to A1 or A2). No reproducible components were found in the middle and long-latency potentials. Stimulus intensity was 95 dB nHL for the ABR and 85 dB nHL for the other recordings.

Auditory middle and long-latency potentials

On 3 separate testing dates, there were no reproducible components for either the middle or long-latency auditory evoked potentials either to clicks or tone bursts (200, 1000 and 4000 Hz) at intensities up to 95 dB nHL (fig. 2, 'Mid' and 'Long'). The stimuli were always suprathreshold in intensity. The patient was asleep during these tests. The failure to detect long-latency components on this test will be compared with the potentials obtained during the performance of an auditory target detection task (*see* 'Cognitive evoked potentials' below).

Frequency following response

No potentials were recorded that followed the microstructure of low-frequency tones.

Auditory sustained 'DC' potentials

In normal subjects a long-duration tone evokes a sustained negative shift, of maximal amplitude at the vertex, that persists for the duration of the tone (Picton *et al.*, 1978). The sustained negative shift is accompanied at its onset by N100 and P200 components (fig. 3, control). When the patient was tested for a long-duration 1000 Hz tone at an intensity of 87 dB nHL, approximately 30 dB above her threshold, a sustained negativity appeared that peaked at approximately 250 ms, almost 150 ms later than the normal latency of the N100 component. The duration of the shift lengthened as tone duration lengthened (fig. 3). The amplitude of the sustained negativity was affected by the level of arousal, being large (up to 12 μV) when she was awake and small (2−4 μV) or even undetectable when she was asleep.

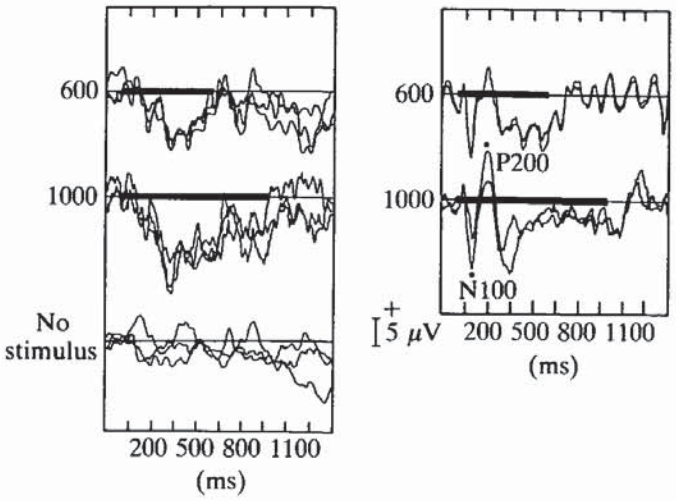

FIG. 3. Sustained potentials to long duration tone bursts presented to the right ear recorded (2/89) from the patient (*left*) and an age-matched control with normal hearing (*right*). The tone's presence is indicated by the thickening of the baseline. Note the sustained negative potential that occurs for the duration of the stimulus and the absence of the onset and offset transient components (N100, P200) in the patient but their presence in the control.

Cognitive evoked potentials

The patient's detection of target notes was accurate (96%) with only an occasional error made to the frequent nontarget tones (98% correct). Reaction times were 740 ms compared with 319 and 490 ms in 2 normal young subjects of the same age. In the patient the evoked potentials to the target notes (fig. 4A) contained a positivity (average baseline-to-peak amplitude 18.5 μV) at a latency of 513 ms, largest parietally, which was markedly attenuated to the nontargets (2.1 μV). A parietal positivity also appeared (latency 571 ms, amplitude 20.3 μV) when the task was varied to require the detection of the occasional and unpredictable absence of a regularly recurring note (fig. 4B). Comparable waveforms from 1 of the normal age-matched subjects are shown in fig. 4. Table 3 contains measures of cognitive evoked potential components and behaviour from both the patient and controls. In the target detection task P300 latencies for the controls were 320 and 344 ms with an amplitude of 28.6 and 21 μV. In the omitted stimulus task P300 latencies were 554 and 501 ms and amplitudes were 11.8 and 14.4 μV. The prolongation of both the RT and the latency of the patient's P300 in the auditory target detection task relative to the normal values cannot be attributed to a specific auditory processing difficulty since both RT and P300 latency in the visual target detection task were also delayed compared with the normals: RT was 500 ms in the patient compared with 355 ms in the control (only 1 control was tested in this task); P300 latency in the patient was 462 ms compared with 300 ms in the control.

The nontarget stimuli in these tasks also evoked a series of components. In the patient the latencies and amplitudes varied considerably (compare A, B and C in fig. 4A collected during different tasks). In the grand average of the nontargets collected during 5 repetitions of the target detection task, the components consisted of an N165 (mean of 173 ± 24 ms) and a P240 (mean of 244 ± 24 ms). The N165 was of equivalent amplitude along the midline scalp whereas the P240 was of maximal amplitude over the parietal region.

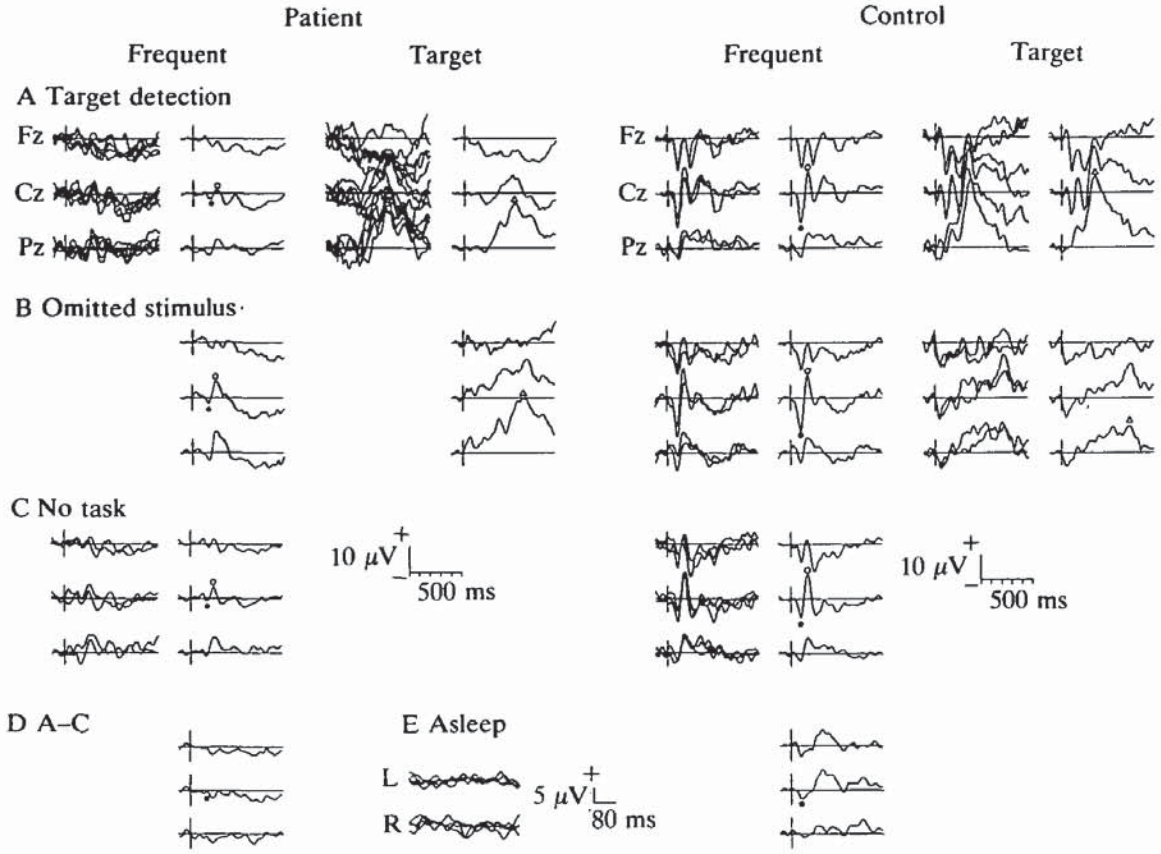

FIG. 4. Cognitive potentials recorded from Fz, Cz, Pz, referenced to linked ears in the patient (6/88 and 2/89) and a normal control (control 1 in Table 3). The potentials to 'nontargets' and to 'targets' are arranged in separate columns in different conditions: A, during performance of the target detection task; B, during performance of the omitted stimulus task; C, during a 'no task' condition; D, the difference waveforms between C and A, i.e. A−C; E, long-latency evoked potentials to a 1000 Hz tone collected when the patient was asleep. The superimposed traces represent repeated averages collected in the different conditions with their grand average displayed to the right. The components are labelled by the polarity at Cz (P for positive and N for negative) and their approximate latency in ms. N160 for the patient and N100 for the control (●); P240 for the patient and P200 for the control (○); P300 for both the patient and control (△). Note the clear P300 component to the target in both the patient and the control in conditions A and B. The N160 and P240 components to the nontargets in the patient when compared with the N100 and P200 components in the controls are delayed in latency, have a different scalp distribution, and are absent when the patient is asleep.

The N165-P240 amplitudes in all the tasks ranged from 4.0 to 9.6 μV and were not present when the patient was asleep (*see* fig. 4E). The characteristics of the N100 and P200 components in the control subjects were quite different from the N160 and P240 components in the patient. In the control subjects, nontargets elicited N100 and P200 components which were of short latency (N100 at 99 and 108 ms; P200 at 163 and 144 ms) that only varied a few ms between repetitions. The N100-P200 amplitudes ranged from 16.9 to 21.3 μV for 1 of the controls and 3.2 to 7.2 μV for the other and had frontocentral maxima. In normal subjects the N100 and P200 components persist in sleep.

A sustained negative shift was identified in the patient's auditory evoked waveforms when the potentials to the nontargets collected during the performance of the tasks were subtracted from the potentials to these same stimuli when the subject was not performing

TABLE 3. COGNITIVE EVOKED POTENTIALS AND BEHAVIOUR

	Evoked potentials								*Behaviour*	
	Latency (ms)				*Amplitude (μV)*					
	N1	*P2*	*P3*	*PN*	*N1*	*P2*	*P3*	*PN*	*RT(ms)*	*Acc(%)*
Patient										
Auditory tasks										
Target (5)	173	244	513	216	−3.3	2.8	18.5	−3.4	740	96
SD	24	24	60		1.2	1.8	3.1		96	2
Omitted (1)	161	235	571		−3.2	6.4	20.3		808	100
No task (2)	163	230	419		−0.9	4.3	4.5			
SD	8	3			1.2	1.8				
Reading (1)	177	251	NM	302	−1.6	2.4	NM	−3.9		
Visual task										
Target (2)	136	181	462		−2.1	3.9	23.9		500	98
SD	3	6	28		1.9	0.1	0.9		26	2
Control 1										
Auditory tasks										
Target (2)	99	163	320	91	−11.1	8.3	28.6	−4.5	319	100
SD	0	3	25		2.3	2.7	2.6		4	
Omitted (2)	99	169	554		−12.7	8.6	11.8		485	87
SD	6	6	107		2.8	3.7	0.1		75	7
No task (3)	98	164	368		−7.3	9.6	3.4			
SD	2	8	55		2.3	0.6	1.1			
Reading	ND	ND	ND		ND	ND	ND			
Visual task										
Target	ND	ND	ND		ND	ND	ND		ND	ND
Control 2										
Auditory tasks										
Target (4)	108	144	344	232	−2.3	0.9	21.0	−5.8	490	100
SD	9	16	21		3.8	6.0	2.9		10	
Omitted (1)	106	161	501		−2.1	1.9	14.4		617	100
No task (4)	107	147	336		−1.8	2.7	4.7			
SD	2	5	9		3.6	3.4	1.4			
Reading (1)	103	161	509	NM	−8.3	−1.1	3.7			
Visual task										
Target (2)	114	188	300		2.6	2.9	18.9		355	99
SD	6	16	8		2.3	2.7	0.4		8	1

Measures are of mean and SD during several cognitive tasks described in the Methods. The number of averages comprising the measures is indicated in parentheses in the left-hand column. N1 and P2 were measured at Cz to nontargets; P3 was measured at Pz to targets; PN was measured at Fz. NM = not able to measure; ND = not done; RT = reaction time; Acc = accuracy; PN = processing negativity.

the task (fig. 4D). The amplitude of the sustained negative shift was 3.4 μV, comparable with that found in normals.

Psychoacoustical studies (see Table 4)

Binaural lateralization

Intensity cues. When using simultaneously presented binaural clicks with interaural intensity disparities of >20 dB, the patient correctly lateralized the clicks to the ear with the more intense stimulus. With smaller interaural differences the probability of

TABLE 4. BEHAVIOURAL TEST RESULTS (RIGHT EAR/LEFT EAR)

	Patient		*Controls*	
Stimulus	*Frequency JND (2/89)*			
Test frequency (Hz)	dF	dF/F	dF	dF/F
250	60/86	0.24/0.34	7/10	0.03/0.04
500	71/61	0.14/0.12	13/15	0.03/0.03
1000	85/138	0.08/0.14	10/9	0.01/0.01
2000	679/784	0.33/0.39	40/47	0.02/0.02
4000	385/326	0.09/0.08	62/73	0.02/0.02
8000	1850/1043	0.23/0.13	74/81	0.01/0.01
	Intensity JND (2/89)			
Test intensity 30 dB SL	10/10 dB			3.9/3.9 dB
	Temporal cues			
Binaural tests (3/88)				
Lateralization				
Interaural time[1]	Absent			300 μs
Interaural intensity[2]	>36 dB			7 dB
MLD	Absent			12 dB
Binaural beats	Absent			Present
Monaural tests				
Paired clicks[3] (3/88)	90 ms			2–4 ms
Duration JND (2/89)				
50 ms	30/30 ms			20/30 ms
500 ms	300/200 ms			200/200 ms
Gap detection (12/89)	20–80 ms			2–5 ms
Threshold/duration[4]	40 dB			10 dB
Somatosensory				
Paired shocks[3] (3/88)	50–60 ms			40–60 ms

JND = just noticeable difference; dF/F = frequency shift/standard frequency; MLD = threshold shift when interaural phase changed by 180°. [1] Interaural time disparity to switch lateralization. [2] Interaural intensity disparity to switch lateralization. [3] Time separation for perceiving stimuli as paired. [4] Threshold difference between 10 and 100 ms duration tones.

lateralizing the binaural stimulus changed in a relatively smooth manner: from a probability of 0.1 when left > right by 16 dB to a probability of 0.7 when left < right by 16 dB (fig. 5A). Throughout this intensity range a high proportion of responses indicated that binaural fusion of the clicks had not occurred since she reported clicks on 'both sides'. Bilateral localization was never reported with monaural stimuli. Performance by the sister with normal hearing on the same task showed that lateralization shifted completely from 'left' to 'right' with a 7 dB interaural difference in contrast to the approximately 32 dB interaural difference for the patient. The normally hearing sister never reported 2 images simultaneously.

Time cues. With clicks of equal intensity, the normally hearing sister had a shift of lateralization over a 0.3 ms interaural time change, reporting 'left' when the click to the left ear preceded the click to the right by 0.2 ms and 'right' when the click to the left ear followed the click to the right ear by 0.1 ms (fig. 5B). Fusion of the binaural

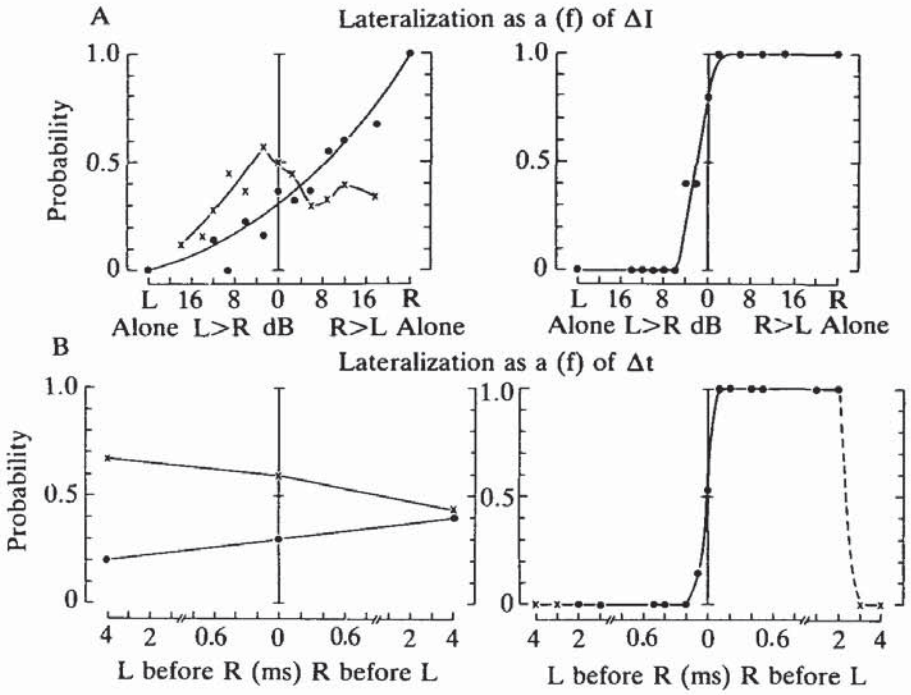

FIG. 5. Lateralization judgements (3/88) based on interaural intensity (A) and time (B) disparities in the patient (*left*) and her sister with normal hearing (*right*). Note the patient's failure to fuse the simultaneously presented binaural signals in A by the frequent report of 'two' clicks (x). For the patient, lateralization using interaural intensity differences was not complete even with a 36 dB difference in contrast to the 7 dB difference required for the sister. The patient's failures of binaural fusion were not altered by introducing interaural time differences over an 8 ms range (B). The ordinate scale for B in the sister does not apply to the report as 'two' (x). With interaural time differences of greater than 2 ms the sister always reported hearing 2 clicks. Report as 'right' (●); report as 'two' (x).

stimuli was lost with interaural time differences of greater than 2 ms and 'two clicks' were reported. In contrast, the patient's probability of hearing either 'two clicks' or localizing a single click was not altered with changes in interaural timing disparities of up to 8 ms (fig. 5B).

Masking level difference

The patient showed no improvement of the masked threshold to a 300 Hz tone when the phase of the signal to one of the ears was reversed 180°. In contrast, the threshold of the normally hearing sister changed by 12 dB with the same procedure.

Binaural beats

The patient reported a 'wiggle' when a physical beat was presented monaurally. No beats were reported when the 2 tones were separated and presented binaurally. In contrast, both physical and binaural beats were discerned by the sister with normal hearing.

Monaural temporal resolution

A time separation of 90–100 ms between clicks was required by the patient to define the presence of 2 stimuli. In contrast, only a 2–4 ms separation was required by the sister with normal hearing for this same discrimination.

Somatosensory temporal resolution

A time separation of 40–50 ms was required by the patient to define the presence of paired stimuli to the median nerve at the wrist and 50–60 ms to the presence of paired stimuli on the skin of the middle finger. Comparable results for the sister were 40–50 ms for both types of stimuli.

Monaural signal duration

Both the patient and controls required comparable increments of duration of a tone burst to recognize it to be different from the 'standard' tone burst. For a 50 ms duration signal, the increment required was 20–30 ms for the patient similar to the mean of 20 ms for the controls; for the 500 ms duration tone the increment required was 200–300 ms, slightly in excess of the mean of 140 ms found in the controls.

Monaural gap detection

The length of the silent period within a tone burst that could be detected ranged between 15 and 20 ms for tones of 25–200 ms duration. When the duration of the tone was reduced below 25 ms, gap detection thresholds rose precipitously to 80 ms for signals of 10, 15 and 20 ms duration and, for signals of 5 ms duration, gap lengths as long as 200 ms could not be detected (fig. 6A). Normal subjects were able to detect silent periods of less than 2 ms for these same duration signals.

Monaural threshold as a function of tone duration

The threshold of a 1000 Hz tone rose 3 dB per halving of signal duration between 300 and 30 ms for both the patient and normals. For signal durations shorter than approximated 30 ms, thresholds for the patient abruptly increased to 20 dB for a halving of signal duration (fig. 6B).

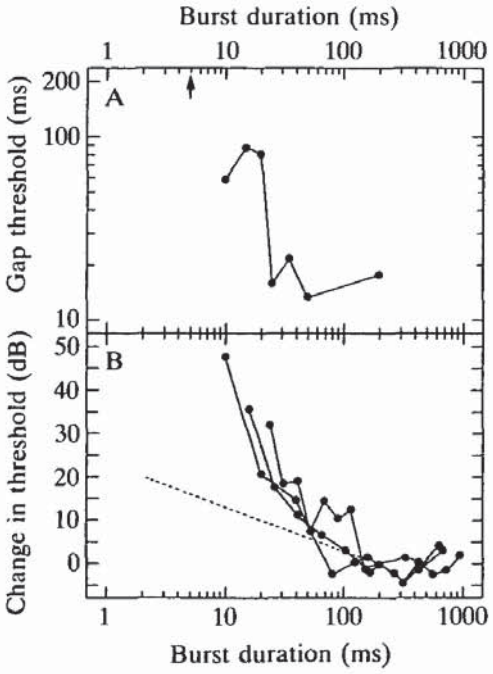

FIG. 6. A, the patient's monaural (right ear) threshold (tested 12/89) for detecting a silent period (gap detection) in a tone burst was approximately 15–20 ms for tones of 25–200 ms duration and increased abruptly to 60–80 ms with tones of 25 ms or less. With signal durations of 5 ms, gaps as long as 200 ms (the upper limit possible with the equipment) were not detectable as indicated by the arrow. B, monaural (right ear) threshold (tested 12/89) for a 1000 Hz tone as a function of signal duration is plotted in solid lines for the patient on 3 separate trials. Typical thresholds from normal subjects are represented by the dashed line. Note that the patients threshold/duration functions deviate from normal when tone duration is less than 40 ms.

Frequency discrimination

The JNDs for pitch were elevated across all frequencies in the patient compared with the controls. The ratio of the absolute change in frequency in Hz divided by the frequency of the standard signal in Hz (DF/F) averaged for both ears showed the patient to require approximately a 3- to 15-fold increase compared with the controls.

Intensity discrimination

The JNDs for intensity were approximately twice those defined for the controls: 10 dB versus 4 dB, respectively. These values were the same at 200, 1000 and 4000 Hz.

DISCUSSION

In this study of a patient with a moderate-to-severe pure tone hearing loss, those auditory evoked potentials (brainstem, middle and long-latency) commonly used to assess the function of the cochlea and the central auditory pathways were absent. Other authors have reported occasional patients in whom auditory brainstem potentials were absent even though the stimuli were clearly suprathreshold (Worthington and Peters, 1980; Kraus *et al.*, 1984; C. Berlin, personal communication; J. Jerger, personal communication). The clinical details of both these patients and the present case are similar (Table 5). The patients first presented as children or young adults. Their audiological functions show a normal to moderate elevation of pure tone thresholds, absent middle ear reflexes, and impaired speech comprehension. Except for the absence or marked abnormality of the auditory brainstem potentials, the patients are neurologically normal. The constellation of these findings suggests a disorder of the eighth nerve and/or brainstem. These results also challenge our assumptions about the relationship between auditory function and evoked potentials.

Auditory brainstem potentials are used as an objective measure of the functioning of the cochlea and brainstem auditory pathway because their appearance correlates well with hearing threshold (Jerger and Mauldin, 1978; Pratt *et al.*, 1985; Kileny and Magathan, 1987). Our patient, and those reviewed above, are exceptions to this rule since they could 'hear' the click and tones employed without having evoked neural components of these traditional tests. In the present study, the failure to record these potentials was associated with an auditory perceptual deficit disproportionately affecting those perceptions dependent on temporal features of the acoustic signal. This finding bears on the suggestion by Worthington and Peters (1980) that 'the ABR is generated by only a portion of the auditory system'. The discussion will focus on the relationship between auditory evoked potentials and auditory perceptual capacities.

Evoked potentials

In this patient, a particular group of auditory evoked potentials was absent—auditory brainstem, middle and long-latency neural components—which reflects the responsiveness of the auditory system to 'transient' features of acoustic signals (Picton *et al.*, 1974). These tests were repeated three times over a 2-yr period and the absence of potentials is unlikely to be a technical error. The amplitude of the 'transient' type of evoked potential is directly related both to the rate at which signal intensity changes (rise and fall-times)

TABLE 5. AUDIOMETRIC TEST RESULTS (dB HL re ANSI) IN PATIENTS WITHOUT AUDITORY BRAINSTEM EVOKED POTENTIALS (RIGHT EAR/LEFT EAR)

	Case[1]	*Case*[2]	*Case*[3]	*Case*[4]	*Case*[5]
Age of onset (yrs)	7	17	2	5	18
Sex	F	M	M	F	M
Audiogram (Hz)					
250	35/50	65/55	25/15	15/55	NT/NT
500	40/55	70/45	10/10	60/35	25/25
1000	45/50	70/60	5/10	85/60	25/25
2000	35/25	65/65	5/5	80/55	25/25
4000	60/40	60/70	10/5	95/55	25/25
8000	50/65	65/65	15/5	90/NR	NR/NR
SRT (dB HL)	50/40	24/30	10/10	25/70	NT/NT
WDS (%)	36/0	0/0	80/80	2/3	65/65
Acoustic reflex	Absent/ Absent	Absent/ Absent	Absent/ Absent	Absent/ Absent	Absent/ Absent
Tympanometry	NT/ NT	Normal/ Normal	Normal/ Normal	Normal/ Normal	Normal/ Normal

SRT = speech reception thresholds; WDS = word intelligibility score; NT = not tested; NR = no response. [1] Test results obtained on 2/88 (Table 1) for our patient. [2] A 19-yr-old male with severely reduced speech discrimination. No ABR found; a broad slow positive wave was noted between 250 and 300 ms post stimulus for both click and tone pips (Case 3, Worthington and Peters (1980) with additional information obtained from Dr Worthington). [3] A 6-yr-old male with language delays from age 2 yrs. No ABR components were observed below 45 dB HL (Case 2, Worthington and Peters (1980) with additional information obtained from Dr Worthington). [4] A 14-yr-old female with a normal neurological examination and normal CT. No ABRs or middle-latency auditory evoked potentials (Case 4, Kraus *et al.*, 1984). [5] A 20-yr-old male with difficulty understanding speech. No ABRs found. A normal slow vertex potential was defined (Case 2, Hildesheimer *et al.*, 1985).

and to the final intensity (Onishi and Davis, 1968; Hecox *et al.*, 1976; Salt and Thornton, 1984). These potentials are time-locked to the onset of the acoustic signal and, if the signal is sufficiently long, to its offset, but not to the steady unchanging portions of the signal (Onishi and Davis, 1968). It is important to recognize that these three evoked potentials are used in the clinical setting to assess both the peripheral and central portions of the auditory pathway without wide appreciation that they actually define the function of only a particular portion of the auditory system, that is, that dealing with responsiveness to rapid stimulus change. Moreover, in our patient the definition of normal amplitude cochlear microphonics when neural components of the evoked potentials, including wave I of the ABR, were absent, provide evidence that receptor hair cell function was most likely preserved, whereas neural activity beginning with the eighth nerve was impaired.

There are other auditory evoked potentials that are also sensitive to rapid stimulus change such as (1) the frequency following response (FFR) evoked by low-frequency signals consisting of components that reproduce the stimulus waveform (Moushegian *et al.*, 1973); and (2) the 40 Hz middle-latency potentials which have their dominant spectral energy at the stimulus repetition rate (Galambos *et al.*, 1981). The FFR was not present in our patient; however, it is often difficult to record in normal subjects (Moushegian *et al.*, 1973) and thus its absence cannot be used to help in the understanding of auditory function in this patient. The 40 Hz middle-latency response was not tested but the standard middle-latency components to 10/s stimulation were absent.

There is another type of auditory evoked potential recorded from the scalp that is sensitive to the unchanging aspects of an auditory stimulus. It is characterized by a sustained negative voltage shift which is maintained for the duration of the acoustic stimulus (Picton *et al.*, 1978). Such sustained potentials have also been recorded directly from the cortex of experimental animals (Gumnit, 1960) and probably represent maintained depolarization of neurons in auditory cortex. Recently, sustained magnetic fields accompanying steady-sound stimulation have been identified in humans as originating from temporal lobe (Hari *et al.*, 1987). The presence of sustained potentials in our patient provides objective evidence of the preservation of auditory cortical processes sensitive to maintained acoustic stimulation.

There are also components of auditory evoked potentials that reflect cognitive activities of the subject rather than sensory features of the stimulus and have thus been labelled 'cognitive' or 'endogenous' components (Hillyard *et al.*, 1978). The patient demonstrated several of these cognitive components while discriminating between two notes. These included a vertex positivity to the target stimuli occurring at a latency of approximately 500 ms, the P300 (Donchin, 1981), and a frontal negativity occurring during attention to the auditory signals (Näätänen, 1982). The amplitude of the P300 was comparable with normals but its latency in both the auditory and the visual target detection tasks was delayed. A P300 component was also elicited during the detection of an infrequent omission of regularly presented stimuli (Michalewski *et al.*, 1982) with a latency comparable with normals. These findings suggest some alterations in the speed of stimulus classification in the patient that are independent of stimulus modality. In keeping with this interpretation was the finding of slowed RTs in the patient compared with normals in both the visual and auditory target-detection tasks.

Auditory nontargets also elicited components (N160, P240) when sensory components of the long-latency evoked potentials collected when the patient was asleep were absent. The N160 and P240 components in the patient have features that are characteristic of endogenous or cognitive components rather than of exogenous or sensory components. First, the N160/P240 components fluctuated considerably in latency between averages even though the evoking stimuli were identical, whereas the N100/P200 components in normals are of relatively constant latency if the stimuli are of constant intensity (Michalewski *et al.*, 1986). Secondly, the N160/P240 are largest in the midline parietal region whereas the N100/P200 components are normally of largest amplitude centrally. Finally, the N160/P240 components were only present when the patient was awake and involved in a cognitive test. In contrast, in normals, the N100/P200 components are only slightly affected by state of arousal. Studies in normal subjects have suggested that cognitive or endogenous components of the auditory evoked potentials in normal subjects can appear as early as 130 ms (Ford and Hillyard, 1981) and peak at approximately 165 ms (Goodin *et al.*, 1978), values that are comparable with the latencies defined for the frontal negativity and the N165 in our patient.

The results of these evoked potential studies are compatible with the patient having a deficit in neural responsiveness to rapid temporal (transient) features of the acoustic stimulus, but preservation of responsiveness to other features such as maintained stimulation. Furthermore, during the performance of auditory discrimination tasks there is electrophysiological evidence of preserved cognitive processes dependent on cortical activity. The patient's deficit appears to involve neural elements in the peripheral portions

of the auditory pathway, the eighth nerve, while sparing hair cells in the cochlea, and the cortical portions of the auditory pathway.

Auditory perceptual deficits

The patient was profoundly impaired in using temporal cues of the acoustic signal for perceptual judgements in contrast to those perceptions dependent on intensity or frequency information. Thus lateralization judgements using interaural time or intensity differences were absent or markedly impaired, whereas lateralization of binaural signals in patients with a cochlear type hearing loss is relatively unaffected (Häusler *et al.*, 1983). Lateralization abilities depend on binaurally sensitive neurons in the brainstem auditory pathway which are differentially responsive to stimuli as a function of the temporal relationship of neural inputs from the two sides (Galambos *et al.*, 1959; Goldberg and Brown, 1968). Interaural time differences are encoded by a delay in the neural input from one cochlea relative to the other. Interaural intensity differences for transient stimuli may be accompanied by differences in the latency of inputs to binaurally sensitive cells and can thus be considered as another example of a temporal code. We can use the binaural temporal code with precision, detecting interaural time differences of 10−20 μs and intensity differences of 0.5 dB by shifts in the intracranial localization of the image (Jeffress and McFadden, 1971). The patient's failure at integrating the temporal aspects of binaural signals was evident by her inability to form a single image on many of the trials and instead reporting that she heard 'two clicks'. She was also unable to hear binaural beats or to show a change in masked threshold of a low-frequency tone as a function of interaural differences in phase. Both these tasks also depend on the proper utilization of interaural differences in the timing of neural inputs (Wernick and Starr, 1968). In contrast, masking level difference effects on threshold have been reported as 'nearly normal' in patients with cochlear type hearing loss (Durlach *et al.*, 1981).

It is likely that the deficits in the use of binaural timing cues are secondary to a fundamental disorder of monaural encoding of temporal features of the acoustic stimulus. The patient required almost a 100 ms separation between monaurally presented paired clicks to distinguish that 2 stimuli were present. Normally, such a distinction is apparent with a time separation of approximately 2 ms (initially described by Exner (1875) and confirmed by Hirsh and Sherrick (1961)). The detection of a brief interruption of a tone or noise signal (gap detection) has also been used to measure temporal recovery functions of the auditory system (Plomp, 1964; Abel, 1972). The patient required almost a 10-fold increase in the silent period compared with normals with tones of moderate length (20 ms vs 2 ms). Gap detection thresholds increased to 80 ms when signal duration was reduced below 25 ms. The magnitude of the disordered gap detection in this patient far exceeds that encountered in patients with the usual cochlear type hearing loss (Tyler *et al.*, 1982). The marked impairment of monaural timing is consistent with our patient's poor speech and word comprehension that was disproportionate to the extent of her pure tone hearing loss. Phonemes comprise rapid changes of signal frequency that are characteristic for the junction between consonants and vowels (Umeda, 1975; Klatt, 1976). It is of interest that the patient had particular difficulty distinguishing words differing in their vowels and could more easily distinguish words based on their high-frequency consonants. The latter ability is usually severely impaired in patients with

cochlear type hearing loss. An additional reflection of the patient's impaired processing of temporal features of acoustic signals was the steep rise in intensity needed for detection at threshold as the duration of the signal was shortened.

In contrast to the loss or marked impairment of auditory percepts dependent on temporal cues which were out of proportion to the changes in threshold, those percepts utilizing frequency or intensity features were less affected. The appreciation of an intensity difference between 2 tones required 5 dB more for the patient than for the controls. In contrast, patients with cochlear type hearing loss have an enhanced ability above normal to detect small increments in intensity, that is ≤ 1 dB (Jerger *et al.*, 1959; Turner *et al.*, 1989). Thus the evidence, with regard to intensity discrimination, is that our patient performed slightly poorer than normals and very differently from patients with a cochlear type hearing loss. With regard to frequency discrimination, the patient required approximately a 10-fold greater change of a test tone's frequency than did the controls to distinguish it from the 'standard' tone. The extent of this change is similar to that found in some patients with a cochlear type hearing loss (Tyler *et al.*, 1983).

Not all perceptions requiring the utilization of temporal cues were impaired. The patient demonstrated relatively normal temporal integration during the estimation of signal duration. Freyman and Nelson (1987) reported that in subjects with cochlear hearing loss, difference limens for duration were poorer (requiring greater stimulus duration increments) for long-duration tones than for short-duration tones as compared with a normal control group. To evaluate generalized rapid temporal processing in our patient we tested the somatosensory system in a manner similar to that used for the auditory system (distinguishing paired stimuli to the median nerve); the patient did not differ significantly from our control, indicating that the disorder of temporal processing was restricted to the auditory system. Tanaka *et al.* (1987) studied a patient with the syndrome of pure word deafness following bilateral lesions of the auditory cortex who had marked impairment in the use of temporal cues for auditory processing similar to our patient. However, in contrast to our results, Tanaka's patient also had a generalized defect in temporal resolving abilities, being deficient in the visual and somatosensory modalities as well.

Mechanisms

A disorder of the peripheral part of the auditory system at the cochlea and/or the eighth cranial nerve principally affecting the temporal precision of the neural coding and/or its transmission centrally could account for the loss of auditory percepts dependent on temporal cues and those evoked potentials sensitive to acoustic transients. There was much less of an effect on other auditory perceptual processes such as the distinction between the frequency of 2 tones, the intensity of 2 signals, and the duration of 2 signals. Moreover, those auditory evoked potentials not dependent on timing cues, such as the sustained negativity accompanying steady acoustic stimulation or those components associated with cognitive processing, were preserved. We propose that the site of the disorder is likely to be in the eighth nerve or at the synapse between the hair cell and eighth nerve since cochlear microphonics were present without accompanying signs of neural activity.

The synapse between hair cells and eighth nerve dendrites functions to preserve temporal cues of acoustic signals by its ability to regulate the timing of eighth nerve

discharges precisely. Thus eighth nerve fibres discharge to low-frequency signals (e.g., up to 3000 Hz) during only one phase of the stimulus waveform and then only to a restricted portion of that wave (Rose *et al.*, 1967). Eighth nerve fibres arising from the basal or high-frequency portions of the basilar membrane sensitive to high frequencies, preserve temporal cues by their precise latency of discharge to the onset of transient stimuli (Kiang *et al.*, 1965).

A disorder of this synapse could affect the precision of eighth nerve fibre discharges. Myasthenia gravis provides an example of the effects of a synaptic disorder on temporal processes. In this disease, the postsynaptic membrane is abnormal due to the accumulation of antibodies at receptor sites (Lindstrom and Lambert, 1978). Normally, all the muscle fibres innervated by the same motor axon discharge within about 50 μs of one another (Stålberg *et al.*, 1971). In contrast, in myasthenic subjects, the discharge of individual muscle fibres innervated by the same axon are temporally dispersed, resulting in a time separation or 'jitter' of up to several hundred microseconds between similarly innervated muscle fibres (Stålberg *et al.*, 1976). A disorder of the synapse between hair cells and eighth nerve dendrites might result in an 'abnormal' temporal dispersion of the timing of eighth nerve discharges similar to that encountered in muscle fibres of myasthenics and thereby account for alterations of those percepts and evoked potentials dependent on temporal cues. Moreover, although the timing of discharge may be altered, transmission still occurs accounting, perhaps, for the relative preservation of information useful for other kinds of perception (i.e., pitch, intensity, duration). The locus of the synaptic disorder need not be at postsynaptic receptor sites, as in myasthenia gravis, but could be presynaptic affecting the release of transmitter and still account for alterations in the timing of eighth nerve fibre discharges.

An example of how temporal 'jitter' can affect evoked potentials was assessed using the cat's auditory brainstem potentials. We simulated 'jitter' in the timing of nerve impulses by introducing small shifts in the occurrence of the click stimuli relative to the averaging process. Usually click stimuli are presented at a fixed delay after the average is initiated to time-lock the evoked potentials to the averaging process. By introducing a variable delay of the click relative to the onset of averaging, the evoked potential components would have a changing temporal relation to the averaging process. In this example of 'jitter' (fig. 7), clicks were presented over a 1 ms period beginning 3 ms following the onset of the average. The brainstem components were effectively abolished whereas the slow potential on which the components arise was preserved, confirming that temporal 'jitter' effectively attenuates the amplitude of the fast neural components of this type of evoked potential. Since a slow potential was also not evident in the patient's ABR, the temporal dispersion may have been even more extensive resulting in the absence of even this slow wave. Alternatively the absence of the slow potential may be due to the high-pass recording filter being set at 100 Hz leading to the attenuation of this slow potential.

The proposed disorder of synaptic function may be related to the differentiation of the auditory periphery into two systems. The ganglion of the auditory nerve consists of two cell types: type I cells comprise 95% of the population and innervate inner hair cells; type II cells comprise 5% of the population and innervate outer hair cells (Spoendlin, 1969). The distribution of the dendrites of these two cell types within the cochlea differs such that several type I fibres make synaptic connections to a single inner hair cell whereas

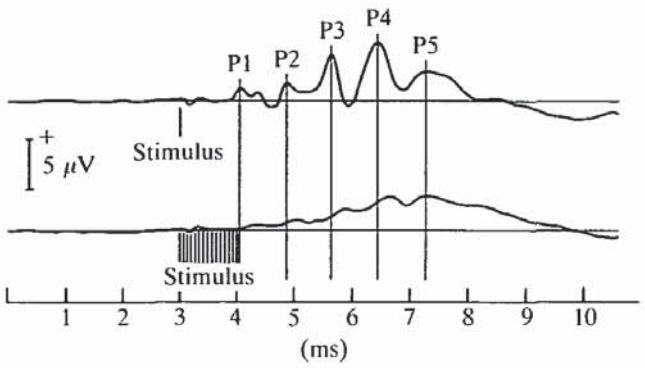

FIG. 7. The effects of temporal 'jitter' on the amplitude of auditory brainstem potentials obtained from a cat. In the top average all the stimuli were presented 3 ms after the onset of the average. In the bottom average the clicks were evenly dispersed over a 1 ms interval, beginning 3 ms after the start of the average. Note the marked attenuation of the components of the ABR accompanying the 'jitter' with the preservation of the slow potential shift. The components are labelled by their polarity at the vertex electrode (P for positive) and their approximate latency in ms. The recordings were made between the vertex referenced to the frontal sinus.

a single type II fibre makes synaptic connection to many outer hair cells (Brown, 1987). The physiological significance of this difference is not known. However, as Lim and coworkers (Lim, 1969; Lim and Anniko, 1985) have suggested, this arrangement could allow for differences in the encoding of auditory cues. Type I fibres are well situated for the preservation of timing cues with several different type I fibres making synaptic connection to just one inner hair cell, thus favouring a relative synchrony of discharge amongst those neurons. In contrast, each type II neuron establishes connections to many outer hair cells which differ from the outer hair cells receiving connections to other type II neurons. The separate connectivities of type II neurons make temporal synchrony between type II cells unlikely. Unfortunately, only a little is known about the functional differences between these two cell types (Patuzzi and Robertson, 1988). The finding of normal cochlear microphonics in our patient is evidence that the outer hair cells are probably preserved since they are the presumed principal generators of this receptor potential. The status of the inner hair cells and the type I fibres cannot be directly assessed. It is the loss of both temporally dependent auditory perceptions and neural components of auditory evoked potentials sensitive to temporal cues that suggests to us that the patient may have a defect of inner hair cell-type I/eighth nerve system as the basis for the auditory impairments.

Generalizations derived from a single case study must be viewed cautiously. However, the results from this patient provide new insights into the auditory and neural bases of auditory evoked potentials by emphasizing the importance of timing information for the generation of certain evoked potentials. The relevance of temporal cues for both evoked potentials and temporal integration has also been noted in patients with multiple sclerosis in whom abnormalities of particular components of the auditory brainstem potentials are accompanied by alterations in lateralization judgements dependent on binaural timing cues (Van der Poel *et al.*, 1988). The mechanism we have suggested to account for the patient's deficits, for example, a disorder of the precision of temporal encoding in the eighth nerve, may also be relevant for understanding other types of

'central' hearing impairment. There is relatively little information available regarding pitch, loudness and temporal auditory processing in patients with disorders of hearing. The results from the patient of this report suggest that these percepts may be differentially affected. The quantification of temporal, frequency and loudness perceptual abilities may be important to classify further and to understand some of the mechanisms underlying the different types of hearing disorders.

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ADDENDUM

Acoustic emissions were recorded from a microphone in the right ear canal to click stimuli at intensities as low as 58 dB SPL. The patient's perceptual threshold for these same click stimuli required intensities of at least 80 dB SPL. The left ear could not be tested because of the presence of a ventilation tube in the tympanic membrane. This finding supports the interpretation that the outer hair cells are preserved in this patient.

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