NCRAR Workshop

Ototoxicity Early Identification & Monitoring

VA Rehabilitation Research & Development
National Center for Rehabilitative Auditory Research

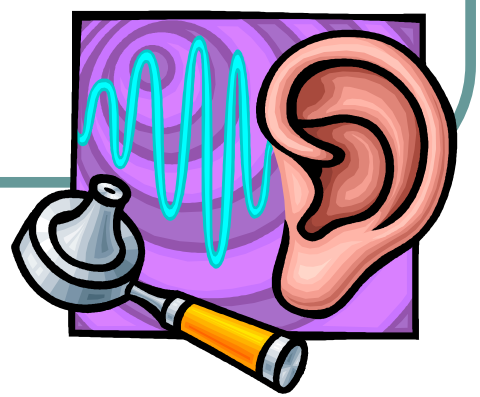
Site by CDR Marketing Group

Outline

I. Learner Outcomes
II. Overview: Basic Principles
III. Tinnitus Monitoring
IV. Ototoxicity Monitoring in Adults
V. Objective Monitoring
VI. Ototoxicity Monitoring in Children
VII. Establishing Program

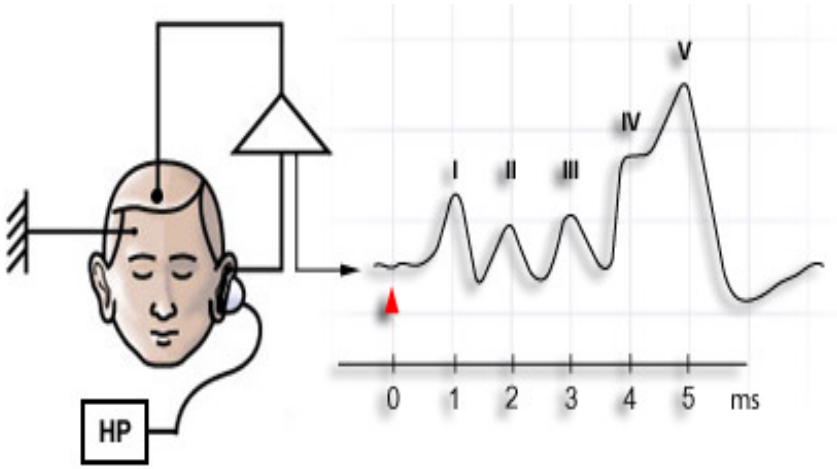
V. Objective Monitoring

Dawn Konrad-Martin, Ph.D., CCC-A



VA RR&D
NCRAR

ABR Basic Principles



Drawing by S. Blatrix from "promenade around the cochlea" EDU website www.cochlea.org by Rémy Pujol et al., INSERM and University Montpellier 1

- Usually elicited by click
- Absent for severe to profound losses
- Correlates best with 2-4 kHz hearing thresholds
- Provides little information about lower (< 1kHz) or higher frequencies (>4 kHz)

Onset Response

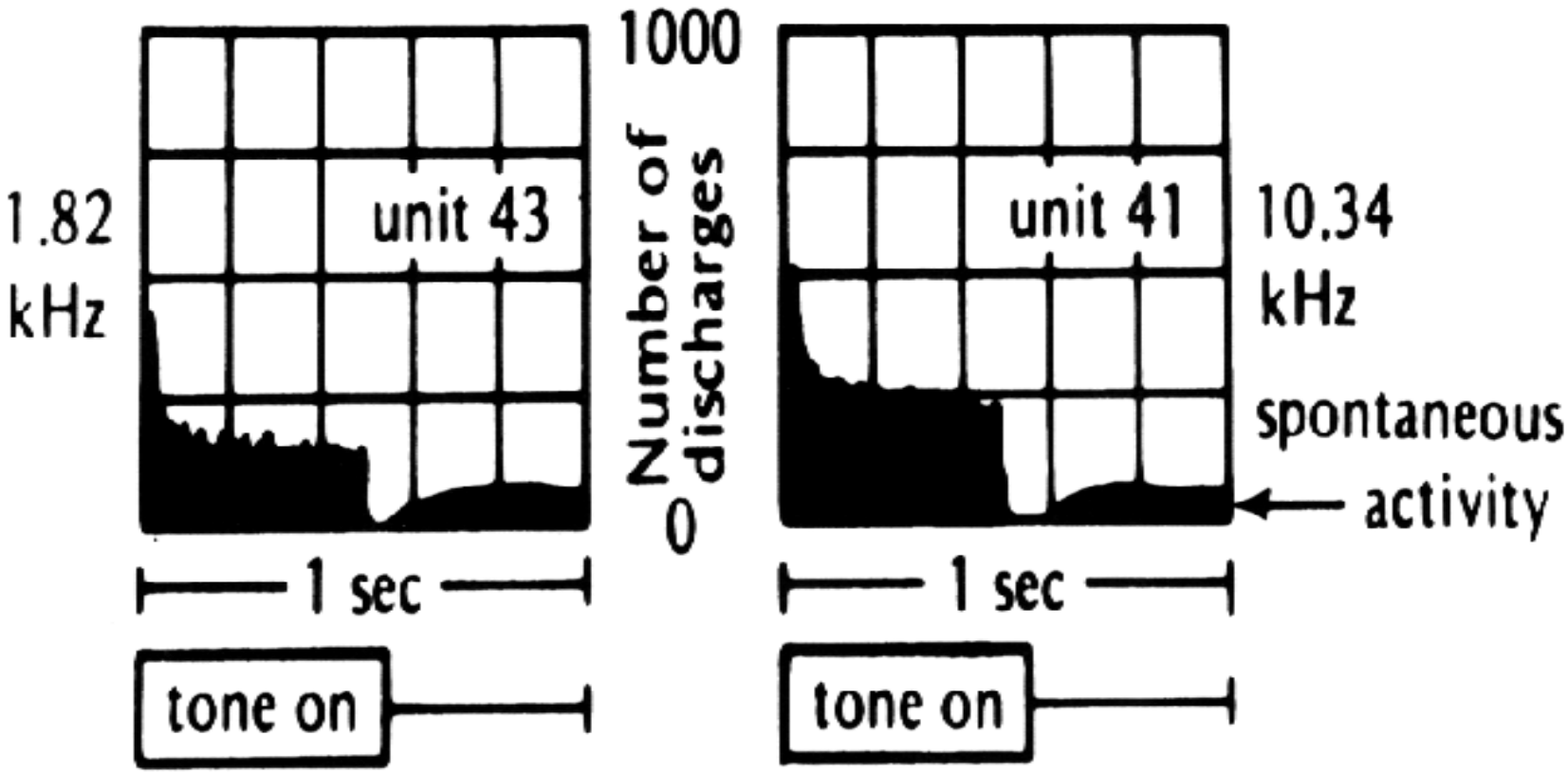


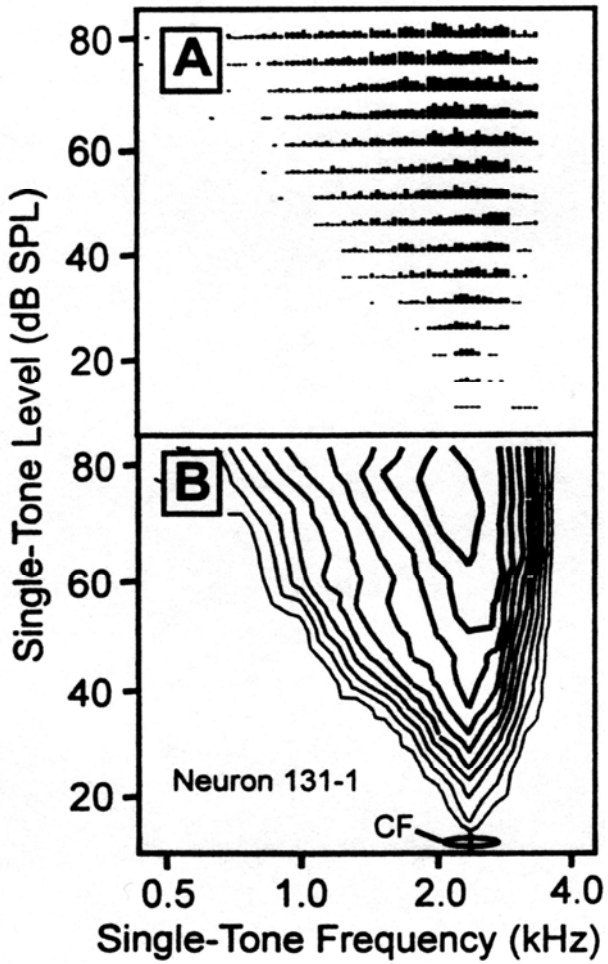
Fig. 9.7 from "Fundamentals of Hearing" Yost (2000) originally by Kiang et al. (1965).

ABR Basic Principles

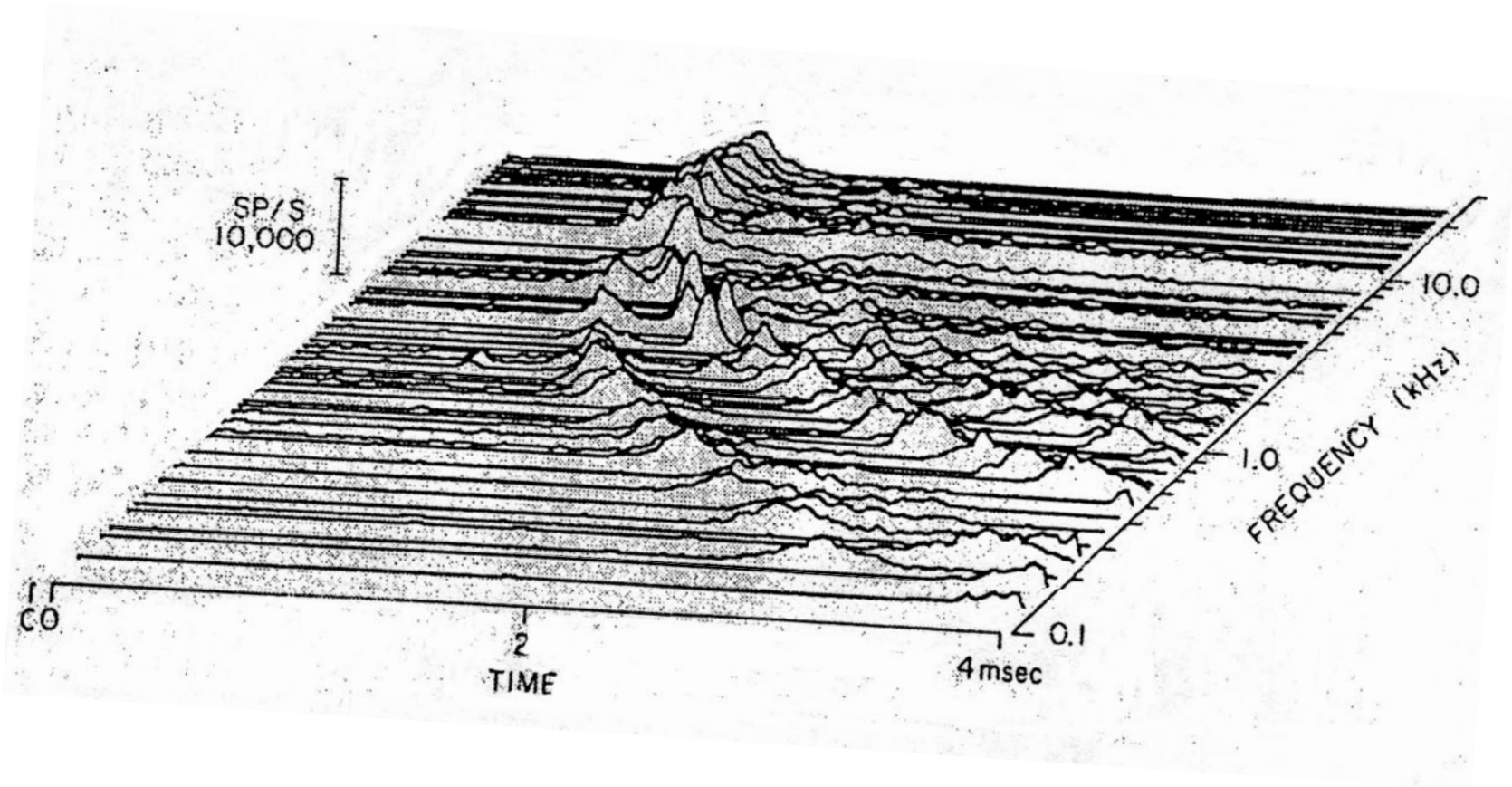
- Two problems at high stimulus levels
  - Increased spectral splatter (stimulus energy spreads)
  - Response could be due to tails of off-frequency neurons
- Pertains to all measures of auditory function with all kinds of stimuli
  - e.g., evoked potentials, behavioral measures
  - Clicks, tone bursts, pure tones

Frequency Specificity

- At a given place in cochlea…
- Low level tones excite response for a restricted frequency range
- At high levels, broad range of frequencies elicits response
- Less frequency specific at high levels



Frequency Specificity



from Kiang (1975)

ABR Basic Principles

- Clicks
- Tone bursts in quiet
- Filtered clicks
- Other techniques
  - Derived-band technique
  - Notched-noise technique

Clicks

- Clicks activate a broad portion of cochlea
- Activation near the (high-frequency coding) cochlear base
  - Many nerve fibers respond synchronously
- Activation nearer to the apex
  - Nerve fiber responses occur at slightly different times
  - Action potentials don’t sum optimally
  - More difficult to detect ABR responses
  - Longer Wave V latencies

Clicks

- High-frequency hearing loss
  - Provides little information about hearing loss > 4 kHz
  - Wave V latency may be normal at high levels (large range of cochlea responding)
  - Wave V prolonged at low and moderate levels (response due to lower frequency-coding regions of the cochlea)

Tone Bursts

- Tone bursts in quiet
  - Energy centered at nominal frequency
  - Some spread of energy, which increases with level
- Underestimates HF hearing loss because stimulus is not frequency specific due to spectral splatter (Stappells, 1984)
  - Response may come from more normal part of the cochlea
- Wave V amplitude is small compared to clicks and testing time is lengthier (need more averaging)

From Gorga et al. 1988

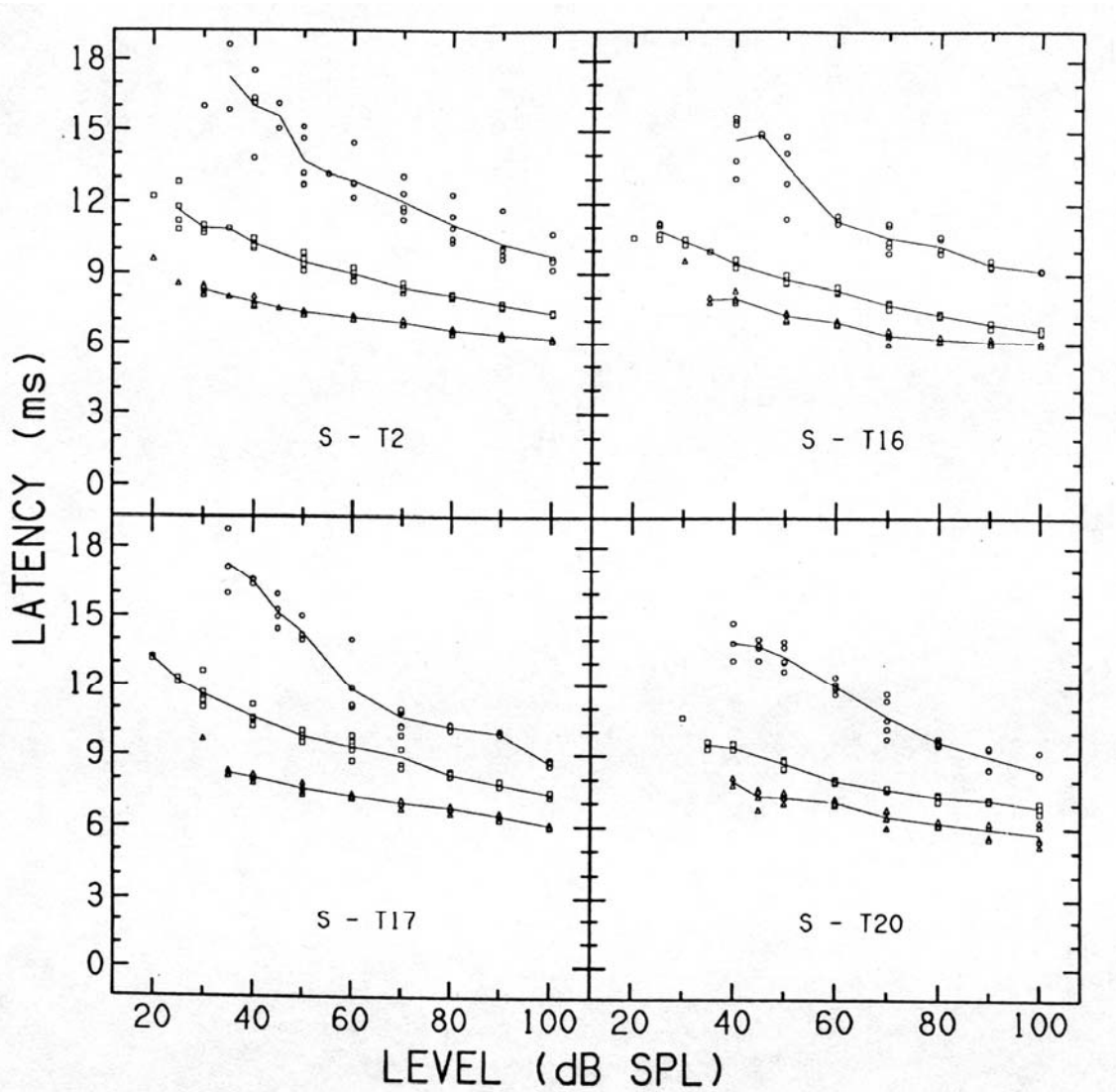


FIGURE 3. Repeated measures of wave-V latencies as a function of level. Data from an individual subject are shown in each of the four panels. Within each panel, circles (○) represent data for 500 Hz, squares (□) represent data for 2000 Hz, and triangles (△) represent data for 8000 Hz. There are five measurements at each level and frequency combination. The lines are drawn through the means for each of the three stimulus frequencies.

TABLE 2. Mean wave V-thresholds and standard deviations for each of 4 subjects at 500, 2000, and 8000 Hz

Subject	Frequency (Hz)					
	500		2000		8000	
	M	*SD*	*M*	*SD*	*M*	*SD*
T2	37.5	4.18	25.83	3.76	27.5	4.18
T16	40.0	0	25.83	4.92	35.0	6.12
T17	38.0	4.47	25.0	5.0	35.0	3.54
T20	42.5	2.73	35.0	3.16	44.17	3.76

From Gorga et al. 1988

Tone Bursts

- Intersession reliability of ABRs to single HF tone bursts (> 8 kHz) (Fausti et al. 1984)
- Reliability of sequenced or trains of tone bursts (Fausti et al. 1995)
- Comparison of reliability to clicks presented singly or high frequency tone bursts presented singly or in trains Mitchell et al., 2004
- Reliability did not vary significantly with stimulus frequencies or intensities tested

Table 3.
Across-session Wave V latency and amplitude differences, means, and standard deviations (SDs) for each stimulus used in first method.

Stimulus	Latency (ms)		Amplitude (μV)	
	Mean (S2-S1)	SD	Mean (S2-S1)	SD
Conventional Click	0.03	0.14	0.01	0.05
Flat HF Click	–0.03	0.18	–0.01	0.03
Sloped HF Click	–0.07	0.23	0.00	0.04
8 kHz	–0.02	0.22	0.00	0.05
10 kHz	–0.05	0.22	–0.01	0.04
12 kHz	–0.03	0.24	0.00	0.03
14 kHz	0.01	0.25	0.01	0.03

From Mitchell et al. 2004

Is it important (or even possible) to have frequency specificity at high levels in the cochlea?

Maybe we can get by with stimulating broad range of high frequencies.

Filtered Clicks

- Mitchell et al., 2004
  - Stimulus was narrow-band filtered with broad spectrum
  - Response from broader portion of cochlea compared to tone bursts
- Wave V amplitude robust compared to tone bursts and testing time shorter
- Clicks presented singly, high frequency tone bursts presented singly or in trains shows similar test-retest reliability

Measurement Variables

- Gating
  - Spectral splatter may excite broad cochlear region
  - Spread of energy reduced by windowing functions (e.g., Blackman, cosine-squared)
- Plateau
  - No plateau, less frequency specific, ABR is onset response only
- Level
  - Input-output functions, 75, 85, 95, & 105 dB peSPL
- Frequency
  - Limited frequency specificity, HF output limited by transducer

ABR Sensitivity

- Significant elongation of latency and/or disappearance of click-evoked wave V following administration of ototoxic drugs (Bernard et al., 1980; Piek et al., 1985)
- Ultra-high frequency tone bursts (8-14 kHz) more sensitive to early identification of ototoxic (high-frequency) hearing loss than clicks
  - Sensitivity was 84% in Fausti et al., 1992
  - Latency changes found
  - However, 60% of all initial changes were from scorable at baseline to non-scorable

Change Criteria (???)

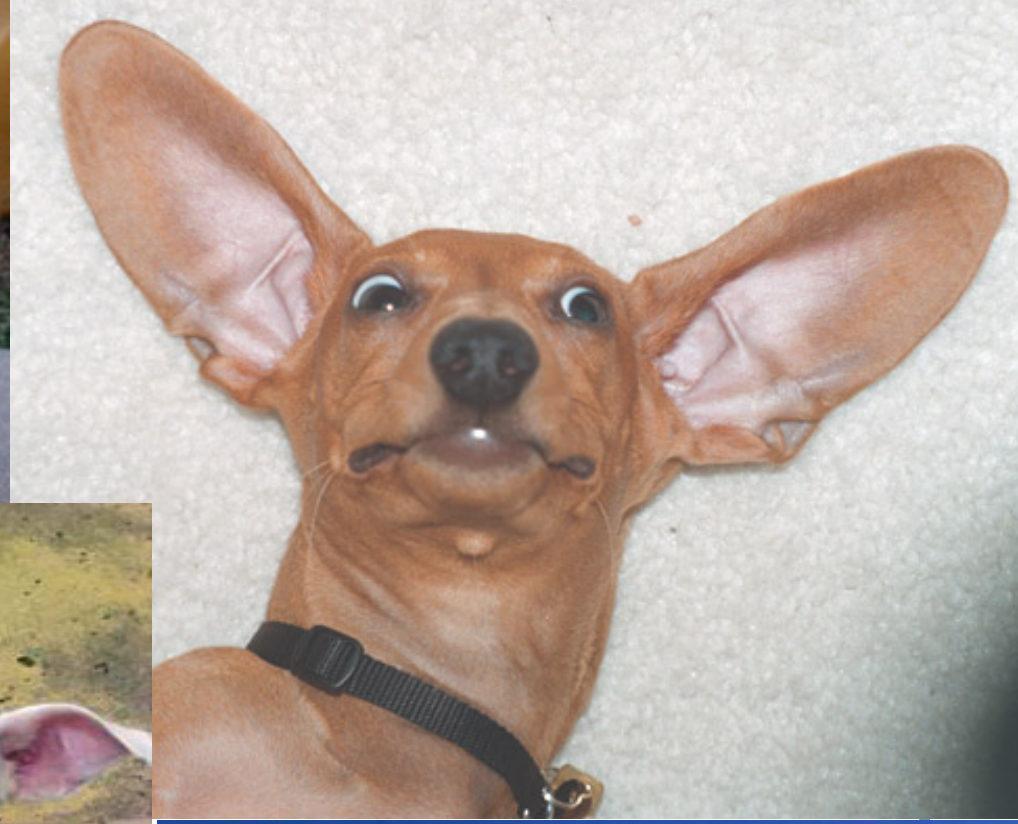
- No broadly accepted ABR latency change criteria
- In veterans receiving cisplatin, shift of 0.3 ms for wave I or wave V or change of a previously scoreable response to non-scoreable (Fausti et al., 1992) was used
- In neonates, latency delay greater than mean test-retest variability in non-drug exposed neonates plus 2 standard deviations, was 1.8 $\pm$ 0.8ms for wave I and 5.7 $\pm$ 0.8ms for wave V (De Lauretis, De Capua, Barbieri, Bellussi, Passali, 1999)

ABR Advantages

- Good test-retest reliability
- Can be performed at bedside
- Can estimate thresholds (magnitude of ototoxicity-induced hearing loss)
- Can obtain in patients with substantial pre-existing hearing loss (up to severe to profound)

ABR Disadvantages

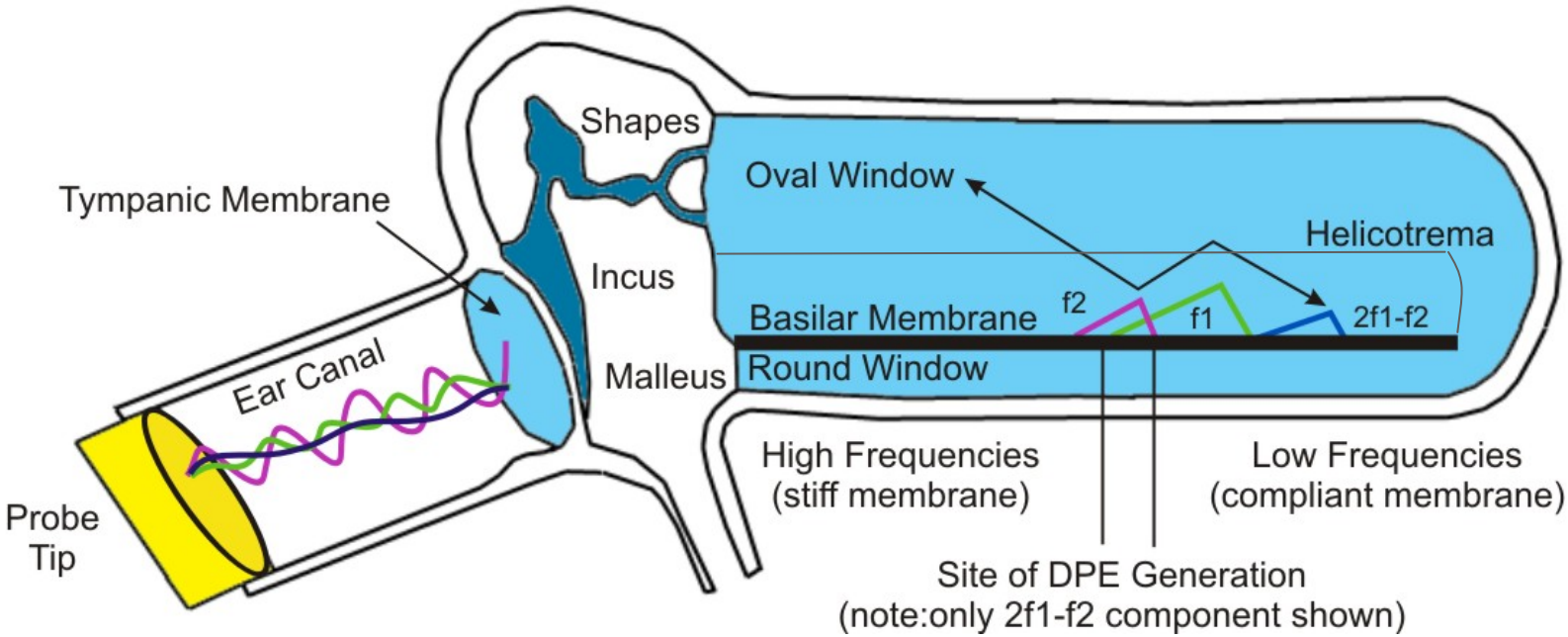
- Time consuming
- Limited frequency specificity (depending on how performed)
- Limited high-frequency output
- Response interpretation at high frequencies
- Subject noise, hearing loss may preclude measurement
- Infants & children may require sedation



OAE Basic Principles

- OAEs are byproducts of active basilar membrane biomechanical processes
- Sources of “active processes” include OHC system
- OHCs are physiologically vulnerable
- Decreased OAE amplitudes indicates OHC damage, which indicates hearing change

OAE Basic Principles



- Acoustic response measured in the ear canal
- Evoked using two-tone stimulation (f1 < f2)

OAE Basic Principles

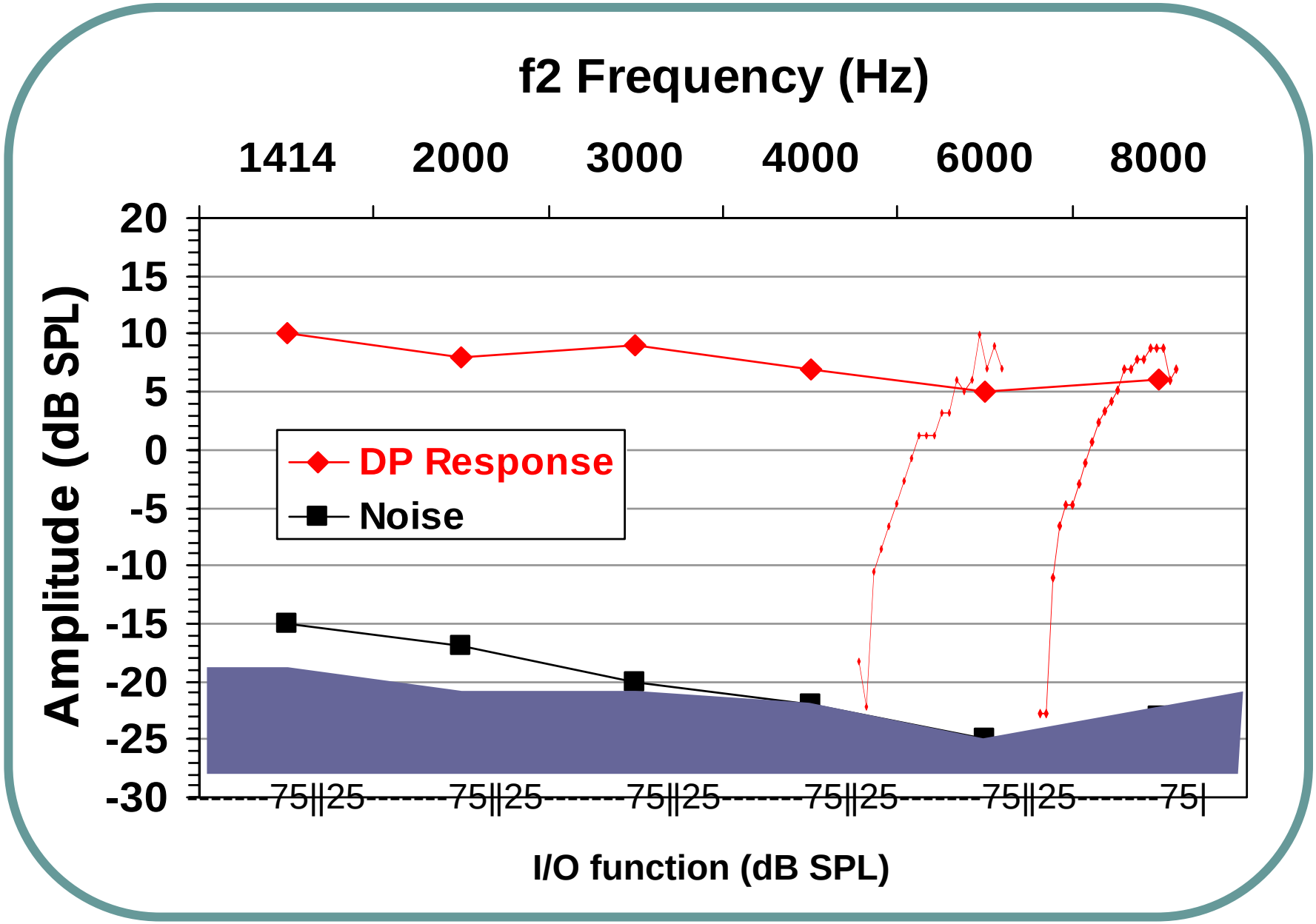
- Link between ototoxic DPOAE changes and OHC changes (for review see Whitehead et al., 1996)
- Conventional audiometric changes occurred later relative to OAE, or not at all (AMG: Katbamna et al., 1999; Stravroulaki et al., 2002; Mulheran & Degg, 1997; CDDP: Ress et al., 1999)
- Compared to behavioral testing within the high frequency (> 8000 Hz) range, DPOAEs showed effects of ototoxicity in similar proportion of ears (Ress et al., 1999)

Measurement Variables

- 1. DP-gram
  - Plot DPOAE level as a function of f2 frequency,while primary levels are held constant
  - Use moderate level, e.g., L1, L2 in dB SPL= 65, 65 or 63,60
  - Question: Should we vary f2 in small frequency steps (e.g., 1/3rd, 1/5th or 1/6th -octave)?
    - Increasing frequency resolution may be particularly important in patients with good hearing (e.g., children) in which DPOAE fine structure could be present
    - Could increase false positive rates
    - No published research looking at different f2 step sizes

Measurement Variables

- 2. Input/Output (I/O) functions near highest measurable DPOAE frequency
  - Plot DPOAE level as a function of primary level while primary frequencies are held constant
  - Vary L2 in 5-dB steps


f2 Frequency (Hz)
1414
2000
3000
4000
6000
8000
Amplitude (dB SPL)
20
15
10
5
0
-5
-10
-15
-20
-25
-30
DP Response
Noise
75||25
75||25
75||25
75||25
75||25
75|
I/O function (dB SPL)

Measurement Variables

- Noise floor
  - Subject noise
  - Ambient noise
- System distortion
- Frequency
- Probe fit
  - Affects both noise floor and system distortion
- Middle ear function

Measurement Variables

- Noise floor
  - Usually the average amplitude in several frequency bins above and below 2f1-f2 bin
  - Greatest at low frequencies
  - Can reduce noise floor by increasing number of averages
  - Keep test ear away from noise sources in the sound booth (e.g., OAE system, air vents, computers, monitors)
  - SLM measurements for ward testing

Measurement Variables

- Signal-to-noise ratio (SNR)
  - dB difference between SPL at 2f1-f2 and the estimated noise
  - To be valid, a DPOAE should have a favorable SNR (e.g., 6 dB, or even 10 dB if conditions are noisy)

Measurement Variables

- System distortion levels
  - Greatest at high frequencies
  - Average until noise floor is the level of your system distortion (e.g., -20 dB SPL) or artifact-free averaging time reaches 32 seconds
- Repeat system distortion measurements to assess system performance

Measurement Variables

- To estimate system distortion, make measurements using testing protocol
- Test using a coupler that mimics the volume and impedance characteristics of the average human ear canal (e.g., 2-cc coupler meeting IEC 711 specifications, such as the 4157 Bruel and Kjaer)

DPOAE must meet some criteria to be valid test of cochlear function

DPOAE Validation

Criteria for a valid response

- Favorable SNR (e.g., 6 dB, or 10 dB in noisy environment)
- OAE amplitude is larger compared to conservative estimate of YOUR system distortion
- Middle ear function stable

Probe Fit

Consistent probe placement critical (both within and across testers)

- Firm vs loose placement
- Ports facing tympanic membrane vs ports blocked
- Sound delivery tubes straight
- Cable from microphone immobile, placed where patient won’t accidentally wiggle it

Change Criteria (???)

1. Construct confidence intervals using

    1a. Standard error of measurement, SEM (see Franklin et al., 1992 and Beattie et al., 1993), or

    1b. Average test-retest difference plus standard deviation (SD)

        ~68% chance that change is not due to random variability > 1 SEM or 1 SD

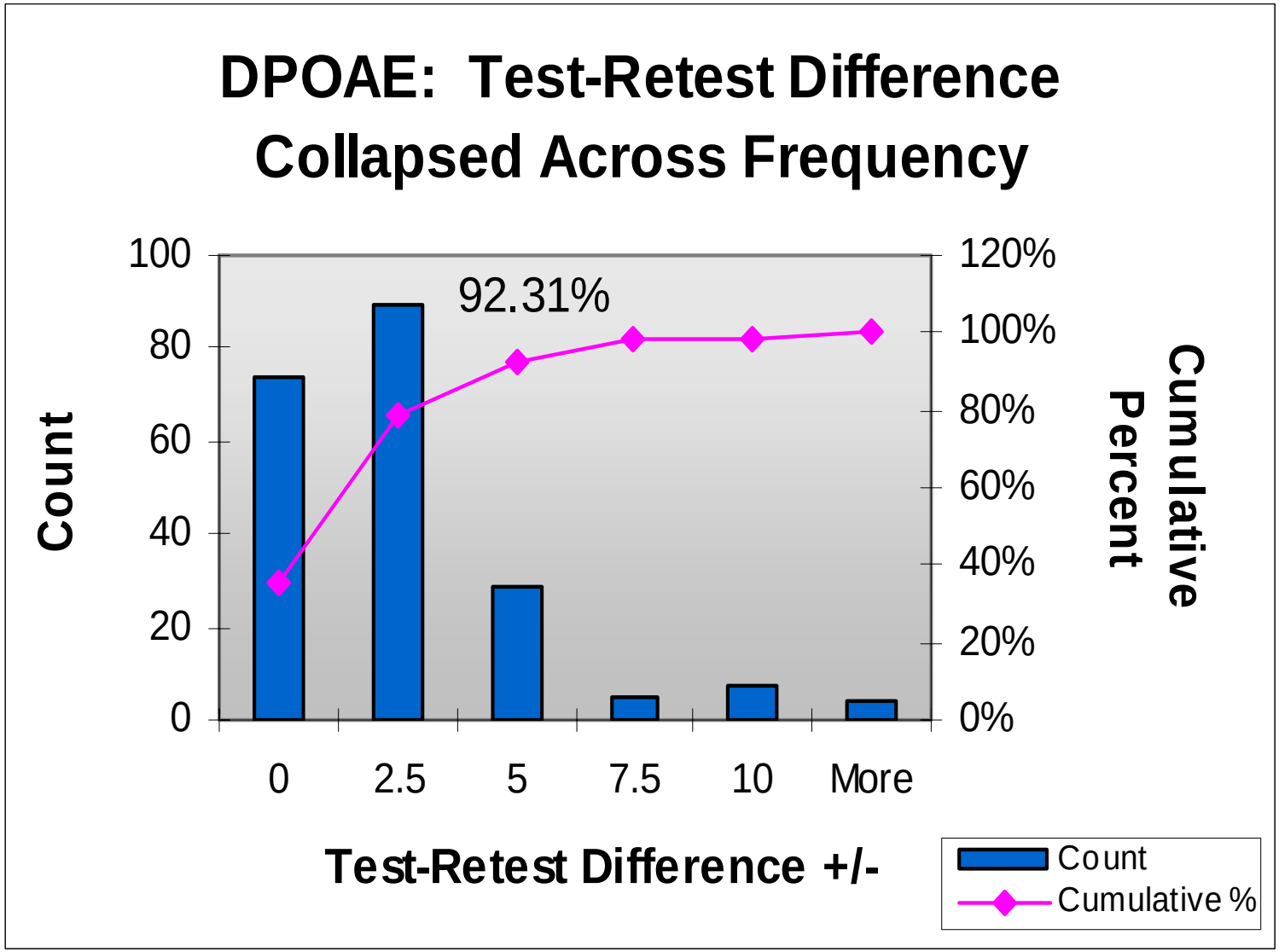
        ~95% chance change > 2 X SEM or 2 SD

2. Construct cumulative distributions

    2a. 95% of subjects had a change of X or less

Change Criteria (???)

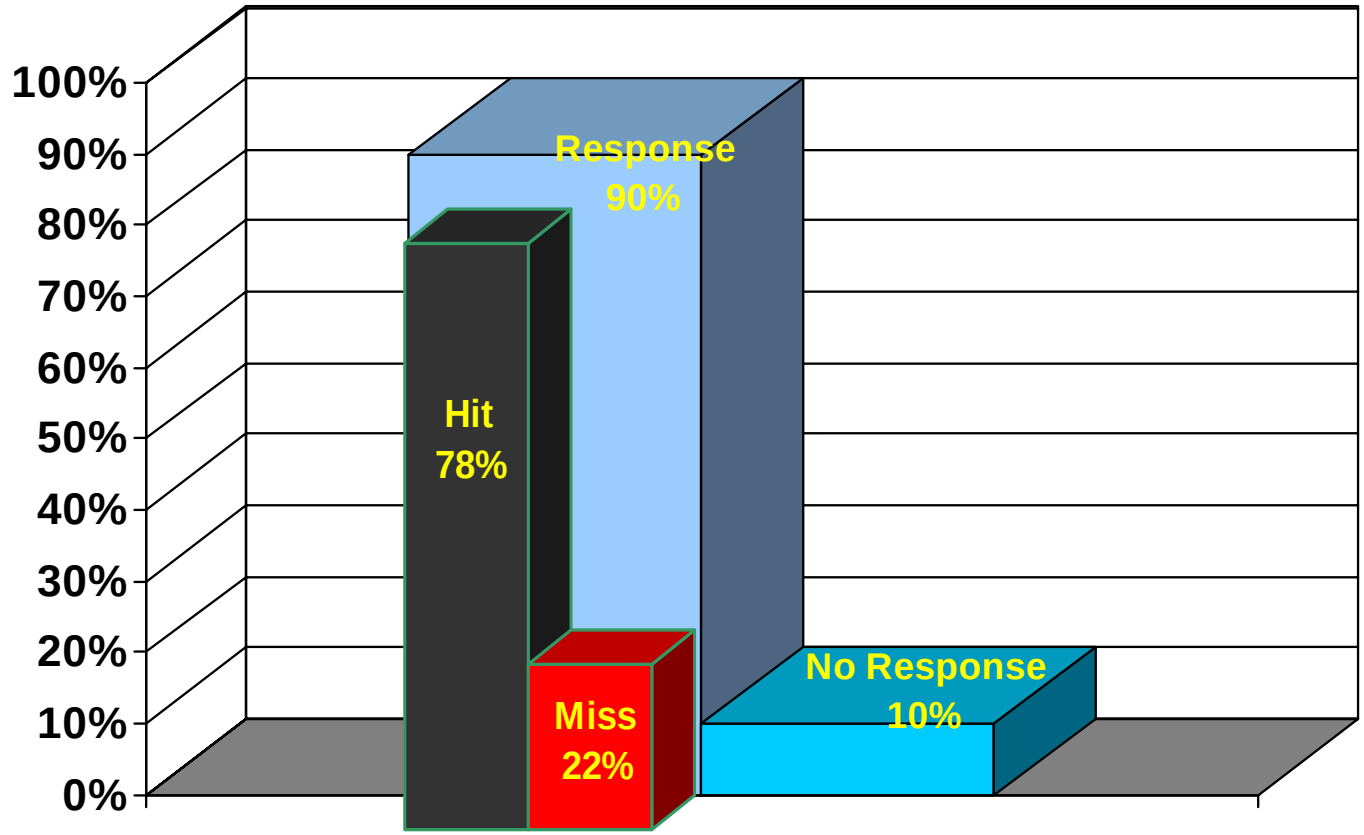
- Standard error of measurement (SEM)
  - Typically 2 X SEM is about 5 dB for frequencies between 1 and 4 kHz (Franklin et al. 1992; Beattie et al., 2003)
- Average amplitude difference plus 2 SD
  - 6 dB for most frequencies between 1 and 6 kHz (Roede et al., 1993)
- Cumulative distributions
  - Our preliminary data show > 90% of ears had test-retest change of 5 dB or less between 1 and 10,000 Hz


DPOAE: Test-Retest Difference
Collapsed Across Frequency
92.31%
Count
Cumulative Percent
100
80
60
40
20
0
120%
100%
80%
60%
40%
20%
0%
0
2.5
5
7.5
10
More
Test-Retest Difference +/-
Count
Cumulative %

Change Criteria (???)

- ≥ 6 dB change
  - Based on test-retest variability in normal subjects
  - 6 dB change was more than variability in about 95% of subjects tested--so likely to be real change
  - Confirm by re-test to decrease false positive rates
  - Change at two adjacent frequencies would decrease false positive rates
  - Verify YOUR own test-retest reliability

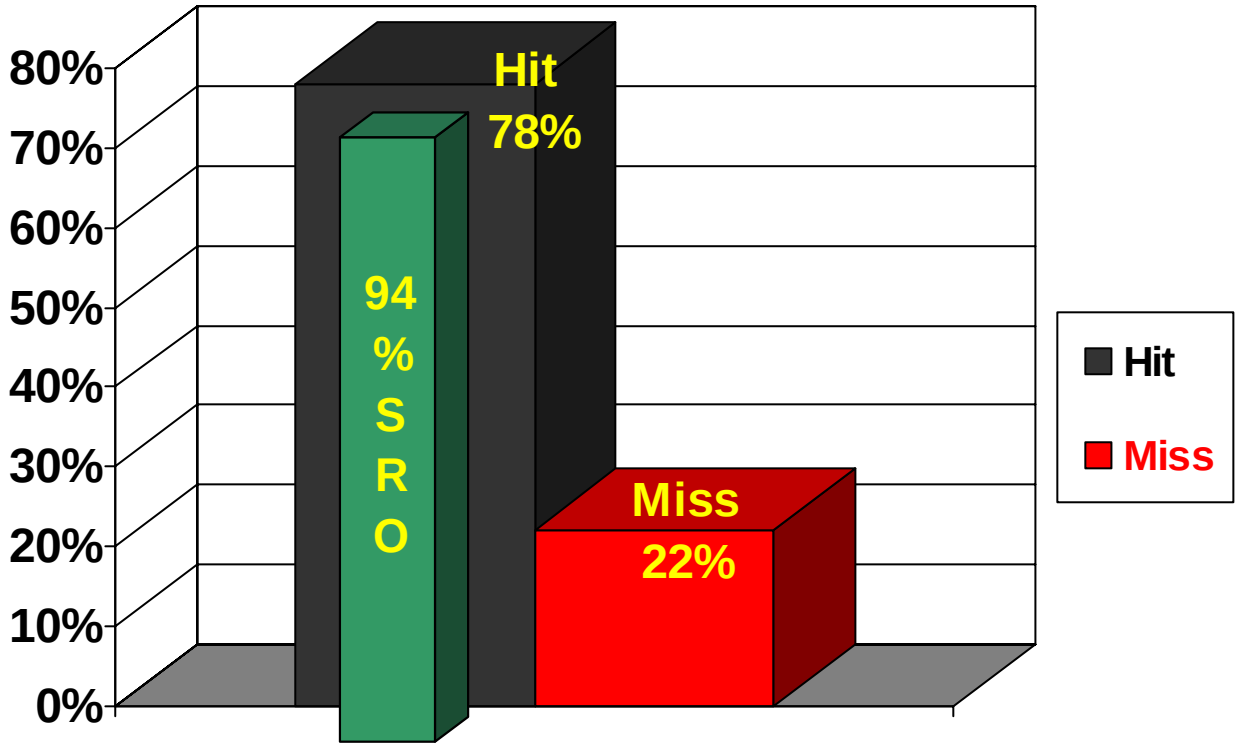
OAE Sensitivity



DPOAE Response to Ototoxic Hearing Loss

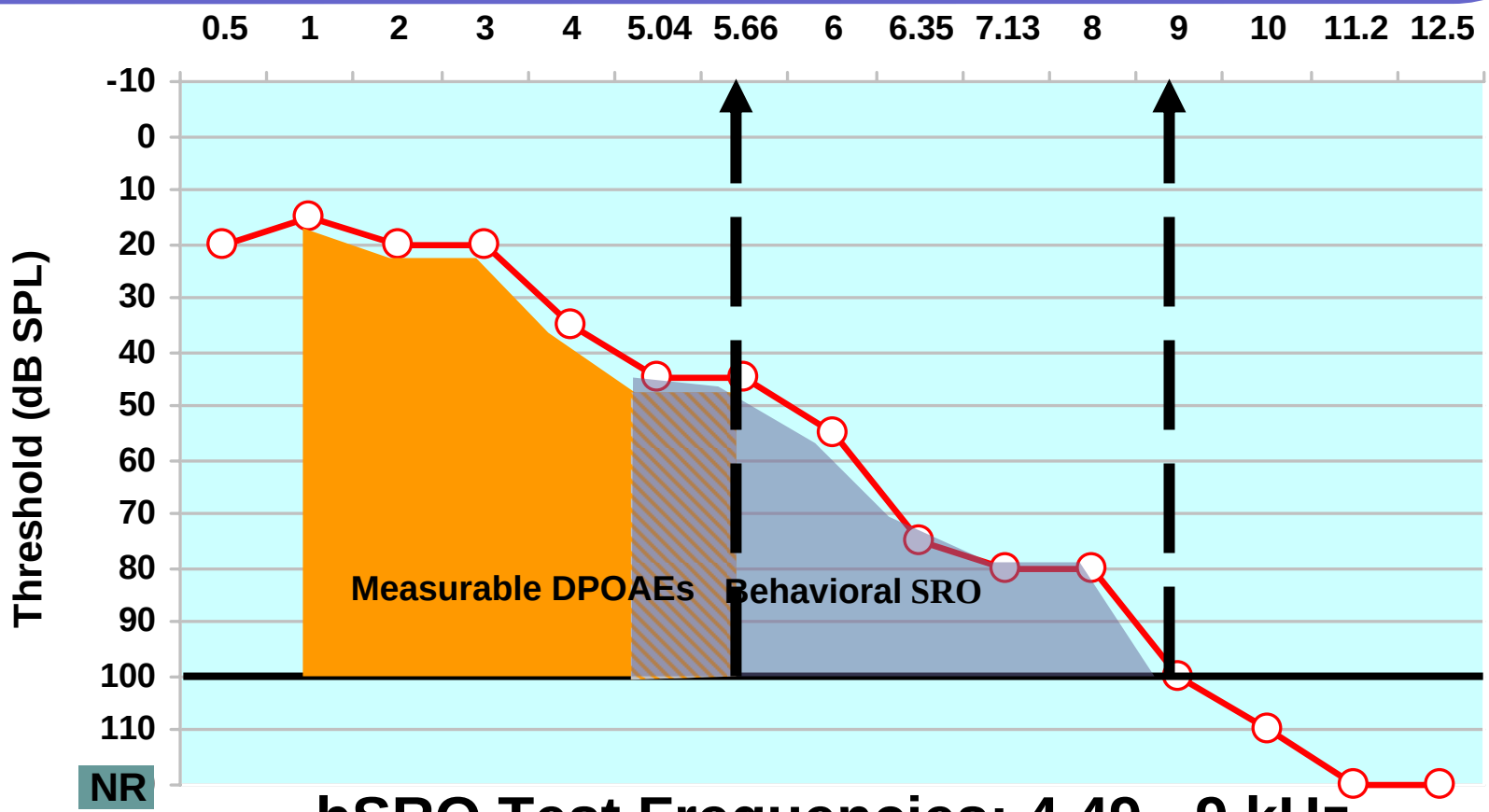
Hit: N = 63 Miss: N = 18 No Response: N = 9

OAE Sensitivity



94% of the DPOAE that reflect change, did so within octave of highest DP frequency able to elicit a response

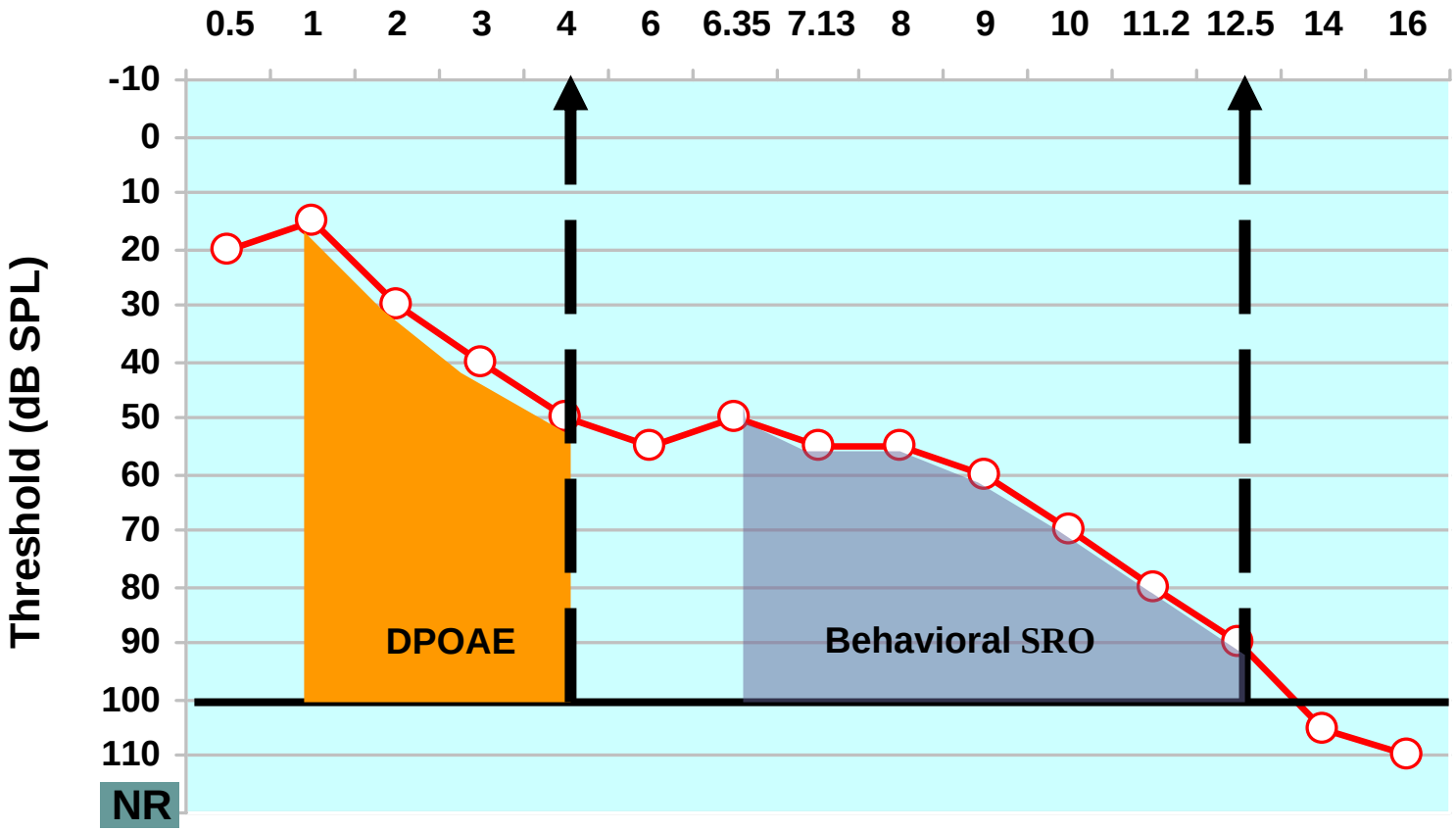
Example SRO Below 8 kHz



bSRO Test Frequencies: 4.49 - 9 kHz

dpSRO Test Frequencies: 2.5 - 5 kHz

Example SRO Below 8 kHz



bSRO Test Frequencies: 6.3 - 12.5 kHz

dpSRO Test Frequencies: 2 - 4 kHz

OAE Sensitivity

- Top DP frequency closer to behavioral SRO ($p < 0.05$)
- Higher Top DPOAE Frequency ($p < 0.01$)
- Better Behavioral Thresholds ($p < 0.01$)

DPOAEs more sensitive to early ototoxic change when DPOAE and behavioral SRO overlap and in ears with better hearing

DPOAE Advantages

- Earliest ototoxicity detection (???)
- Frequency specific and can measure over a wide frequency range
- Good test-retest reliability
- Rapid
- Can be performed at bedside

DPOAE Disadvantages

- Limited high-frequency (> 6 kHz) measurements
- DPOAE amplitudes linked to hearing sensitivity only for losses < 50-60 dB
- Hearing loss may preclude measurable responses at baseline
- Depends on normal middle ear function

Current NCRAR Research

- Auditory brainstem response (ABR)
  - High frequency stimulus trains
- Otoacoustic emission (OAE)
  - DPOAE and SFOAE
    - high frequency measurements
    - emission fine structure
    - input-output functions
    - estimates of gain