Intraoperative Round Window Recordings to Acoustic Stimuli From Cochlear Implant Patients

Baishakhi Choudhury, MD, **Douglas C. Fitzpatrick, PhD**, **Craig A. Buchman, MD**, **Benjamin P. Wei, MD, PhD**, **Margaret T. Dillon, AuD**, **Shuman He, MD, PhD**, and **Oliver F. Adunka, MD**
Department of Otolaryngology/Head and Neck Surgery, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Abstract

Hypothesis—Acoustically evoked neural and hair cell potentials can be measured from the round window (RW) intraoperatively in the general population of cochlear implant recipients.

Background—Cochlear implant performance varies greatly among patients. Improved methods to assess and monitor functional hair cell and neural substrate prior to and during implantation could potentially aid in enhanced non-traumatic intracochlear electrode placement and subsequent improved outcomes.

Methods—Subjects (1–80 years) undergoing cochlear implantation were included. A monopolar probe was placed at the RW after surgical access was obtained. The cochlear microphonic (CM), summating potential (SP), compound action potential (CAP), and auditory nerve neurophonic (ANN) were recorded in response to tone bursts at frequencies of 0.25 – 4 kHz at various levels.

Results—Measurable hair cell/neural potentials were detected to one or more frequencies in 23 of 25 subjects. The greatest proportion and magnitude of cochlear responses were to low frequencies (<1000 Hz). At these low frequencies the ANN, when present, contributed to the ongoing response at the stimulus frequency. In many subjects the ANN was small or absent while hair cell responses remained.

Conclusions—In cochlear implant recipients, acoustically evoked cochlear potentials are detectable even if hearing is extremely limited. Sensitive measures of cochlear and neural status can characterize the state of hair cell and neural function prior to implantation. Whether this information correlates with speech performance outcomes, or can help in tailoring electrode type, placement or audiometric fitting, can be determined in future studies.

Keywords

Cochlear Implant; Cochlear Electrophysiology; Hearing Preservation; Electrocochleography; Intraoperative monitoring; Auditory Nerve Neurophonic; Cochlear Microphonic

Correspondence: **Oliver F. Adunka, MD**, Associate Professor, Otology, Neurotology, Skull Base Surgery, Department of Otolaryngology/Head and Neck Surgery, University of North Carolina at Chapel Hill, POB, 170 Manning Drive, CB# 7070, Chapel Hill, NC 27599-7070, Phone: (919) 966-3342, Fax: (919) 966-7656, adunka@med.unc.edu.

INTRODUCTION

Speech recognition with cochlear implants remains quite variable among patients and different factors affecting outcome have been postulated (1–3). Examples of relevant factors include pre-implantation residual hearing (4,5), age of onset and duration of hearing loss (4–6), and patterns of intracochlear electrode placement (7–10). A factor often considered important is neural survival. Although not all studies agree, it is widely assumed that cochlear implant performance relies on the number, distribution and viability of neural elements (11–18). Unfortunately, actual nerve survival and function has been difficult to estimate prior to implantation. One possible approach is to use cochlear electrophysiological responses to sound stimuli, called electrocochleography (ECoG) (19–22). Different components of the ECoG waveforms provide information about different cochlear structures. The cochlear microphonic (CM) is primarily an outer hair cell response, and represents the current flow through the mechanoelectric transducer channels in the stereocilia (23,24). The summating potential is generally considered an inner hair cell response at low intensities and a mixed response from inner and outer hair cells at high intensities, and represents the sustained depolarization in the hair cell body during sound presentation (25–28). The compound action potential (CAP) is derived from nerve fibers, and represents the sum of the well-timed responses to the onsets and offsets of sounds (29–32). For this study ECoG potentials were measured from the round window (RW) of subjects at the time of cochlear implantation. There were two goals. One goal was to determine if high-quality measurements of each ECoG potential could be obtained from cochlear implant recipients, so that the differential survival of hair cell and neural elements could be estimated. The second was to introduce an additional ECoG measurement that can provide information about temporal processing capabilities of the auditory nerve. This potential is the auditory nerve neurophonic (ANN), which represents the phase-locked responses of auditory nerve fibers (33). Temporal information derived from phase-locking is used for critical auditory functions such as sound localization based on interaural time differences, noise reduction based on interaural correlation, and pitch perception based on spike intervals. Deficits in temporal processing represent a major category of impairment in auditory neuropathy spectrum disorder.

The ANN has been described in animals but has not been used in human ECoG recordings, as far as we are aware. In animals, it has been recorded from the RW (34,35) or from electrodes placed directly on the auditory nerve (33,36,37). It is an ongoing response that follows the waveform of a tonal stimulus, and thus can be separated from the CAP, which occurs only at stimulus onset and offset. It can be isolated from the CM, which is also present while the sound is on, by alternating the phase of stimulus presentation, as shown in Fig. 1. The top row, labeled "Stimulus", shows the sinusoidal waveforms of a tone burst alternated at 180° (Condensation and Rarefaction). In each case the RW recorded response waveform would consist of both the CM and ANN, since both hair cell and neural responses follow the waveform of the tone. However, the auditory nerve fibers only respond to the positive half of each cycle of the tone, shown in the waveforms in the second row (labeled "Rectified Nerve Response"), and this positive-only rectification causes harmonic distortion not present in the CM. If the responses to both phases are averaged (alternating phase response) the CM is removed, but because of the positive only rectification, the ANN is present at twice the stimulus frequency, as shown in the bottom row (labeled "Alternating Response") (34). The ANN is the auditory nerve analogue of the frequency following response (FFR), which is the phase locked activity of brainstem nuclei (38). For this study, we measured ECoG potentials, including the ANN, intraoperatively from the RW of cochlear implant patients to tone bursts of varying frequency.

MATERIALS AND METHODS

The procedure was to record responses from the RW of all cochlear implant recipients to acoustic stimuli intraoperatively prior to electrode array insertion. Twenty-five subjects were included. The procedures were in accordance with the ethical standards of the institution's IRB and informed consent was obtained for all subjects enrolled (Protocol number 05-2616).

Human Subject Inclusion Criteria

All pediatric and adult subjects undergoing cochlear implantation were potential participants. The IRB for this study did not permit consent through an interpreter; so non-English speaking patients were excluded, as were patients without an external auditory canal, those undergoing revision surgery, or those with malformed cochlear anatomy.

Surgery and Recording Set-up

After induction, a foam insert attached to a sound tube was placed in the external auditory canal of the ear being implanted. A sterile disposable monopolar probe (Neurosign, Magstim Co., Wales, UK) served as the active input for recordings, a surface electrode on the contralateral mastoid was the return and the common was a surface electrode on the glabella. A standard transmastoid facial recess approach was used to access the promontory. The bony overhang was removed and the monopolar probe was placed on the membranous portion of the window. Figure 2 is an intraoperative photograph demonstrating recording electrode placement. The Bio-logic Navigator Pro (Natus Medical Inc., San Carlos, CA) was used to generate acoustic stimuli and make all recordings using the AEP hearing diagnostics software. Impedance measurements were obtained and saline was added if impedance was greater than 16k Ohms.

Sound Stimulation and Evoked Potential Recording

Recordings from the RW in response to 500 repetitions of alternating phase tone bursts were obtained. Tone bursts had 1–4 ms rise and fall times shaped by a Blackman window and a 10 ms plateau for the higher frequencies of 1, 2 and 4 kHz, and 28 ms for the lower frequencies of 250, 500 and 750 Hz. Sound was delivered through Etymotic speakers calibrated to normal hearing level (nHL). Typically, the series of frequencies was first tested at 90 dB nHL. Then, a frequency with a good response (typically 500 Hz) was used for a level series (decreasing from 90 dB nHL in 5 – 10 dB steps). Recordings with the sound tube crimped were taken at 90 dB nHL at each frequency to estimate electrical artifact, if any. A stimulating rate of 23.3 Hz was used for the lower frequency tones and a rate of 29.3 Hz was used for the higher frequencies. Recordings were started 4 ms prior to stimulus onset and the recording epoch was 32 ms for each stimulus. The sampling rate was 8,000 Hz for the 0.25–1 kHz and 16,000 Hz for the 2 and 4 kHz stimuli. Filters were high-pass at 10 and low-pass at 3,000 Hz or 5,000 Hz. Artifact rejection was set to 47.50 µV and the acoustic delay accounted for was 0.8 ms. It routinely took less than 10 minutes to administer the intraoperative recording protocol used in the study.

Data Analysis

The data from condensation and rarefaction phases was stored separately. A difference curve was determined by subtracting the response to the condensation from the rarefaction phase, and an "alternating" curve was determined from the average. The spectrum of each signal was obtained from the fast Fourier transform (FFT). To avoid contributions from the CAP, windowing was used prior to calculating the FFT (5–25 ms for low frequencies and 5–15 ms for high). A response at the signal frequency or one of its harmonics was considered significant if the magnitude of the peak in question exceeded the noise level by three

standard deviations. The noise and its variance were determined from six bins, three on each side of the signal starting two bins away from the peak.

RESULTS

Measurable potentials to sound were obtained in 23 of 25 subjects. The two without measurable potentials, and six subjects excluded for clear technical reasons for unsuccessful recordings, will be described later. Information about the 25 subjects is given in Table 1. Figure 3 shows a typical recording to a 500 Hz tone at 90 dB nHL. At this intensity there is considerable distortion in waveforms, also visible as additional peaks in the spectrum (Fig. 3B). The spectrum shows that the distortion appears at 1 and 2 kHz, the first two even harmonics of the stimulus frequency (500 Hz). Taking the difference between the two waveforms (Fig. 3C) removes most of the distortion yielding a single peak at the stimulus frequency in the spectrum (Fig. 3D). Averaging the waveforms (Fig. 3E, called alternating) removes the energy at the stimulus frequency as the alternating phase makes this energy sum to zero when added, yielding a residual response at twice the stimulus frequency. This residual response is labeled the ANN, because our interpretation is that its represents the rectified phase-locking to low frequencies from the auditory nerve (Fig. 1). Evidence that the distortion is due to asymmetry in the waveform, such as can be caused by rectification, is that only even harmonics are present (39,40).

Responses Across Frequency

The magnitude of response at the stimulus frequency was obtained from the FFT analysis of the difference plot (e.g., Fig. 3D). This energy contains the entirety of the CM and that proportion of the ANN that is at the stimulus frequency. Note that the ANN can either add to or subtract from the size of the difference peak depending on if the two sources are in or out of phase. Figure 4A shows the percent of subjects that had a significant peak (see Methods) in the FFT of the difference curve to each frequency. A greater percentage of subjects had significant responses at 250–1,000 Hz compared to 2,000–4,000 Hz. Also, most subjects showed the largest response to lower frequencies. The magnitudes of the response at each frequency, normalized to the maximum for each subject, declined over the frequency range (Fig. 4B). Some subjects did have maximal responses to frequencies other than 250 Hz - four showed the maximal response to 500 Hz, three to 750 Hz, and one to 2,000 Hz.

Response Thresholds

For most subjects (n=21) we obtained an intraoperative threshold for the difference and alternating curves from a level series at a single frequency. In Fig. 5, we compare these intraoperative thresholds to the preoperative audiogram threshold at the frequency used for the level series. For the thresholds from the difference curves (Fig. 5A), six of the subjects had RW thresholds within 10 dB of the audiogram threshold (dashed lines) and nine of the patients had difference thresholds >10 dB higher than the behavioral audiogram. Somewhat surprisingly, six had difference thresholds that were >10 dB lower than those in the audiogram.

Figure 5B compares intraoperative thresholds from the alternated curves with the preoperative audiogram thresholds. Of the 21 subjects, all but one had intraoperative thresholds that were the same or >10 dB higher than that determined by preoperative audiogram. There were four subjects that had no detectable ANN to the highest level tested, 90 dB nHL (asterisks), though each of these four did have significant responses in the difference curves (Fig.5A). Of these four, three had thresholds >100 dB HL in the audiogram. Thus, the thresholds from the alternating curves were in general less sensitive to the audiogram threshold than were thresholds from the difference signal. These results mean

that for some cases the sensitivity of intraoperative measures of hair cell function was greater than the behavioral sensitivity, suggesting the presence of surviving hair cells not connected to auditory nerve fibers, which can be interpreted as a form of auditory neuropathy. An example from one case where the difference response had lower threshold than the ANN is indicated by the arrows in Figs. 5A and B, and further illustrated in Fig. 6. In Fig. 6, a robust response in the rarefaction and difference curves was evident, but there was no response in the alternating curve. In addition, there was no CAP in the alternating curve. The CAP was small or absent at other frequencies as well, as was the ANN. Thus, in this subject, as was true in other cases where the difference curve showed a lower threshold than the audiogram, the neural potentials were attenuated compared to the hair cell potentials, which may be indicative of pathology in the synapses onto the auditory nerve dendrites or of the auditory nerve itself. This condition would be similar to an auditory neuropathy (see Discussion). There is one final case that is also interesting. In this subject, the RW responses were significant only to higher frequencies and the level series was taken at 2 kHz. There was no ANN, but a large CAP was present. This combination indicates the presence of neural responses that could support the hearing threshold, but the neural responses are to frequencies above the phase-locking range of the auditory nerve and therefore no ongoing neural response is seen.

In general, the CAP was small or absent to the 250 Hz stimulus, which was typically the frequency with the best response. When present, the CAP thresholds were typically 10 dB or more higher than the ANN thresholds.

Summating Potential

A summating potential (SP), or envelope response, was often present in the alternating curves. An example of a subject with a strong SP is shown in Figure 7. The SP began at 500 Hz and was present at all higher frequencies. The ANN was attenuated at 2,000 Hz, and absent at 4000 Hz.

Additional subject information

Table 1 summarizes the age, sex, frequency with lowest behavioral threshold prior to implantation, and hearing loss etiology of the 25 subjects included in this study. The two subjects that did not show a measureable response are depicted in italics. One of these underwent radiation therapy for a nasopharyngeal carcinoma, and a total lack of cochlear function was expected. The other was a case with sickle cell disease, and since some hearing was detected in the preoperative audiogram, responses were expected from the recording. The reason for no response in this case is not clear. Six additional subjects had clear technical reasons for a lack of response and were not included. One of these had a surface electrode dislodge, two had large amounts of artifact that were consistently found in a particular operating room, two others were due to kinking of the sound tube resulting in no sound delivery, and one was excluded because the cochleostomy was made prior to recording, a breach in the protocol.

DISCUSSION

The major results were 1) measureable cochlear potentials were found in 23 out of 25 tested subjects, 2) most subjects showed the largest potentials to low frequencies (<1000 Hz), 3) along with the CM, SP and CAP, the ANN is a component of ECoG potentials at low frequencies, and 4) many subjects showed evidence of differential neural and hair cell pathology.

Prevalence of Cochlear Potentials in Cochlear Implant Subjects

The aim of the study was to generate ECoG data from recordings at the RW of the general population of cochlear implant recipients, in order to determine the presence and characteristics of acoustically evoked potentials, if any. The hypothesis was that because most patients have at least some residual hearing, potentials would be present. However, the percentage of patients undergoing cochlear implantation that would have measurable potentials was unknown. Obtaining a measurable ECoG potential in 23 of 25 subjects to at least one frequency was an unexpected and interesting result given that the preoperative audiograms of many subjects showed severe-profound hearing loss at all frequencies. Even subjects with audiogram thresholds >100 dB HL typically showed measurable responses (CM and ANN) at 90 dB nHL. In a recent study, Harris et al. (21) reported measurable ECoGs in 11 of 16 cases, excluding five cases that failed for technical reasons. Similarly, six of six patients showed ECoG responses pre-implantation in a study by Radeloff et al. (20). Taken together, these results show that the functional status of remaining hair cells and nerve fibers in individual patients is measureable, which may in turn be useful for determining cochlear trauma during surgery, predicting the success or failure of electrical hearing outcomes, and audiometric fitting. Whether the degree of functional connections between hair cells and neural elements is proportional to the survival of neural elements that can be electrically stimulated is a hypothesis that may prove true for at least some etiologies of hearing loss, as can be determined from further studies.

Hair Cell and Neural Potentials

The ECoG is typically considered to consist of the CM, CAP and SP, which can be separated through windowing and filtering the raw signal. However, animal studies have shown that the RW response to low frequencies is a mixture of the CM and ANN (34,35,41,42). In this study, we have shown that the same is true in human subjects. The presence of the ANN results in one source of the distorted ECoG waveform compared to the tone burst stimulus. The distortion arises from the auditory nerve contribution to the recorded response, which is a rectified version of the stimulus waveform (Fig. 1). The presence of predominantly even harmonics of the stimulus frequency indicates that rectification is responsible for the distortion (39). In animals, evidence that the ANN is due to neural responses is that the distortion largely disappears after administration of drugs that block sodium channels (34) and it is subject to forward masking (35), which the CM is not. Thus, the presence of mixed hair cell and neural sources in RW responses to low frequencies seems clear.

The ANN provides useful information about temporal processing as will be further discussed below. However, its presence represents challenges in analyses of human ECoG potentials that have not been previously considered. When a pure tone is synthesized and rectified, there is energy at the stimulus frequency as well as at the second harmonic. Thus, the estimate of the ANN magnitude from the alternating stimulus, which isolates the distortion, only captures a portion of the total energy from the neural response. Determining the actual magnitude is not straightforward because the relative phases of the CM and ANN will affect the measured magnitude of the potentials. While the phases of all the signals are measureable, because these are evoked potentials the sources can vary in location with frequency, so the analysis is more complicated than can be considered here. Chimento and Schreiner (1990) used forward masking to separate the CM from the FFR (40). The FFR is similar to the ANN but its source is phase-locking in the brainstem rather than the auditory nerve. Complicating this procedure is that the intensity where the neural response can be fully masked is difficult to know in cases of hearing loss, and intraoperative recording time does not permit testing at many different frequency/intensity combinations.

A possible further confound to the analysis is rectification that occurs in the CM. At high stimulus levels, the CM can rectify because the resting position of the hair bundle is displaced in the direction of closed rather than open channels (43). Still, a wide range of motion is available to the hair bundles, so this rectification is less complete than is the case with the auditory nerve. In many subjects the ANN was present at low intensities where hair cell rectification is unlikely, so this confound is not likely to be large. In addition, in several cases the responses were large and there was no distortion at the highest level tested, 90 dB nHL (as in Fig. 6A and B). Thus, hair cell rectification is unlikely to be major contaminant in the current recordings, but they may play a larger role in ECoGs derived from normal hearing subjects.

Other than the CM and ANN, the ECoG also contains the CAP and SP. The CAP is purely neural in origin, while the SP is purely a hair cell potential. Thus, these potentials provide additional clues about the status of the different elements. At the low frequencies where the majority of significant potentials at the stimulus frequency occurred, the presence of the ANN was more reliable than the presence of a CAP. That is, there were numerous cases to 250 and 500 Hz where there was an ANN response in the alternating response with no CAP, but not the reverse. The SP is thought to be due to the build-up of depolarization inside hair cells, predominantly inner hair cells (25–28). The SP could be prominent (e.g., Fig. 7) but was not seen in all cases. When it was prominent, it was absent to 250 Hz, first appeared to 500 Hz, and increased in magnitude to higher frequencies (Fig. 7). This pattern is similar to that reported for the intracellular depolarization during tone bursts in inner hair cells (44), and has implications for the low pass filter that is a prominent feature of cochlear models (e.g.,45).

Evidence of Auditory Neuropathy and other Cochlear and Neural Pathology

In many cases there was a large signal with little distortion and little or no ANN (e.g., Fig. 6). This result indicates functioning hair cells producing a CM but a limited auditory nerve response, i.e., an auditory neuropathy. The threshold of the difference response can determine the threshold of the CM, if it is an undistorted response (which was usually the case at threshold intensities). The fact that it was at times lower than the audiogram threshold also indicates that hair cell responses can occur in the absence of connections to auditory nerve fibers. Recent work in animals has shown that excitotoxicity can cause the synapse to retract with subsequent fiber and ganglion cell loss. The lack of hair cell loss in these cases overturns the previous view that hair cells were the most vulnerable site for hearing loss in the cochlea (46,47). The presence of hair cell responses without neural responses is evidence that the hair cell-nerve fiber synapse is also a particularly vulnerable site in humans.

Measurable responses (CM and ANN) were detected a greater percentage of the time to frequencies of 1000 Hz or less than to 2000 and 4000 Hz. and the responses to lower frequencies were also larger in magnitude. Given that the majority of the subjects had a progressive high frequency sloping hearing loss pattern, the results are consistent with this pattern of pathology. However, a few subjects had the largest responses to frequencies other than the lowest tested. Too few cases have been obtained to determine if these have a specific etiology.

It is important to note that a precise etiology is not required for a determination that an implant will be beneficial; instead this determination is made based on the hearing condition itself. Thus, one future aim of these recordings is to assess whether particular suspected etiologies correlate with a particular cochlear state. Another aim is to correlate the state of cochlear survival of hearing elements with speech outcomes. A reasonable hypothesis would be that patients with the best-preserved functional neural elements would have the best

outcomes. A correlate to this hypothesis is that if functional hair cells and neural elements are well-preserved, the patient *should do well* with the implant, and if functional hair cell and neural elements are not preserved, the patient *may not* perform well. These considerations could affect fitting strategies and efforts. Finally the recordings themselves can be extended and used during insertion to determine cochlear trauma due to electrode placement, which may also correlate with hearing outcomes.

Acknowledgments

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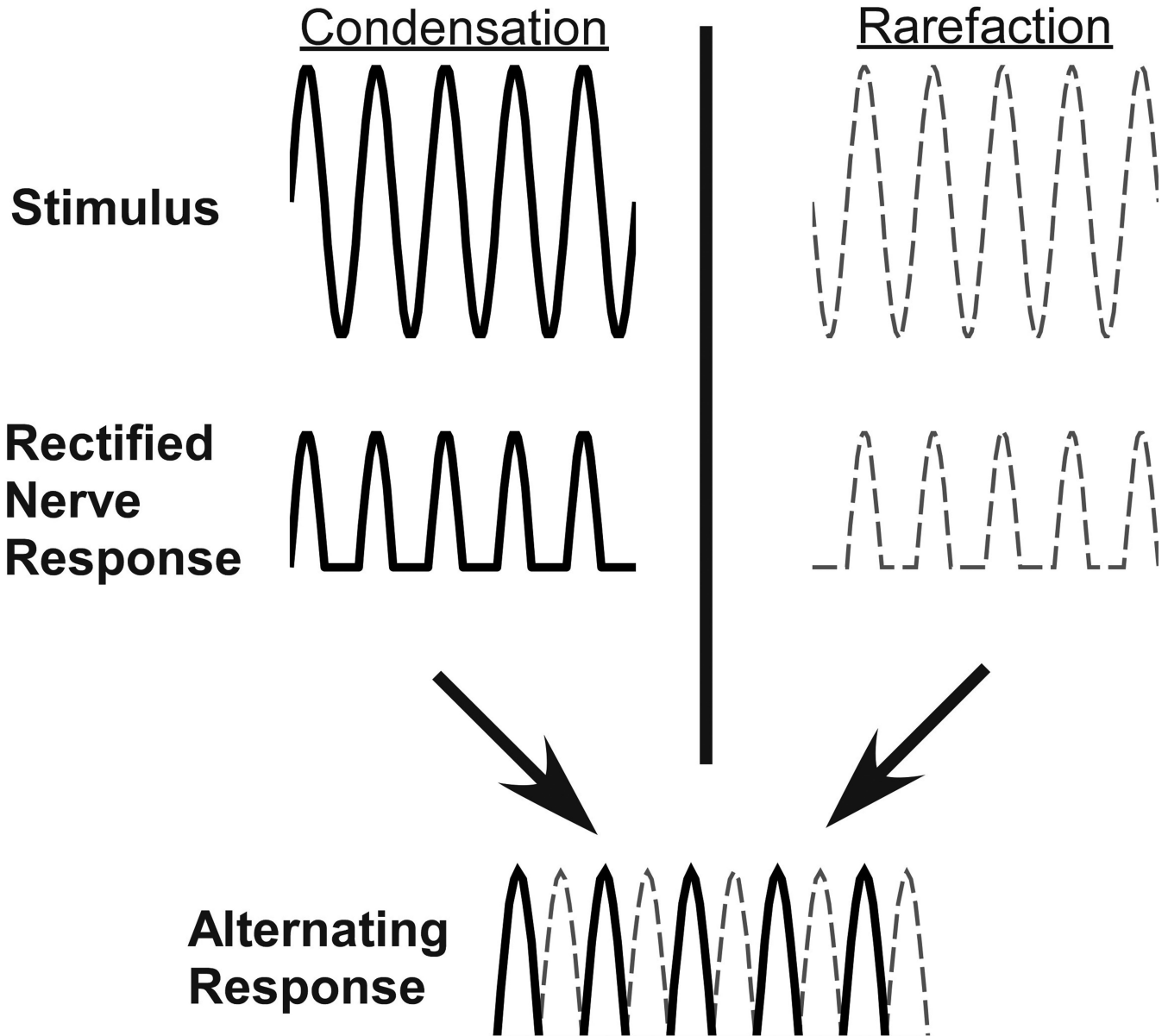
Figure 1.
Schematic showing the origin of the auditory nerve neurophonic (ANN) in the alternating response waveform. First row, labeled "Stimulus" shows a sinusoidal tone burst in two phases with a difference of 180 degrees (Condensation and Rarefaction). Second row, labeled "Rectified Nerve Response", shows the ANN component of the response to each phase of the sinusoidal stimulus. A positive going response to each positive going portion of the sinusoidal stimulus is seen (1/2 wave rectification). The last row, labeled "Alternating Response" shows the combination of the ANN response to each phase, which results in a waveform that is twice the original stimulus sinusoidal wave frequency. This response is the alternating phase response, which isolates the neural response.
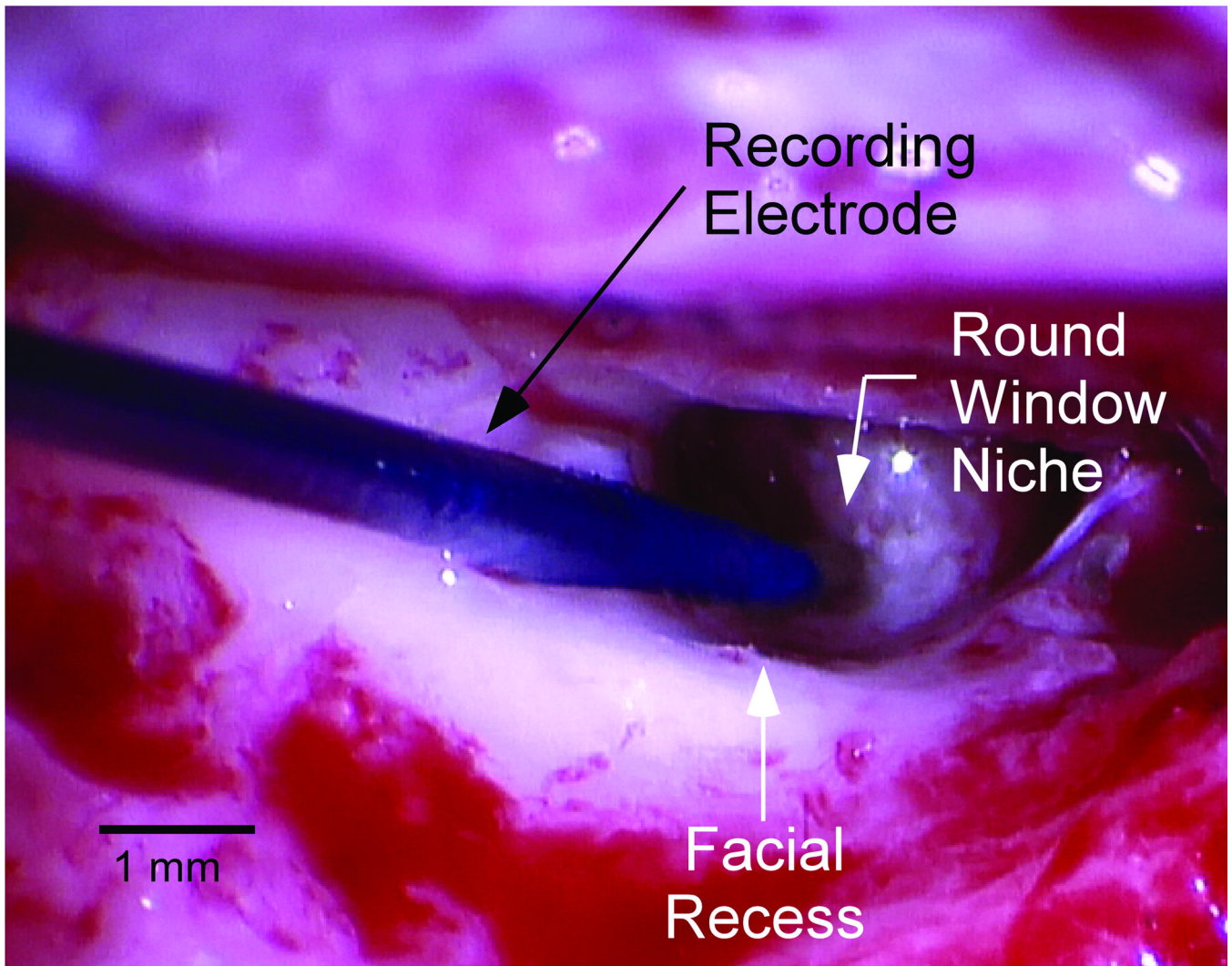
Figure 2.
A photograph taken through the operating microscope of the intraoperative recording setup showing the sterile monopolar probe placed in the round window niche after surgical access was gained.
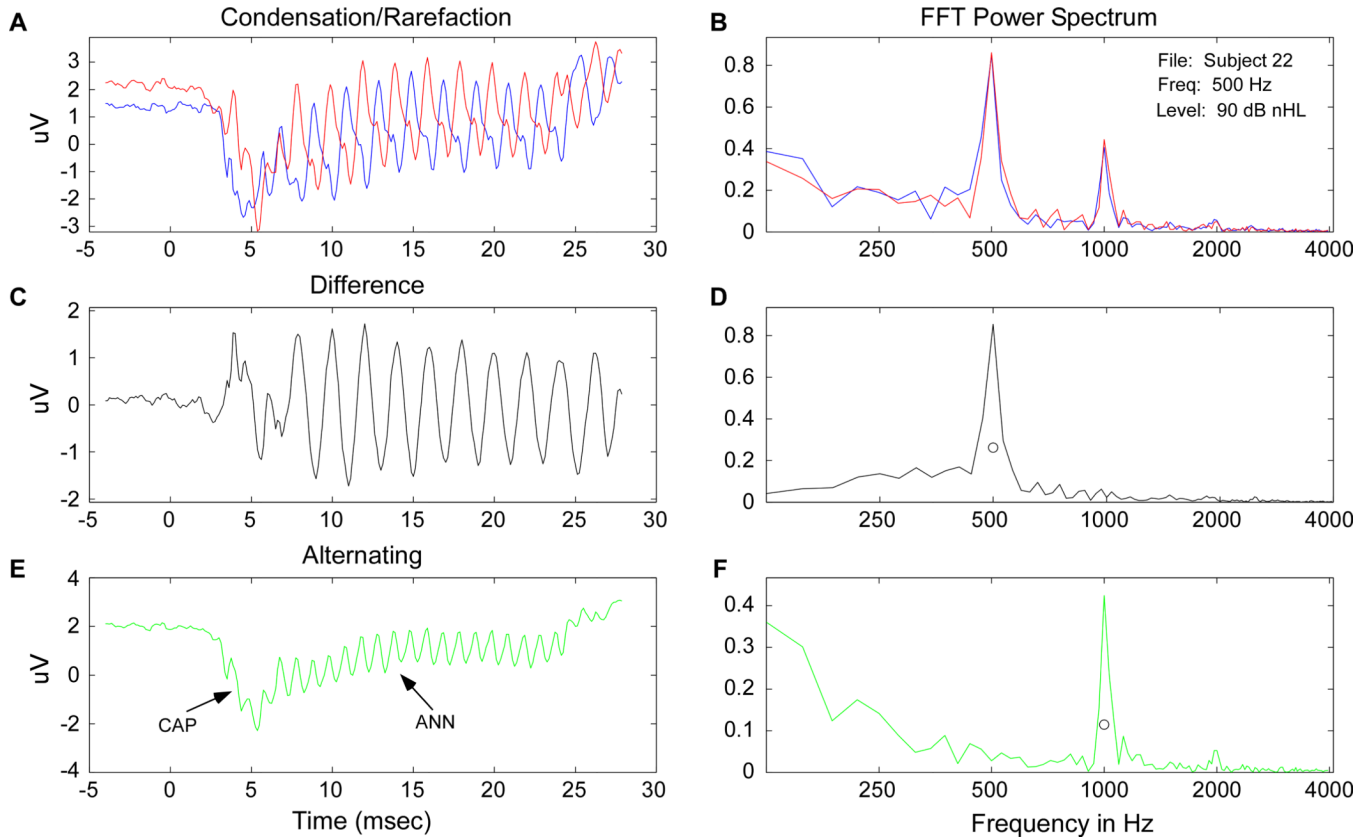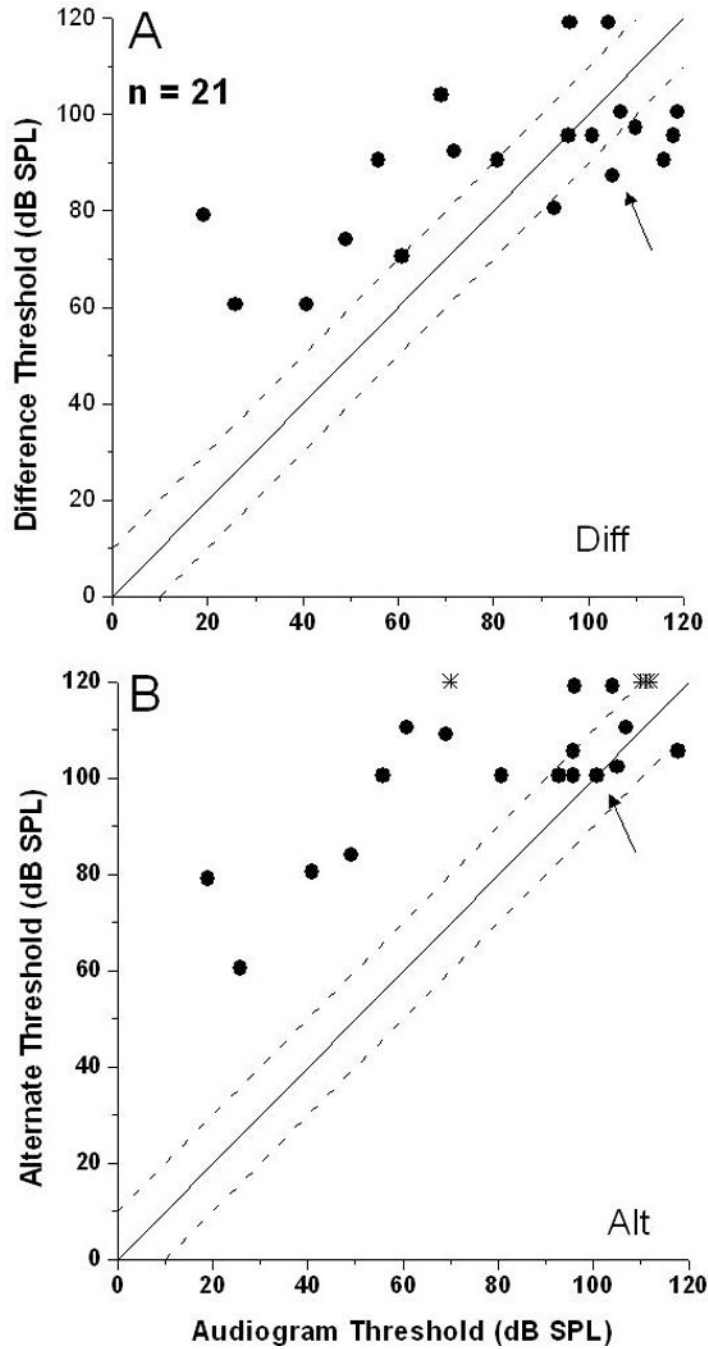
Figure 3.
Example of a typical response seen to a 500 Hz tone at 90 dB nHL. **A**. The averaged waveforms for both the condensation and rarefaction phases show distortion compared to the tone stimuli. **B**. Fast Fourier Transform (FFT) spectral analysis of 2A, shows that the distortion is harmonically related to the stimulus frequency, appearing at 1 and 2 kHz. **C**. The difference between the two waveforms in 2A. **D**. The subtraction removes most of the distortion yielding a single peak at the stimulus frequency in the spectrum. Open circle depicts calculated noise floor plus three standard deviations of the noise. A peak larger than this was determined to be significant. **E**. The averages of the waveforms in 2A, called alternating. The averaging removes the energy at the stimulus frequency and yields a residual response at twice the stimulus frequency. The compound action potential (CAP) is seen towards the beginning of the stimulus, and the auditory nerve neurophonic (ANN), phase locked neural response, is shown lasting the duration of the stimulus. **F**. The FFT retains only the energy of the harmonic distortion, with the largest peak at twice the stimulus frequency. Again, the open circle represents the calculated noise floor plus three standard deviations of the noise.
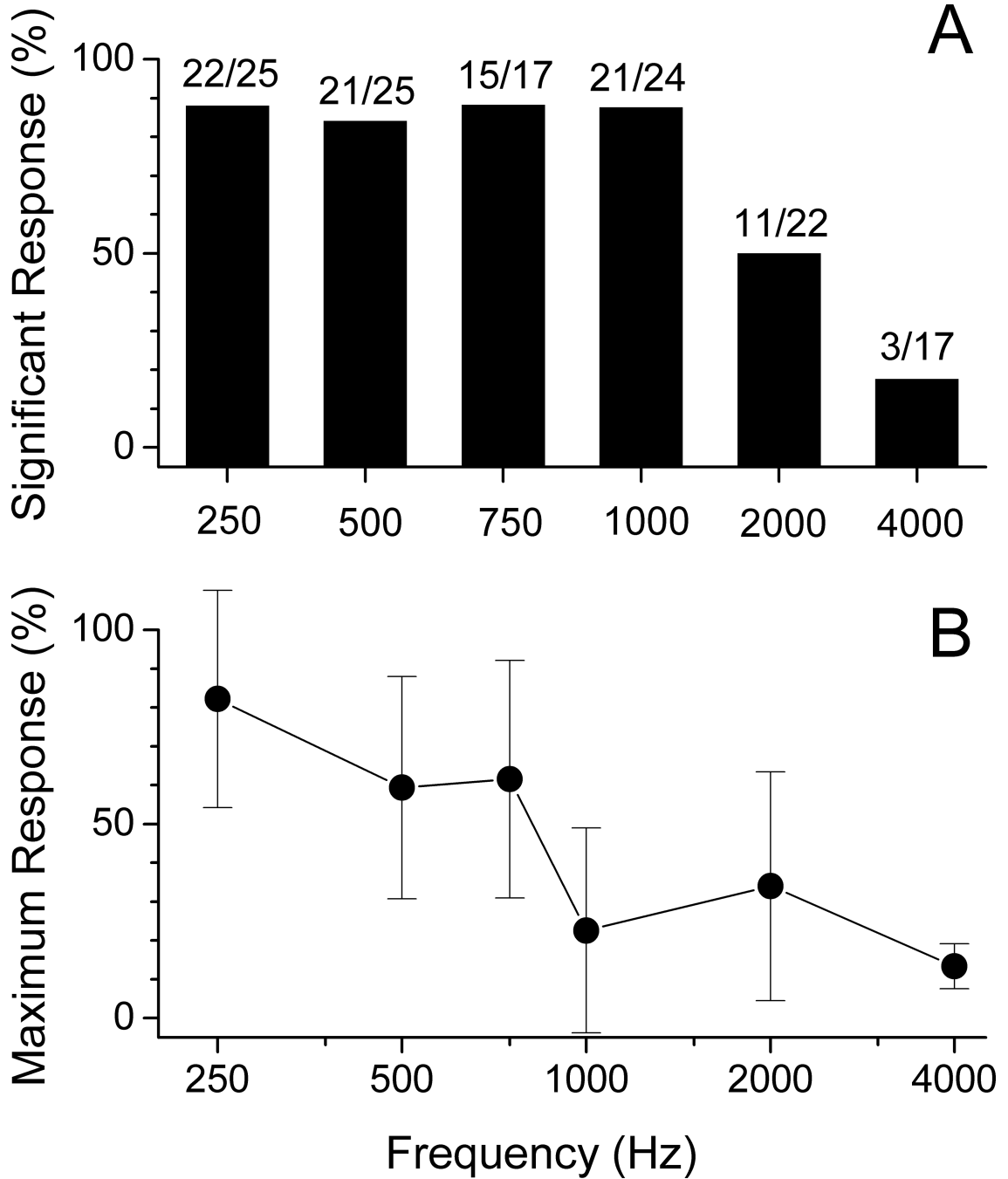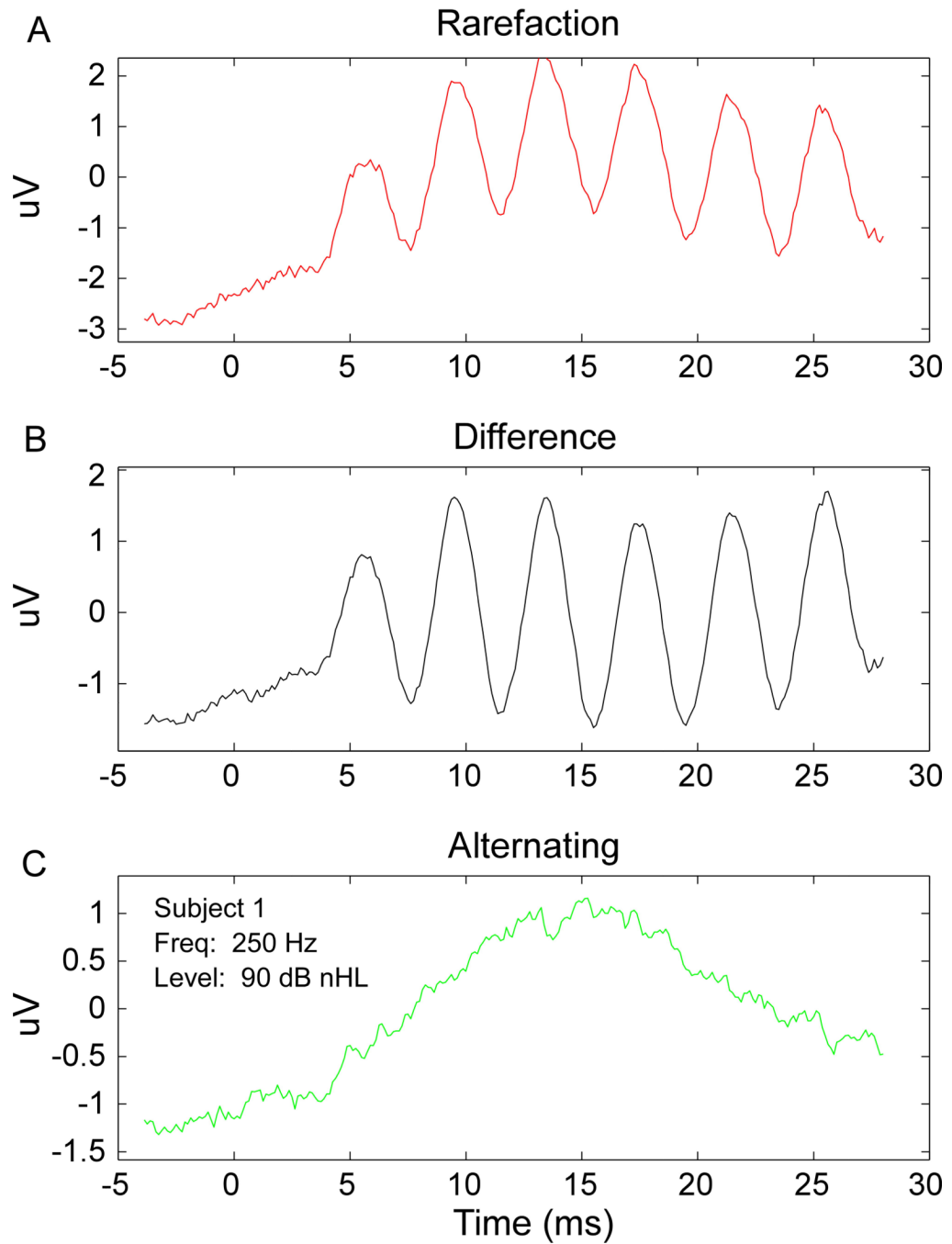
Figure 4.
A. Summary of the percent of subjects that had a significant response at each frequency. A greater percentage of subjects were noted to have significant responses (defined as responses greater than the noise level plus three times the standard deviation in the six bins used for the noise measurements) at 250–1,000 Hz compared to 2,000–4,000 Hz. **B**. Depicts the magnitudes of the response at each frequency across subjects, normalized to the maximum for each subject. The bars are standard error of the mean. Most subjects showed the largest responses to lower frequencies, the magnitudes of the response declined over the frequency range.
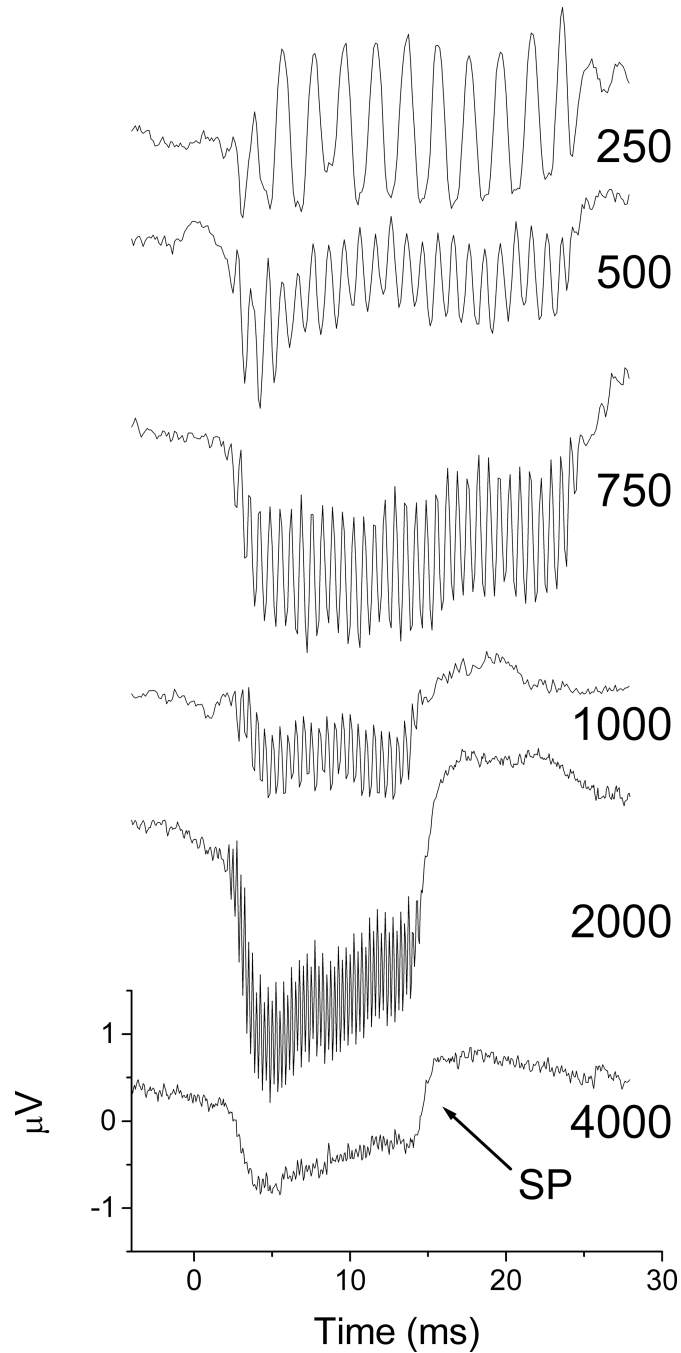
Figure 5.
Comparisons of intraoperative threshold recordings at a single frequency and preoperative audiogram threshold at the same frequency. **A**. Shows comparison for difference waveform response. The arrow highlights one of the cases where the physiological threshold was less than behavioral threshold. **B**. Compares preoperative audiogram threshold with threshold from twice the stimulus frequency using the alternating waveform. The arrow points to the same subject as in 4A, which now shows a better match to the behavioral threshold. Asterisks represent subjects that did not show a response in the alternating waveform at the highest level tested (90 dB nHL).

Figure 6.
The rarefaction, **A**, difference, **B**, and alternating, **C**, waveforms are shown for Subject 1. Given this stimulus (250 Hz tone at 90 dB nHL) a robust response in the rarefaction and difference waveform is evident, with no distortion in the rarefaction waveform. No response is noted in the alternating waveform. In addition, there is no CAP, indicating a differential hair cell and neural response to the stimulus.

Figure 7.
Alternating responses across frequencies at 90 dB nHL for Subject 15 that showed a large summating potential (SP). A SP was present at 500 Hz and increased at higher frequencies. The auditory nerve neurophonic (ANN) represents phase-locking of neural elements, and is a ½-wave rectified version of the original signal. The phase-locked response was present until 2 kHz.

TABLE 1

Age, sex, frequency with lowest audiogram threshold (TH), and etiology of hearing loss of each subject tested

Summary of subjects tested. Subject number, age, sex, lowest threshold (TH) per preoperative audiogram, frequency of lowest TH, and etiology of hearing loss are listed.

Subject	Age	Sex	Lowest TH per Preoperative Audiogram (dB HL)	Frequency of Lowest TH per Preoperative Audiogram (Hz)	Etiology of Hearing Loss
1	12 mon	M	90	250	unknown/possibly genetic (sibling with AN)
2	13 mon	F	70	250	unknown infection with antibiotics administered
3	21 mon	M	>100	all frequencies	Waardenburg syndrome
4	2 yr	F	>100	all frequencies	unknown/connexin 26 variant of unknown clinical significance present
5	2 yr	M	80	250	unknown etiology but likely genetic
6	2 yr	F	90	250	unknown
7	3 yr	M	>100	all frequencies	Congenital CMV infection
8	7 yr	F	15	250	unknown/onset age 4
9	8 yr	F	>100	all frequencies	Congenital CMV infection
10	10 yr	F	55	250	1555A>G mutation in MT-RNR1 gene
11	18 yr	M	>100	all frequencies	Progressive since kindergarden, asymmetric
12	*39 yr*	*M*	*75*	*250*	*sickle cell disease*
13	41 yr	F	70	2000	pontine infarction
14	42 yr	F	5	250	NIHL/Presbycusis
15	47 yr	F	60	250	unknown/onset age 5 - progressive
16	*48 yr*	*M*	*100*	*500*	*Radiation*
17	49 yr	F	70	4000	sudden HL at age 34, antibiotic use
18	66 yr	M	40	250	NIHL/Presbycusis
19	66 yr	F	100	250, 4000	NIHL/Presbycusis
20	69 yr	F	35	250	NIHL/Presbycusis
21	70 yr	F	80	250	NIHL/Presbycusis
22	71 yr	M	15	250	NIHL/Presbycusis
23	75 yr	M	50	250	NIHL/Presbycusis
24	78 yr	F	>100	all frequencies	onset age 5 after measles/Presbycusis

Subject	Age	Sex	Lowest TH per Preoperative Audiogram (dB HL)	Frequency of Lowest TH per Preoperative Audiogram (Hz)	Etiology of Hearing Loss
25	80 yr	F	45	250	NIHL/Presbycusis

AN = Auditory Neuropathy; CMV = Cytomegalovirus; NIHL = Noise Induced Hearing Loss; HL = Hearing Loss.