A Sound Foundation Through Early Amplification

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The strategic application of otoacoustic emissions to infants and children

Carolina Abdala, Ph.D.

Abstract

It has been almost 40 years since OAEs were first discovered and reported. They have since been developed into a useful clinical tool for the screening of hearing and the detection of hearing loss. There are two distinct classes of OAEs, nonlinear distortion and linear reflection; using the combined information each can offer might provide advantages. At present, OAEs are under-utilized and clinically applied in a rote manner with a highly abbreviated test protocol. Here we discuss how distortion and reflection OAEs are different, and how combining them in a strategic approach and using a more flexible test protocol could improve their clinical utility. There are innovations looming on the horizon that will enhance measurement and analysis of OAEs and facilitate the application of more comprehensive test protocols.

Introduction

Otoacoustic emissions (OAEs) are low-level sounds produced by the healthy cochlea as a byproduct of normal cochlear function. These byproducts travel in reverse from their site of origin in the cochlea, backwards towards the stapes, through the middle ear, and into the ear canal where they can be recorded with a sensitive microphone. OAEs require normal or near-normal outer hair cells (OHCs) to provide "amplification" of these backward traveling waves so that this small outgoing energy can be detected in the ear canal. One type of OAE—the distortion-product OAE—also relies on OHCs for its generation. These low-level acoustic byproducts of the normal hearing process provide an invaluable window into the cochlea and a gauge of cochlear health and hearing.

When OAEs were first discovered (Kemp, 1978), it was thought that each type of emission was basically a duplicate of the other; that is, although some were evoked with clicks and others with two tones, we assumed that they all came about the same way and provided redundant information about the cochlea. However, in the last decade or so, we have come to understand that *all OAEs are not alike* (Shera & Guinan, 1999). There are two basic types of OAEs: nonlinear distortion and linear reflection. These have also been termed, wave- and place-fixed OAEs (Knight & Kemp, 2000, 2001). The two emission types not only arise from different sites in the cochlea, they arise by two unique and distinct processes or generation mechanisms. They are not exact copies of one another.

Distortion-type emissions are evoked by two tones presented simultaneously; they arise near the overlap of the two traveling waves elicited by these two tones or *primaries*. Distortion-type OAEs come about due to nonlinearities in cochlear processing. The cochlea's response to sound grows as stimulus level is increased but only to a point; then the growth saturates and the response compresses. This compression is evidence of nonlinearity. Nonlinearity in the cochlea likely originates at the ion channels found on the tips of OHC stereocilia. A stimulus vibrates the basilar membrane within the cochlea and in doing so, displaces OHCs and the stereocilia atop these specialized cells. The thin filaments attached to the tips of the stereocilia sway with the motion and pull open the ion channels, like trap doors, on the ciliary tip. Opening the ion channels allows current to flow, changing the voltage within the OHC, and causing the OHC to expand and contract. The cell's motility augments the vibratory motion of the basilar membrane in a frequency-specific way and enhances our sensitivity to sound and our frequency tuning. We term this motility and its effect on hearing the "cochlear amplifier". Once the mechano-electric transduction channels near the tips of the stereocilia are all forced open by a stimulus, the OHC force saturates (there are no more channels to open); and the growth of the cochlear response saturates with it. Distortion-type emissions provide one piece of evidence for this compressive nonlinearity in the cochlea.

Reflection-type emissions are quite different. Reflection OAEs arise through a linear reflection process; that is, a back-scattering of waves. Theoretically, they do not require cochlear nonlinearity for their generation. The cochlear spiral has irregularities throughout—perhaps the width or shape of OHCs is irregular along the length of the cochlea or the number of prestin proteins in OHCs vary, or the stereocilia array is not uniform. No biological membranes are perfectly smooth and uniform along their length. When a sound is presented to the ear, traveling waves are launched down the cochlear spiral on the basilar membrane. As they propagate, they encounter these irregularities, which disrupt the smooth forward flow of energy and give rise to scattered wavelets that turn back toward the base of the cochlea. The physics of this scattering process indicates that the strongest reflection occurs near the peak of the traveling wave (Zweig & Shera, 1995). When enough of these back-scattered wavelets sum in a coherent way, they produce an emission that is large enough to be recorded in the ear canal as a reflection OAE.

The familiar distortion-product OAEs (DPOAEs) are nonlinear distortion emissions, though they also include a small reflection component. Thus, DPOAEs are really mixed OAEs with the distortion part being dominant under common recording protocols. Click-evoked OAEs, stimulus-frequency OAEs (OAEs generated with one low-level pure tone), and even spontaneous OAEs are linear reflection emissions. The two classes of OAEs—distortion and reflection—have distinct phase signatures, which tell of their generation process; this is a convenient way of distinguishing them. The reflection-emission phase rotates rapidly across frequency, whereas distortion-emission phase is relatively invariant if a fixed f_2/f_1 ratio is used (Shera & Guinan, 1999; Shera, 2004). Additionally, distortion and reflection OAEs have different amplitude spectra; distortion is smooth with less variation across frequency, and reflection emissions include fine structure that tells of its backscattering nature (Figure 1).

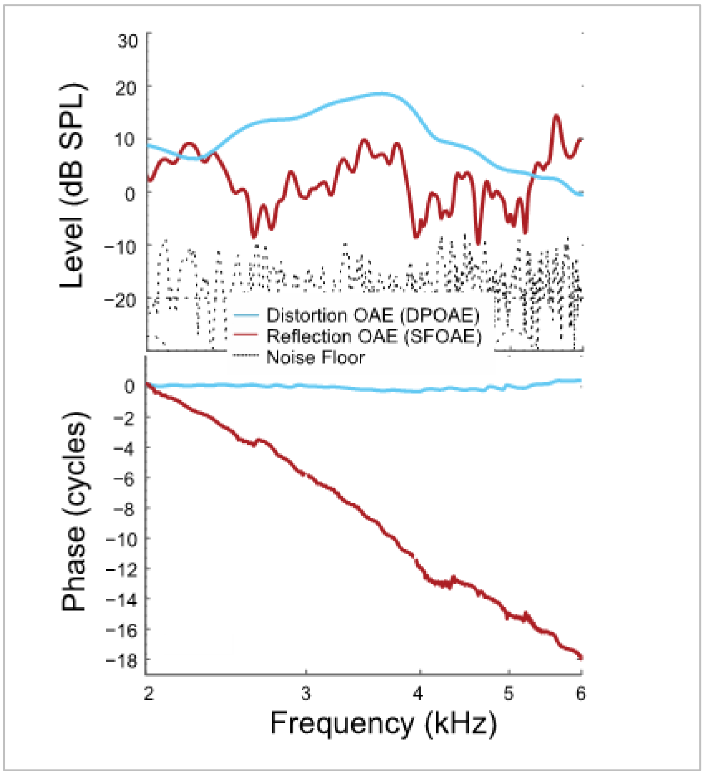

Figure 1. The upper panel shows amplitude spectra for a distortion-type otoacoustic emission (cyan) and a reflection-type otoacoustic emission (red). Distortion OAEs have smoother spectra and little fine structure (once the reflection energy is removed from the DPOAE, as shown here). In contrast, the stimulus-frequency OAE, a reflection emission, has fine structure with many peaks and valleys due to its origin in back-scattered wavelets. The lower panel shows a phase versus frequency function for each OAE type; OAE phase is used to classify emissions as distortion or reflection. Distortion OAE phase is relatively invariant across frequency (when a fixed f_2/f_1 is used), whereas reflection OAE phase rotates rapidly across frequency and has longer delays. These very different patterns of phase across frequency provide evidence that each OAE comes about by a distinct process within the cochlea (See Shera and Guinan, 1999 for more information about OAE generation mechanisms).

Are these two OAE-types fundamentally different? And, can each tell us something different about cochlear health? The answer to the first question is a strong, yes. Empirical evidence is abundant. First of all, their remarkably different phase responses provide evidence that the two OAEs come about in very different ways (see Shera, 2004 for a detailed discussion). Experimental manipulations also suggest distinct sources. For example, both aspirin (which reduces OHC motility) and sound-evoked activation of the descending medial efferent tract reduce reflection emissions more than they do distortion emissions. Age also impacts the two OAE types differently. During maturation, distortion emissions appear to be nearly mature early in life with the exception of distortion OAE phase measured from the apical half of the cochlea; however, this material is beyond the scope of this paper. The interested reader can read Abdala and Dhar (2012). Reflection emissions, by contrast, show non-adult-like features in newborns that, ironically, are bigger than adult OAEs, and have steeper phase versus frequency functions, which might be partly due to middle ear immaturities (Abdala & Dhar, 2010, 2012; Abdala et al., 2011). During aging, it appears that distortion emissions are reduced by the aging process more rapidly than are reflection emissions (Abdala & Dhar, 2012). Finally, a strong piece of evidence firmly establishing that these two types of OAEs are indeed distinct can be found in genetic mutations causing hearing loss and deafness. Genetically engineered mice have been developed with targeted mutations in genes known to regulate and influence the ear. One such mutation (the Stereocilin mouse) has lost its thin thread-like links between stereocilia and has no DPOAEs but sensitivity and tuning are near normal, suggesting that reflection emissions would be present if measured (Verpy et al., 2008). A second mutant mouse (the Ceacam16 mouse) has holes in its tectorial membrane. This mouse produces very high-level reflection emissions (well beyond the normal range for this species) and unremarkable, normal distortion products (Cheatham et al., 2014). These interesting mouse mutations cause pointed lesions and anomalies in the cochlea, which impact reflection and distortion emissions in unique ways. *Thus, both human and mouse evidence tells us that the two OAE types do indeed reflect distinct processes in the cochlea.*

The answer to the second question is less certain. Can each OAE type tell us something different about cochlear function and dysfunction? We think so. There is anecdotal evidence from the clinic suggesting that these two emission types behave differently in hearing-impaired patients. Most clinicians will tell you that the click-evoked OAE becomes unmeasurable (and yields an "absent" result) with milder degrees of hearing loss than the DPOAE, which is often present even with moderate amounts of hearing loss. How can we relate this observation back to our OAE generation sources? Reflection emissions reflect from the peak region of traveling waves in the cochlea, which is the region where the cochlear amplifier effect is strongest. Even a slight-mild hearing loss can affect reflection emissions. The DPOAE in contrast, is strongest at moderate stimulus levels where cochlear response growth is compressed and distortion is created. Some empirical research also suggests that the click-evoked OAE is more sensitive to slight amounts of hearing loss than the DPOAE (Gorga et al., 1993; Lapsley-Miller et al., 2004). If these two OAE types were of similar origin, they would not show individual and non-uniform responses to cochlear pathology. However, research is required using both OAEs to confirm and define these distinct sensitivities to hearing loss in a large group of individuals with hearing impairments of varying etiology.

Given the distinct origin of both OAEs, why record only one type of OAE in the clinic? If each of the two types—distortion and reflection—offer unique and non-redundant information about the ear and provide a more complete picture of the hearing loss when considered together, why limit information? The parable of the elephant and the blind men might help us consider the benefits. Hearing loss is the elephant. We want to describe it, understand it, know it in all its complexity so as to better intervene. And the auditory tests we use to probe the hearing loss are the various blind men, each handling one limited part of the elephant—the trunk, the flank, the tail, etc—and potentially coming to flawed conclusions about the beast they seek to describe. Audiologists must put all of these pieces together to understand hearing loss in the most comprehensive way. The more pieces, the more complete the picture. If they only have one tool, surely the animal will be described as a tail or a flank. During auditory assessment, OAEs can provide a *dual* probe for understanding hearing loss. And, these two OAE responses, combined with all other auditory assessment tools, can allow the full elephant to emerge.

As a caveat, either reflection (click-evoked) or distortion (distortion-product) OAEs alone can be used effectively to *detect* a hearing loss for screening purposes (Norton et al., 2000). But once an audiologist moves beyond the detection stage and is conducting diagnosis, considering both OAEs together might be maximally informative. This is when we could use a *strategic* application of OAEs to exploit the power of both OAE sources together. At present, the audiological field is under-utilizing these powerful metrics of cochlear health by accepting a thumbs-up/thumbs-down answer. This under-utilization is partly due to a paucity of strong clinical research defining how the combined OAE profile can enhance diagnostics; and partly because clinicians might be stuck in their familiar, limited routine of OAE usage. The abbreviated OAE clinical protocol at present resembles the following. Only one type of OAE is applied during hearing assessment, at one stimulus level (typically, 65-55 dB SPL for DPOAEs; 80-86 dB pSPL for CEOAEs) and across an abbreviated range of frequencies (1.5-4 kHz or 2-3 discrete frequencies if it is a screening). The above parameters are the most effective in *detecting* hearing loss in large groups of hearing-impaired and normal-hearing individuals (Gorga et al., 1993, 1997). However, in a diagnostic capacity, we are interested in going beyond detection of hearing impairment toward a more strategic application of OAEs.

How might the audiologist be more strategic with OAEs? An audiologist dissatisfied with the simple absent/present distinction OAEs are expected to yield and the limited role they currently play becomes deliberately strategic when he or she is willing to stray from the default parameters programmed into most commercial systems and allows an awareness of OAE generation mechanisms to influence the choice and flexibility of a test protocol. Here are three concrete suggestions about how an audiologist might consider an expanded, strategic use of OAEs: (1) Record both OAE types in a patient's ear when possible; (2) Record DPOAEs at more than one stimulus level—go to higher levels than the default 65-55 dB SPL; and (3) Do not simply use absent/present decision-making to interpret results but consider whether OAEs fall within a range of normal amplitude given patient demographics.

(1) Record both OAE types together. Many of the mouse mutations presented previously have been identified as hearing loss genes in *human* families as well. An individual with untethered stereocilia (i.e., showing a stereocilin deficiency) or a porous tectorial membrane (showing a Ceacam16 deficiency) might walk into an audiology clinic tomorrow. If only one or the other OAE-type is impacted by these mutations, how will an audiologist identify the genetic hearing loss and refer them for appropriate genetic testing and counseling? It is true that these mutations are relatively rare, but perhaps they are more common than we think—perhaps we have simply failed to identify them due to our limited testing protocols (much like auditory dysynchrony/neuropathy went undetected for decades).

A thought experiment might help establish rationale and merit for this guideline. A child comes into the clinic and has an absent click-evoked OAE. What does it tell the audiologist? It tells him/her that hearing loss is present but, unfortunately, we know only that it ranges from mild to profound. Thinking strategically, the audiologist records a DPOAE as well. If the DPOAE is present (low in amplitude perhaps, but measureable with adequate signal-to-noise or SNR), the audiologist's understanding of the hearing loss expands. She has recorded an absent CEOAE, which is a reflection emission sensitive to even small amounts of hearing loss, and a present DPOAE, which is sometimes measureable even with moderate levels of hearing loss. What does this combination of results tell us? It tells us that the sensorineural hearing loss (SNHL) is more likely to be mild-moderate in nature than profound. Profoundly hearing impaired ears do not produce cochlear nonlinearities. Cochlear nonlinearities like the distortion product are hallmarks of the healthy, normal (or near-normal) cochlea. The results of these two OAE tests combined allow the audiologist to estimate the degree of SNHL.

(2) **Record the DPOAE at higher stimulus levels.** In our first example, perhaps the DPOAE was initially absent when recorded at default stimulus levels. The strategic-minded audiologist will present slightly higher-level primary tones, 75-75 dB SPL perhaps, in an attempt to evoke a distortion-product OAE. It is often the case that DPOAEs are not measurable above the noise (and are erroneously deemed

"absent") at low-to-moderate default levels in a mildly hearing-impaired ear, but present at higher levels. If this is the case in our example, we will have a familiar diagnostic combination—absent reflection emissions and present distortion emissions, albeit evoked with higher-level primary tones. And, we can interpret this combination in the same way as outlined in guideline #1 above. Of course, a threshold test such as an ABR or behavioral probe will be needed to verify and confirm the estimate, but this combination of OAE results lessens the likelihood of profound hearing loss. (Note: the audiologist must know the *system distortion* levels in the equipment. An amplifier or transducer can generate nonlinear distortion much like the ear does, in particular at higher stimulus levels. One can define system distortion by putting the probe in an appropriate coupler and running the test protocol. In the absence of an ear, this measure provides the baseline system distortion. The DPOAE evoked with high primary-tone levels must be well above both the noise floor and system distortion to be considered a true biological response.)

(3) **Look at Normative Data to Interpret OAEs.** If an audiologist deems the OAE—whichever the type (reflection or distortion)—absent or present and proceeds no further, the diagnostic process is incomplete (see Abdala & Shera, 2012). An OAE recorded in the clinic is typically considered "present" if it is 3-6 dB above the noise floor recorded in the ear canal (the actual SNR criteria varies from clinic to clinic). This "present" designation is solid information but the strategic audiologist will compare the amplitude of the OAE result to those published in the literature or to the normative amplitudes generated in their own clinic, which is arguably better, and determine if the response falls within the amplitude ranges that a normal ear produces. As an example, newborns have click-evoked OAEs that are robust. It is not unusual to observe 10 to 20 dB SPL responses from neonatal ears and they are often present across the entire test frequency range. If the audiologist sees a newborn with –5 dB SPL CEOAE (and perhaps it is only present from 1-3 kHz), is this normal? No. Even if the noise floor is -15 dB SPL, ensuring a SNR of 10 dB, the result is not normal given the patient's age; it is atypical for a newborn ear, and the result should prompt retest or follow-up. Awareness of OAE amplitude trends across the human lifespan, and normative values at various ages and frequencies is key to the strategic application of OAEs to infants and children.

These three guidelines—consider recording both OAE types together, measure DPOAEs at increasing primary-tone levels, and use normative data in interpretation—will help audiologists utilize the rich and varied information OAEs offer about cochlear health and hearing.

The last section of this paper explores advances in OAE measurement and analysis looming in the near future. Recording both OAE types or presenting more than one primary-tone level takes more time than a default protocol, and this is a realistic concern for all clinicians. How can the tester make-up this added test time? OAEs can be recorded with sweeping tones versus the more conventional paradigm using discrete pure tones. In swept-tone paradigms, tones are swept upward or downward at rapid rates of about 0.5 octave/second or faster (Long et al., 2008; Kalluri & Shera, 2013; Abdala et al., 2015) and the OAE is extracted from the sound recording in the ear canal after the test has been completed. The resolution of the swept-tone OAE is unparalleled because it is possible to estimate amplitude and/or phase offline at any point along the frequency range. The resulting waveform is not a gross clinical DP-gram with 6-8 DPOAE values but a complex DPOAE spectrum (see Figure 2). It is a well-defined record of the response across frequency showing characteristic peaks and valleys (Long et al., 2008; Abdala et al., 2015). This fine structure gives evidence of a DPOAE that is comprised of nonlinear distortion, but also some reflection elements; their constructive and destructive interference produces the peaks and valleys. Recording the DPOAE in this way allows one to be careful of minima in the spectra that do not actually reflect the strength of the DPOAE from the ear but cancellation between the two components.

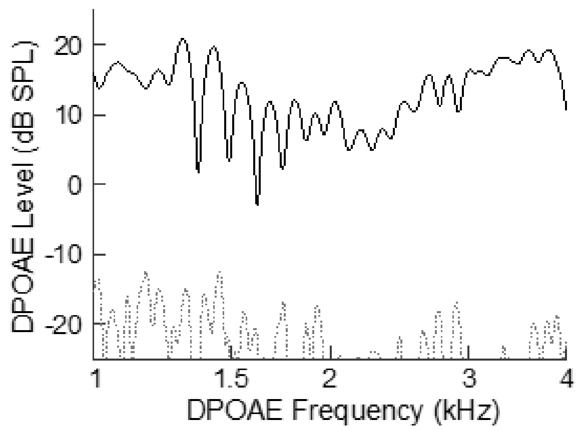

Figure 2. The DPOAE shown here was recorded using swept-tones and analyzed with fine frequency resolution (approximately 500 points across frequency). Because the DPOAE is comprised of both distortion and reflection components, the spectrum shows fine structure, peaks and valleys, when recorded with sufficient resolution. Component-separation programs can be used to isolate the distortion part of the response from the typically smaller reflection part (as done in the upper panel of Fig. 1 for the cyan curve). This DPOAE spectrum provides a much more detailed picture of cochlear distortion across frequency than a conventional clinical DP-gram.

A second innovation that might make it into the audiology clinic in the not-too-distant future is a program to separate the mixed DPOAE into its constituent parts—a distortion component and a reflection component, so that the tester collects a measure of both OAE types simultaneously. This sounds ideal but unfortunately, the reflection component of the DPOAE is small and confounded by other factors. However, component separation *does* allow for a more pure measure of nonlinear distortion (uncontaminated by reflection elements), and we know that nonlinearity is a hallmark of cochlear health. Separating DPOAE components is an offline signal-processing technique. However, it does require the collection of high-resolution data; ideally it couples with swept-tone protocols to achieve this resolution. Component separation and swept-tone OAEs are currently in use in several research laboratories. Optimizing and abbreviating these techniques for clinical application is a realistic goal.

A third OAE innovation is the stimulus-frequency (SF) OAE. Although applied in laboratories for many years, this type of reflection OAE, which is evoked by only one single low-level tone, has not been tested in the clinic. The SFOAE can be effectively measured by a swept tone also, and recent reports defining its normative features in the healthy young and aging ear (Dewey & Dhar, 2016; Abdala et al., 2017) and to a limited extent in hearing-impaired ears (Ellison & Keefe, 2005; Abdala & Kalluri, 2015; Charaziak et al., 2015) suggest that it might provide diagnostic information about hearing loss. The SFOAE appears to show increased sensitivity to slight-mild hearing loss. However, a large-scale, careful study of its features and sensitivity to normal and impaired hearing has not been conducted.

Lastly, we are hopeful that OAE phase and its derivative, OAE delay, will make its way into the clinic as a diagnostic tool in the near future. The OAE delay, which is unfamiliar to most clinicians, can be thought of as a response latency. In laboratory studies, the SFOAE delay has been linked to cochlear tuning—the longer the SFOAE delay, the narrower the tuning (Shera et al., 2002, 2010). Recent work has also shown DPOAE phase to be sensitive to changes in intra-cranial pressure—it might offer a non-invasive probe of this important neurological indicator (Voss et al., 2006). The OAE itself offers both level (magnitude) and phase (timing) information and to ignore half of this informative bundle might be limiting our ability to see the entire elephant. We are hopeful that studies linking OAE delay with hearing and hearing pathology will make their way into the research literature in the near future.

Conclusion

Many of our research labs currently use the advanced algorithms and protocols described here to test and analyze OAEs; all of these methods are feasible at present. Their application in normal and impaired ears has led to a refined understanding of cochlear function and dysfunction. However, the ultimate sign of success and progress is when these discoveries and innovations are applied in the audiology clinic to guide the treatment of auditory pathology and positively impact the individual lives of those with hearing impairment. OAEs have yet to reach their full potential in this realm.

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Author

Carolina Abdala, Ph.D.
Professor of Otolaryngology
Keck School of Medicine
University of Southern California
Los Angeles, California, United States
carolina.abdala@usc.edu

Editors

Anne Marie Tharpe, Ph.D.
Chair, Phonak Research Advisory Board
Professor and Chair
Department of Hearing & Speech Sciences
Vanderbilt University School of Medicine
Nashville, Tennessee, United States

Marlene Bagatto, Ph.D.
Research Associate and Adjunct Research Professor
National Centre for Audiology
Western University
London, Ontario, Canada