Ototoxicity Monitoring using Otoacoustic Emissions

Dawn Konrad-Martin, Ph.D., CCC-A
VA RR&D National Center for Rehabilitative Auditory Research
Dept. Otolaryngology-HNS, Oregon Health & Science University

Laura Dreisbach Hawe, Ph.D., CCC-A
School of Speech, Language, and Hearing Sciences
SDSU/UCSD Joint Doctoral Program in Audiology, San Diego State University

Gayla L. Poling, Ph.D., CCC-A
Division of Audiology, Mayo Clinic Rochester

Jake Hulswit, B.S.
VA RR&D National Center for Rehabilitative Auditory Research

Kara Nofstker
VA RR&D National Center for Rehabilitative Auditory Research

Outline

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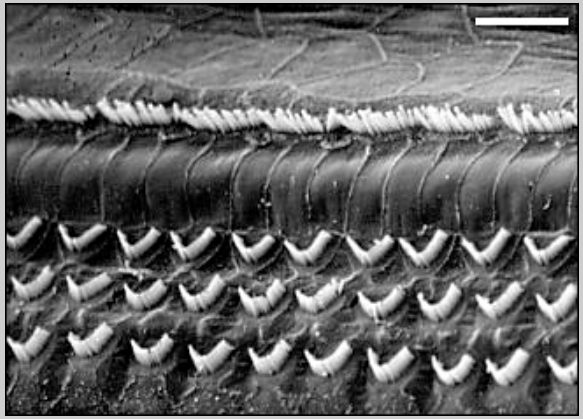
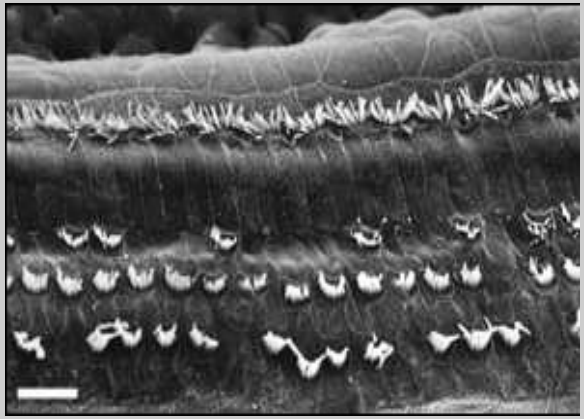
Basic Principles

- Objective test of outer hair cell (OHC) function
- OHCs must be normal for hearing thresholds to be normal
- Damage from ototoxins impacts OHCs
- OAE changes signal changes in cochlear function
- OAE changes can occur prior to PTS
- Clinically, a change in OAE level is evidence of cochlear damage and associated with a change in hearing





Photos courtesy of Dr. Marc Lenoir, from “Promenade around the cochlea” EDU website: http://www.cochlea.org, by Remy Pujol et al., INSERM and University of Montpellier

Basic Principles

- DPOAEs are often affected in more ears than conventional audiometry
  - Noise: Lapsley Miller & Marshall, 2007; Helleman & Deschler, 2012
  - Aminoglycosides: Katbamna et al. 1999; Stavroulaki et al., 2002; Mulheran & Degg 1997
  - Cisplatin: Stavroulaki et al., 2001

- High frequency DPOAEs are most sensitive to ototoxic damage (Reavis et al. 2008); SRO principle works for DPOAEs

Case Study

68 year old Vietnam Veteran

- Unknown agent orange exposure
- Currently smoking and 40-50 py smoking history

Diagnosed with Lung Cancer

- Right upper lung adenocarcinoma (T1bN2M0, stage IIIA)

Recommended Neoadjuvant Chemoradiotherapy

- Cisplatin + Etoposide + Radiation (May – June)
  - ***Cisplatin 50mg/m2, IV, on days 1, 8, 29, and 36***
- Surgery (RU lobectomy in October)

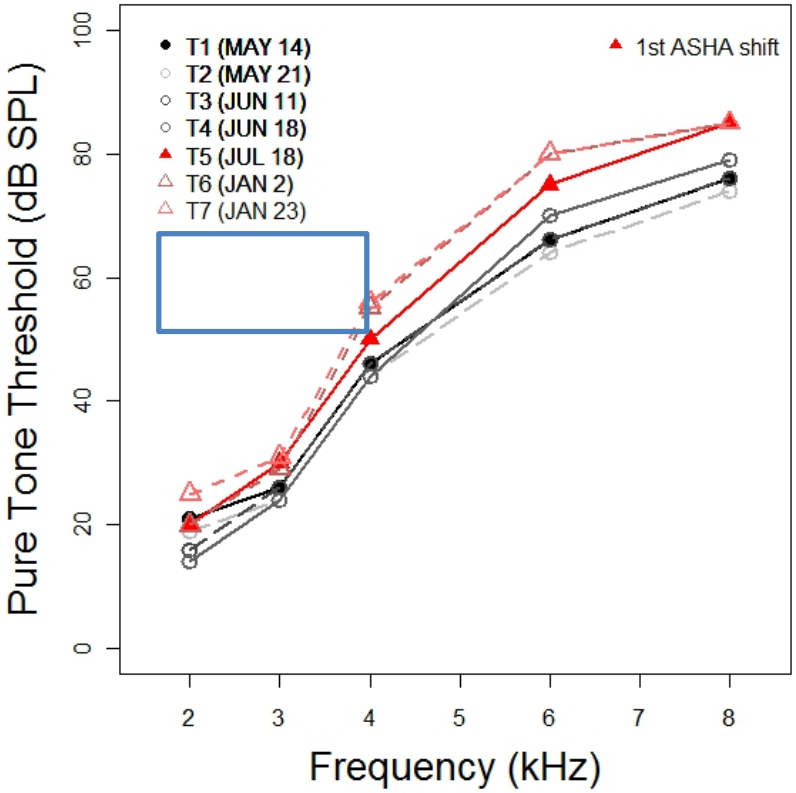
Recommend Adjuvant Chemotherapy

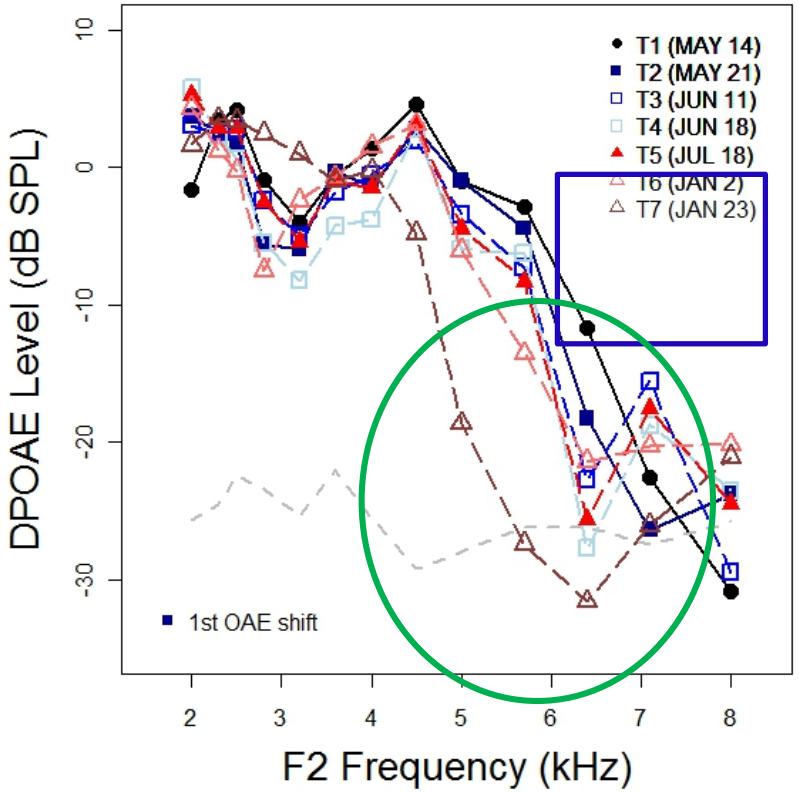
- Cisplatin + Etoposide (Following January)
  - ***Cisplatin 75 mg/m2, IV, on days 1, 22***

Total Cisplatin Exposure = 350 mg/m2 or 620 mg

Case Study: Sensitive/Early Index

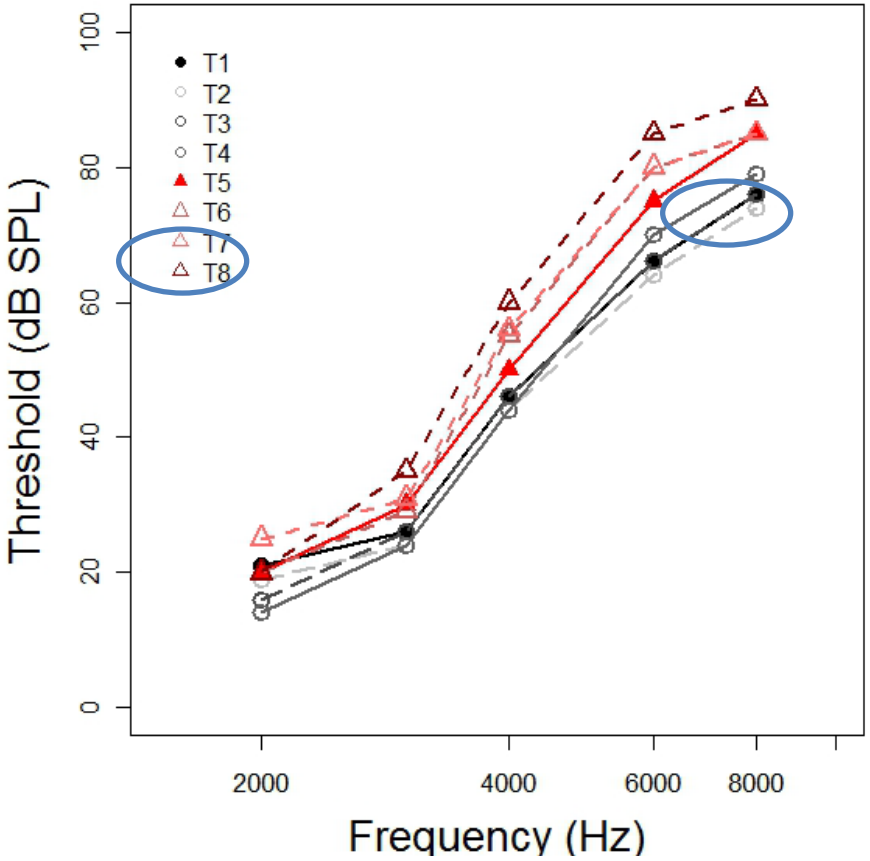
OAE change appears to have earlier time course than HL from cisplatin



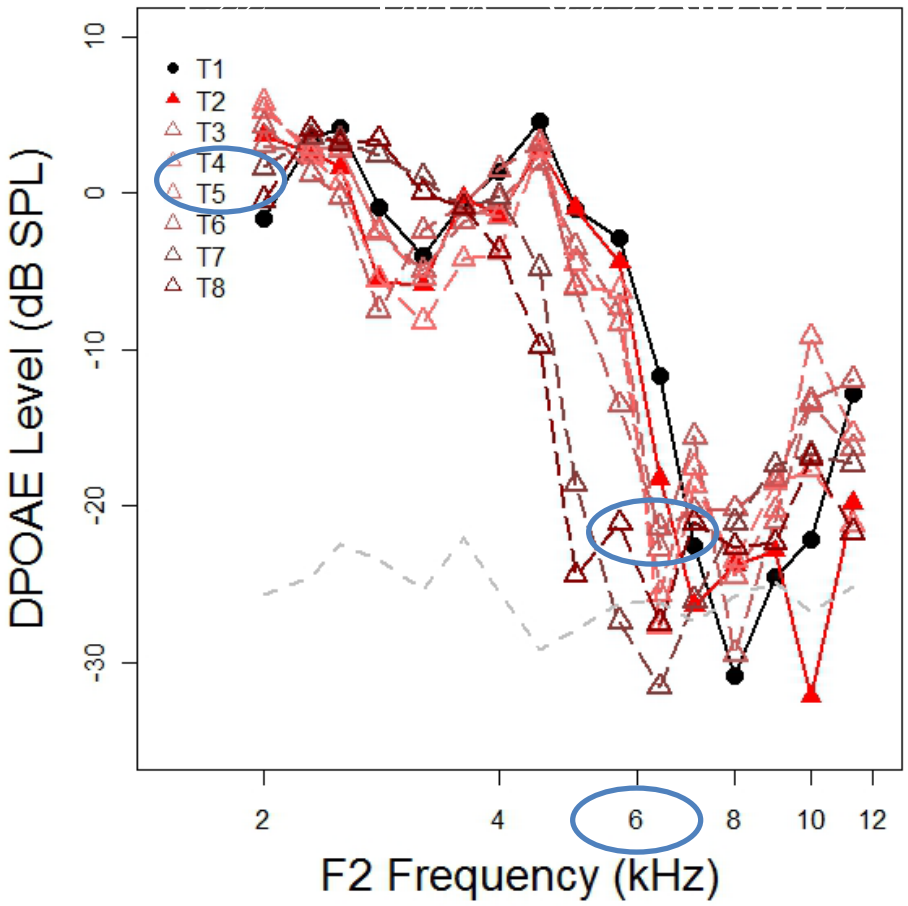


Case illustration of serial measurements obtained in a 68-year-old patient receiving Cisplatin treatment with A, behavioral hearing thresholds as a function of frequency and B, DPOAE level as a function of f2 frequency. Different lines/symbols represent data from eight trials, with the filled circle indicating Trial 1 (baseline).

Case Study: Serial Measurements during Cisplatin treatment

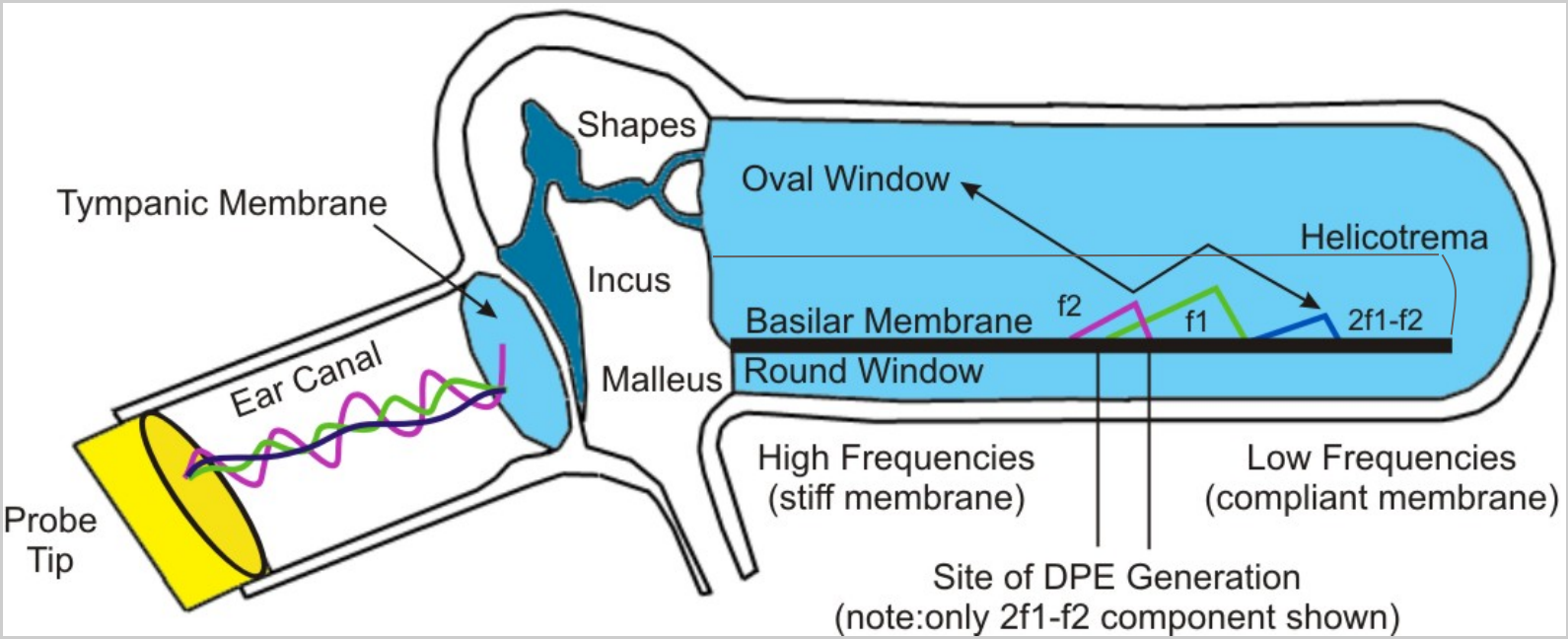


A. filled triangles denote Trial 5, the trial for which the initial ‘‘significant threshold shift’’ or STS was documented using American Speech-Language-Hearing Association (ASHA) criteria (40).



B. filled squares highlight Trial 2, the trial for which the initial ‘‘significant OAE shift’’ from baseline occurred at f2 6 kHz based on a meta-analysis of normal test-retest variability (41). The dashed line denotes the average noise floor across all trials.

DPOAE Measurement

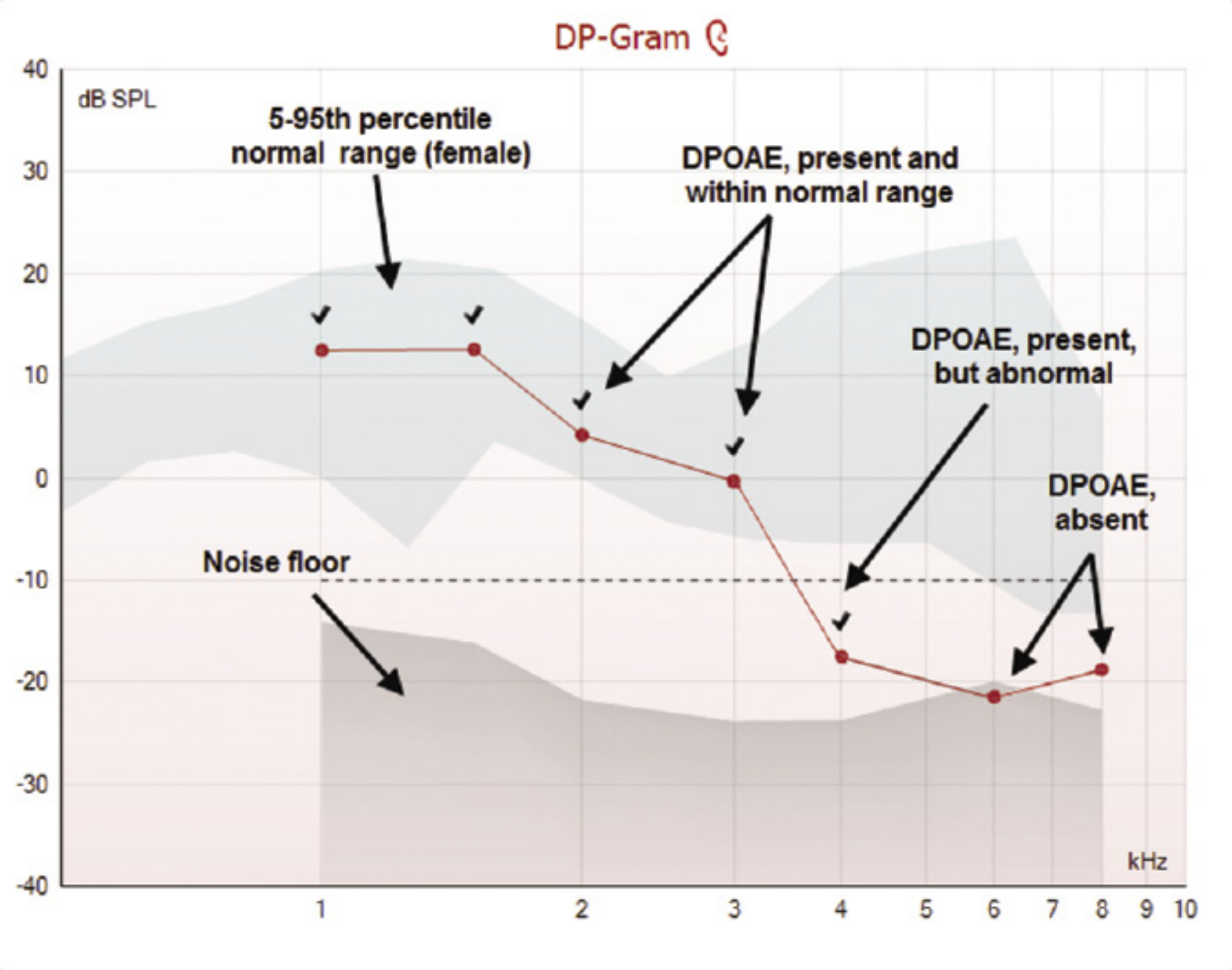


- Acoustic response measured in the ear canal
- Evoked using two-tone stimulation (f1<f2)

Konrad-Martin, Dawn., San Diego State University presentation, 2016.

DPOAE Measurement

- Factors:
  - Noise Floor
    - average amplitude in several frequency bins above & below $2f_1$-f_2
    - *Worse at low frequencies*
  - Signal-to-noise ratio (SNR)
    - dB difference between SPL at $2f_1$-f_2 and the estimated noise
    - *Worse at low stimulus levels and frequencies, & in impaired ears*
  - System distortion (sometimes called “system noise”)
    - Distortion/noise from the equipment that occurs at the 2f1-f2 frequency
    - *Greatest at high frequencies and high primary levels*



Ramos JA, et al., Hearing Review, 2013

DPOAE Measurement

- Test-Retest reliability is key
  - Low noise and distortion generated by system
  - Normal middle ear function
  - Quiet test environment, equipment and patient
  - Consistent probe placement

DPOAE Protocol

- No consensus on a universal protocol
  - Need more research
  - Need better equipment
- No consensus on OAE criteria for a “significant change”
  - Most studies have used standard error of measurement (McMillan et al., 2013)
- Protocol should be:
  - Based on DPOAE theory, patient population and known patterns of damage associated with the exposure
  - Fast, sensitive, specific and repeatable
  - Generate valid results in the majority of individuals tested

Konrad-Martin, Dawn, et al., Otology & Neurotology, 2016

DPOAE Protocol

- Start with whatever canned protocol you have
  - Provides gross assessment of broad range of frequencies
  - Determine which baseline DPOAE measures are valid (e.g., 6 dB SNR or greater; DPOAE response at least -20 dB SPL)
- Let knowledge about damage patterns and mechanisms guide additional in-depth measures
  - Add a lower level frequency sweep (f_2=45 dB SPL)
  - Using SRO concept, test in fine frequency steps, and/or use of multiple levels near the highest DPOAE with a robust response
- Examine valid responses for significant changes
  - Convert to binary, pass-fail outcome based on pre-determined frequency or frequency range

Konrad-Martin, Dawn, et al., Otology & Neurotology, 2016

DPOAE Protocol (at NCRAR)

- DP-gram search for highest f_2 yielding a DPOAE level
- Fine step DP-gram in half octave range for highest DP frequency with 6 dB SNR and a response level of greater than or equal to -20 dB SPL
  - Helps identify fine structure
  - Helps define putative lesion site
- DP I/O's at three highest frequencies tested in 1/3rd octave steps (Kummer et al., 1998)

DPOAE Protocol

(1) Fine Step Frequency Sweep (DP-gram)

- Helps identify fine structure
- Helps define putative lesion site

(2) Level Sweep (I/O function)

- Includes the more sensitive lower-level measurements
- Can be used to estimate a DPOAE threshold

(3) Ratio Sweep (Group Delay)

- Can be used to determine latency

Reavis, K. M., et al., Ear and hearing, 2015.

DPOAE Protocol

- Katbamna et al. (1999) compared different DPOAE paradigms for purposes of monitoring CF patients and found..
  - DPOAE group delay and detection threshold values (determined from I/O functions) were earlier indicators of cochlear ototoxicity compared to conventional and HF hearing thresholds
    - Group delay values were reduced or prolonged, dependent on cumulative doses of tobramycin
    - Some of the subjects' demonstrated significant elevations in DPOAE detection thresholds compared to controls
  - Common DPOAE level measures obtained from frequency sweeps in a group of children and young adults with cystic fibrosis (CF) receiving tobramycin
  - Results suggest that assessment of DPOAE group delay and detection thresholds may be more effective tools for monitoring cochlear ototoxicity than the more traditional DPOAE frequency sweep.

Katbamna, Bharti, et al., Ear and Hearing, 1999

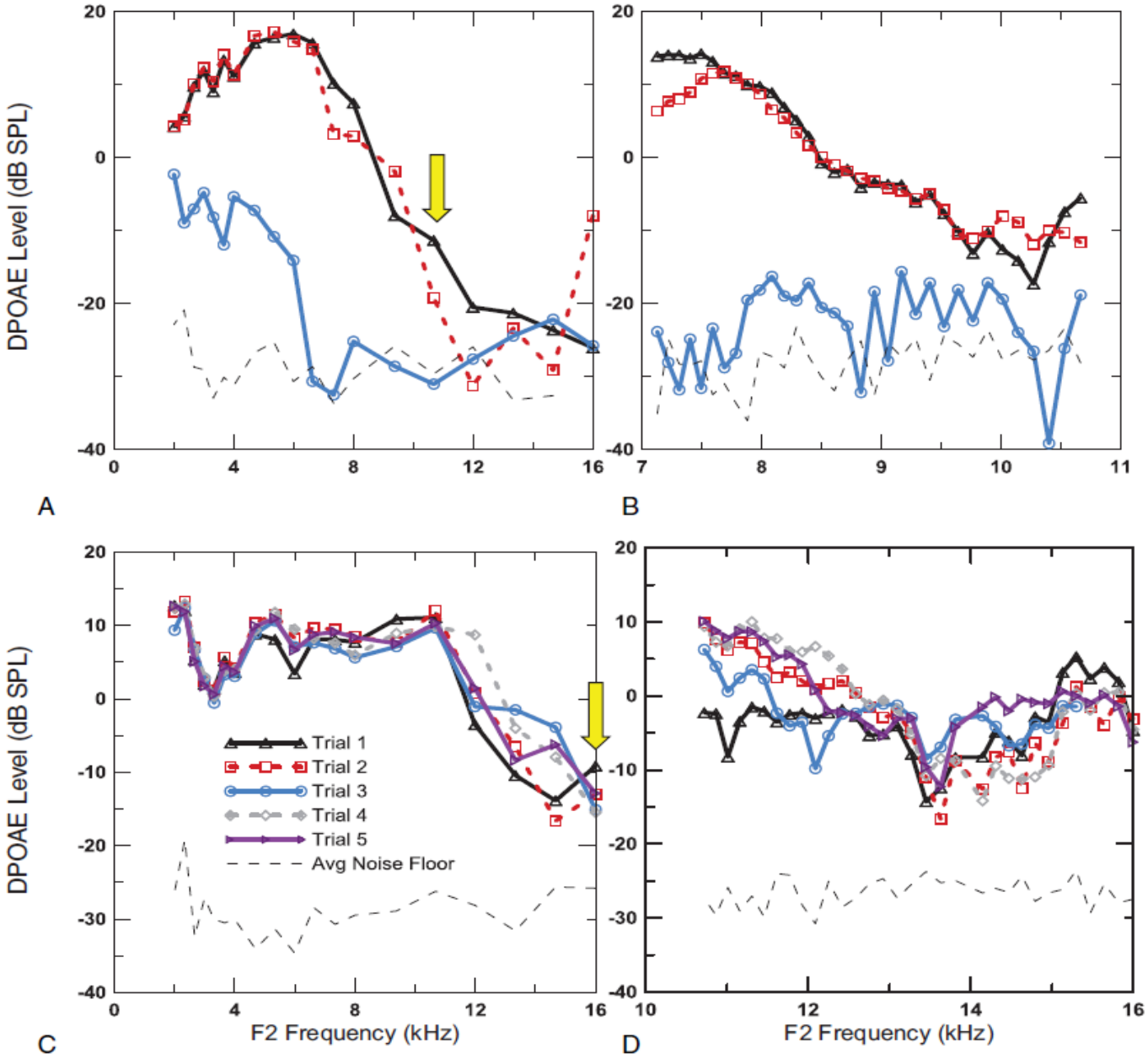


FIG. 2. DPOAE level as a function of f2 frequency for a patient receiving Cisplatin (top panels) or Oxaliplatin (bottom panels). Different lines/symbols represent data from different trials and the thin, dashed line denotes the average noise floor across all trials shown in each plot. (A and C) Broad DPOAE f2-sweep completed in gross frequency steps (three octaves in 1 of 6 octave steps). For each row, the arrow indicates the highest f2 yielding a DPOAE level >6dB above the noise floor and an absolute level >20 dB SPL obtained at baseline. This frequency determined the endpoint of a DPOAE f2-sweep completed in finer frequency steps over a narrower range, shown in panels b and d. (B and D) DPOAE fine f2-sweep (2 of 3 of an octave in 1 of 48 steps).

DPOAE Change Criteria

- For DPOAE interpretation
  - Should be driven by mechanisms and damage pattern with agent, and population sampled
  - A prior selection during baseline testing of single frequency band or frequency-band-average to monitor
  - Use absolute value (decrement or increment)
  - Criteria should differ by test (e.g., DPOAE vs TEOAE)

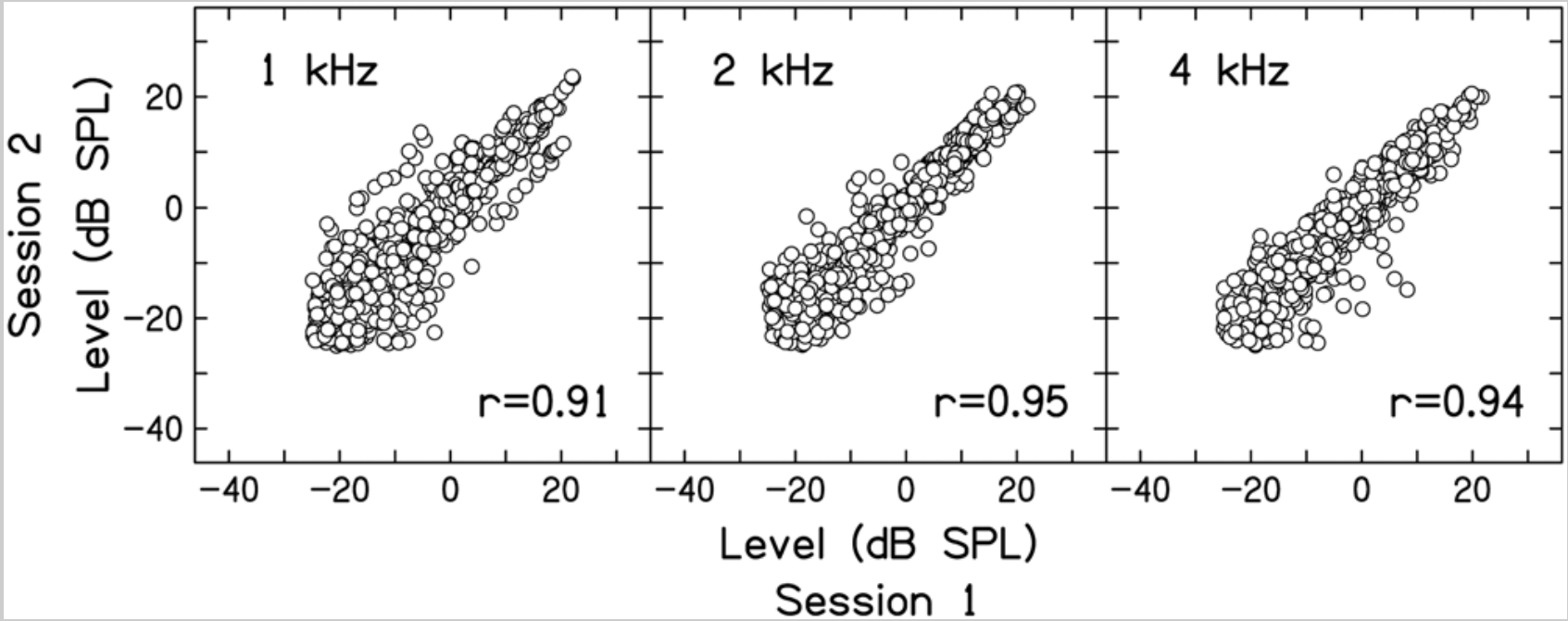
DPOAE Change Criteria

- Normative Reference Limits
  - Works the same way as confidence intervals for determining whether an ear is normal or impaired using DPOAEs (from Gorga lab or Vanderbilt lab)
  - Use established norms for DPOAE level shifts to determine if OHC function has changed or is stable
    - Meta-analyses provides accurate estimate (Reavis et al. 2015)
    - Also see Konrad-Martin et al. 2018
  - Evaluate your own test-retest reliability while monitoring to ensure your results are comparable to the published data

DPOAE Change Criteria

- Weak emissions (i.e. near DPOAE threshold) less reliable than robust emissions
  - Expect less reliable emission for low stimulus levels, at low and very high frequencies, and in impaired ears
- Test-retest variability decreases with increasing time between measurements
  - Thorson et al., 2012; Helleman & Dreschler, 2012; Reavis et al. 2015

DPOAE Change Criteria: Test-retest Correlations in Impaired Ears



74 subjects, ages 11—76 years. 16 had normal hearing; 58 had hearing loss. DPOAEs obtained at 3 frequencies with L2 ranging from -20 to 80 dB SPL.

Figure shows DPOAE level in session 2 as a function of the DPOAE level from session 1.

Note correlations are poorer for low level (and therefore low SNR) recordings. Also note frequency effect.

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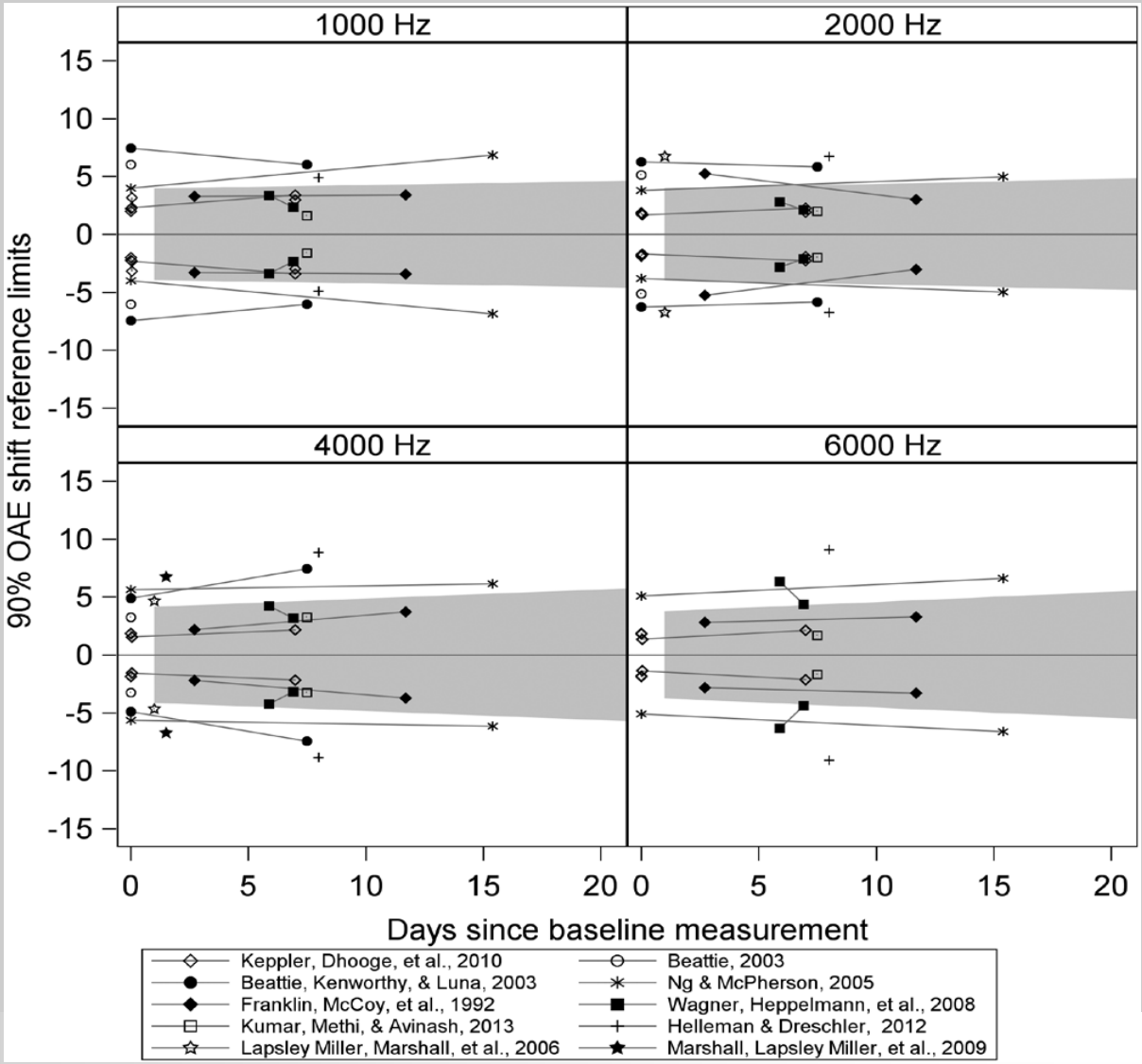
FIG. 2 from Thorson et al. Ear and Hearing, 2012

DPOAE Change Criteria: A Meta-Analysis to Establish Test-retest Reference Limits in Control Ears

-The 90% confidence interval limit is shown on the y axis. Days since initial test is on the x axis.

-Test-retest variability increases with the number of days between tests.

-There is a frequency effect with widest interval at 1000 Hz. Thorson (2012) noted this likely has to do with decreased SNR at that low frequency due to subject noise)



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Reavis, McMillan, Dille, Konrad-Martin, Ear and Hearing, 2015

DPOAE Change Criteria: A Meta-Analysis to Establish Test-retest Reference Limits in Control Ears

TABLE 3. Table of mean SEM with upper and lower 90% reference limits of each f_2 primary frequency by days since baseline test

	f_2 Frequency							
	1000		2000		4000		6000	
Days From Baseline	SEM	90% Reference Limits	SEM	90% Reference Limits	SEM	90% Reference Limits	SEM	90% Reference Limits
1	1.7	±3.95	1.7	±3.98	1.8	±4.16	1.6	±3.76
2	1.7	±3.98	1.7	±4.03	1.8	±4.23	1.7	±3.85
3	1.7	±4.02	1.7	±4.07	1.9	±4.31	1.7	±3.93
4	1.7	±4.05	1.8	±4.11	1.9	±4.39	1.7	±4.02
5	1.8	±4.08	1.8	±4.15	1.9	±4.47	1.8	±4.11
6	1.8	±4.11	1.8	±4.19	2.0	±4.54	1.8	±4.20
7	1.8	±4.15	1.8	±4.23	2.0	±4.62	1.8	±4.29
8	1.8	±4.18	1.8	±4.27	2.0	±4.70	1.9	±4.37
9	1.8	±4.21	1.9	±4.31	2.1	±4.78	1.9	±4.46
10	1.8	±4.24	1.9	±4.35	2.1	±4.85	2.0	±4.55
15	1.9	±4.41	2.0	±4.56	2.3	±5.24	2.1	±4.99
20	2.0	±4.57	2.0	±4.76	2.4	±5.63	2.3	±5.43

The 90% reference limits can be computed at other days not shown using the equation $\pm 1.645 \cdot \sqrt{2} \cdot \overline{SEM}(D)$. However, results beyond about 15 days need to be extrapolated and should be used with caution. Results at 20 days, shown below, are extrapolated from the fitted model.

SEM, standard error of the measurement.

A meta-analysis that compares results across a number of studies to develop robust norms, and norms that cover time span closer to a course of cisplatin.

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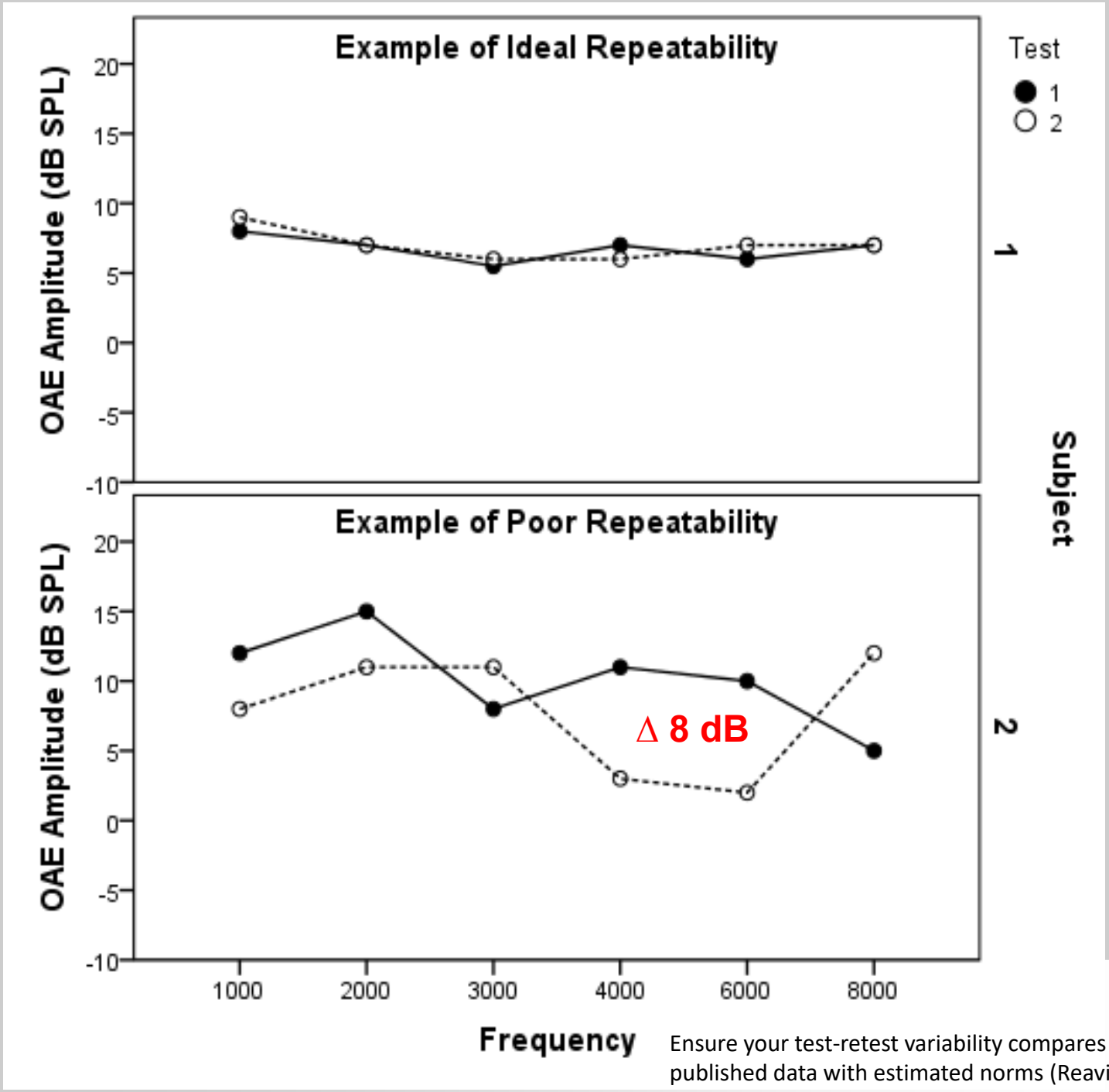
Reavis, McMillan, Dille, Konrad-Martin, Ear and Hearing, 2015



Ensure your test-retest variability compares to the published data with estimated norms (Reavis et al., 2015)

Caveats for Interpretation

- Middle ear function must be normal to interpret results
- Hearing loss precluding baseline
- OAEs are poor predictors of hearing thresholds when hearing loss is due to factors other than/in addition to OHC damage
- High-frequency measurements limited with current clinical systems
- Multiple stimulus frequencies and test levels used, generating complex multivariate outcomes
- Current calibration techniques, probe placement
- “Mixed-source” OAEs challenging to interpret
  - Responses may decrease or increase following damage
  - Basal components” may “fill in” regions of damage

Bramhall, N. F., et al., American Journal of Audiology, 2019

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