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Posture-Induced Changes in Distortion-Product Otoacoustic Emissions and the Potential for Noninvasive Monitoring of Changes in Intracranial Pressure

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Noninvasive detection of changes in intra-cranial pressure using distortion-product otoacoustic emissions from the inner ear

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Abstract

Introduction: Intracranial pressure (ICP) monitoring is currently an invasive procedure that requires access to the intracranial space through an opening in the skull. Noninvasive monitoring of ICP via the auditory system is theoretically possible because changes in ICP transfer to the inner ear through connections between the cerebral spinal fluid and the cochlear fluids. In particular, low-frequency distortion-product otoacoustic emissions (DPOAEs), measured noninvasively in the external ear canal, have magnitudes that depend on intracranial pressure. Postural changes in healthy humans cause systematic changes in ICP. Here, we quantify the effects of postural changes, and presumably ICP changes, on DPOAE magnitudes.

Methods: DPOAE magnitudes were measured on seven normal hearing, healthy subjects at four postural positions on a tilting table (angles 90°, 0°, $-30°$, and $-45°$ to the horizontal). At these positions, it is expected that ICP varied from about 0 (90°) to 22 mm Hg ($-45°$). DPOAE magnitudes were measured for a set of frequencies $750 < f_2 < 4000$, with $f_2/f_1 = 1.2$.

Results: For the low frequency range of $750 \leq f_2 \leq 1500$, the differences in DPOAE magnitude between upright and $-45°$ were highly significant (all $p < 0.01$), and above 1500 Hz there were minimal differences between magnitudes at 90° versus $-45°$. There were no significant differences in the DPOAE magnitudes with subjects at 90° and 0° postures.

Conclusions: Changes in ICP can be detected using the auditory-based measurement of DPOAE magnitudes. In particular, changes are largest at low frequencies. Although this approach does not allow for absolute measurement of ICP, it appears that measurement of DPOAE magnitudes may be a useful means of noninvasively monitoring ICP. **Key Words:** intracranial pressure; cerebrospinal fluid, intracranial monitor, distortion-product otoacoustic emissions, random effects regression model

I. Introduction

Intracranial pressure (ICP) is commonly monitored in a wide range of devastating brain pathologies that cause brain swelling or bleeding, including head injury, stroke, hydrocephalus, and brain surgery. Because the skull is fixed in volume, changes in the volume of its contents result in changes in ICP. Elevations of ICP can lead to worsening brain injury or death by compressing both the blood vessels that supply the brain and vital brain structures themselves. Detecting and treating increases in ICP is crucial to protecting the injured brain. Existing methods to monitor ICP are invasive and require direct entry of a probe system through the skull.

The skull contains brain, blood, and cerebrospinal fluid (CSF). Because the inner ear fluid is connected to the CSF (via the cochlear aqueduct, the vestibular aqueduct, and the space surrounding the auditory nerve), changes in ICP produce changes in intracochlear pressure (ICoP). When increases in ICP lead to increases in ICoP, at least two mechanisms have been suggested to contribute to changes in auditory function: (1) the modified ICoP may alter cochlear responses by acting directly on the structures of the cochlea (e.g., the hair cells) or (2) the modified ICoP may stretch and alter the stiffness of the annular ligament that attaches the stapes of the middle ear to the oval window of the inner ear. Although Böhmer (1993)[1] demonstrated that changes in ICoP have little if any direct effect on cochlear function (mechanism #1), it is well documented that increases in the stiffness of the annular ligament substantially reduce middle-ear sound transmission at frequencies below 1000–2000 Hz[2–5] Increases in ICP are therefore most likely to be detected from the ear canal as reductions in middle-ear transmission that result from an increased stiffness (reduced compliance) of the annular ligament.[6,7] Theoretically, effects of increased stiffness should be most prominent at frequencies below the resonant frequency of the middle ear (i.e., below roughly 2000 Hz).

A class of auditory responses known as otoacoustic emissions (OAEs) have recently been shown to be sensitive to changes in ICP.[3,6–10] OAEs are sounds generated within the cochlea and transmitted via the middle ear to the external ear canal, where they can be recorded noninvasively with low-noise microphones.[11,12] Although the physiologic mechanisms that generate OAEs are still under active investigation,[13] OAEs have great clinical utility because they are involuntary and can be easily measured noninvasively. For example, OAEs are widely used in tests to screen for normal/abnormal hearing (e.g., newborn hearing screening[14,15]). These same features, and their sensitivity to changes in middle-ear transmission, make OAEs a promising noninvasive probe for changes in ICP.

Other measures of middle-ear transmission could in principle be used to detect changes in ICP, including middle-ear impedance[16] and the vibratory patterns of the tympanic membrane.[17] Although measurements of these quantities indicate that they are indeed sensitive to changes in intracochlear pressure, the measured changes are small. An advantage of evoked OAEs is that they are affected by two reductions in middle-ear transmission: once in the forward direction as the stimulus is transmitted to the cochlea and once in the reverse direction as the emission returns to the ear canal.[18] We therefore focus here on the use of evoked OAEs as a potential assay of ICP changes.

A summary of the existing work that relates ICP changes to OAEs in humans[3,7–10] is that in both healthy subjects on tilting tables and surgical patients with medically necessary ICP invasive monitoring, evoked OAEs show qualitative changes in magnitude and phase angle that are largest at low frequencies. However, these preliminary reports failed to provide a systematic or controlled picture of how OAEs and ICP changes relate. For example, the existing measurements show substantial intersubject variability and did not control for the parameters of middle-ear static pressure and intrasubject variations in OAEs.

In the work presented here we describe the first steps toward the development of a noninvasive diagnostic monitoring system for changes in ICP pressure using otoacoustic emissions as a response. Our approach is to relate changes in intracranial pressure to the noninvasive auditory measure of distortion-product otoacoustic emissions (DPOAEs). Of all the OAE types, DPOAEs are likely to be the most practical evoked emission for a diagnostic test because measurements can be made at relatively high yet safe sound-pressure levels, resulting in large signal-to-noise ratios. Because ICP changes systematically with posture,[20] we measured the effects of posture on DPOAEs in healthy, normal-hearing subjects placed on a tilting table. Our protocol included monitoring the subjects' middle-ear static pressure and assessing the intrasubject variability in DPOAEs over time.

II. Methods

A. Overview

Measurements of DPOAEs were made both (1) to characterize how posture, and presumably ICP, affects DPOAE magnitudes and (2) to characterize the intrasubject variability of DPOAEs both from minute to minute and from day to day.

B. Human Subjects

The experiments were performed on seven healthy female subjects with normal hearing (ages 19 to 36). All experiments were approved by the Smith College Science Center Institutional Review Board. Audiometric thresholds were normal ($\leq$ 20 dB hearing level) at all audiometric test frequencies (500, 1000, 2000 and 4000 Hz) in all ears. Each subject was given an otoscopic examination to ensure no excessive ear wax was present in the ear canal. Tympanometric measurements are described below in Section II- E. All measurements were made in the right ear of each subject.

C. Measurement of DPOAEs

DPOAE magnitudes were measured with an Etymotic ER-10c probe using software and hardware developed by Mimosa Acoustics (HearID v3.1). When the cochlea is stimulated by primary tones at frequencies f_1 and f_2 (with $f_2 > f_1$), intermodulation distortion in the nonlinear cochlea generates energy at the combination-tone frequency $f_{\rm dp} = 2f_1 - f_2$ that is subsequently transmitted through the middle ear to the ear canal, where it can be measured as a DPOAE in the ear-canal pressure using Fourier analysis at f_{dp}. To maximize the response, we fix $f_2/f_1 = 1.2$ and $L_1 - L_2$ at 10 dB, where $L_1 = 65$ dB SPL and $L_2 = 55$ dB SPL are the levels of the two tones at f_1 and f_2, respectively. Response magnitudes were obtained from discrete Fourier transforms of the time-domain average of N responses.

For each subject, and in each postural position, DPOAE magnitudes were measured for two frequency ranges. In the first range, five measurements with f_2=[750, 891, 1078, 1266, 1500] were made with $N = 469$. In the second range, nine measurements with f_2=[984, 1172, 1406, 1688, 2016, 2391, 2813, 3375, 3984] were made with $N = 187$. More averages were performed at the lower frequencies in order to reduce the noise floor. The noise floor was estimated from a narrow frequency band surrounding the response measured at f_{dp}. We eliminated data that fell less than 6 dB above the estimated noise floor.[19]

D. Tilting table protocol and resultant ICP

Subjects were placed on a tilting table (Hangups®II Inversion Table) at four postures: 90° (upright), 0° (supine), −30° relative to the horizontal, and −45° relative to the horizontal. Measurements were made at all four positions on six of the subjects and at three positions in one subject who declined to be measured at the −45° position. Since de Kleine et al. (2000)[9] demonstrated that stability in emission measurements is typically reached within 30 seconds after a postural change, DPOAE measurements were made after a subject was in position for at least one minute.

Chapman et al. (1990)[20] measured the effect of posture on ICP, and de Kleine et al. (2000)[9] applied a least-squares fit to the Chapman ICP data to obtain an equation that estimates ICP as a function of postural tilt. The equation is based on data taken at postures between 90° (upright) to −30° relative to the horizontal, and we extrapolated the equation to the −45° position. The estimated ICPs of our subjects at the four measurement positions are: 0 at 90°, 7 mm Hg at 0°, 17 mm Hg at −30°, and 22 mm Hg at −45°.

E. Tympanometric measurements

Subjects were asked to swallow at each postural position in order to maintain middle-ear pressures as close to zero as possible. Middle-ear pressure was monitored at each postural position before each measurement was made. To avoid removing and reinserting the ear plug of the ER-10c, a tympanometric-like system was designed that could maintain an ear-canal static pressure.[21] Ear-canal admittance was measured using Mimosa Acoustics' HearID software with ear-canal static pressure as a parameter. Admittance magnitude was analyzed as a function of static pressure at 500 Hz, and the middle-ear pressure was assumed to equal the ear-canal static pressure where the admittance magnitude was a maximum. Measurements were made with ear-canal static pressures at: $-150, -100, -50, 0, 25, 50, 100, 150$ daPa. In the total of 135 measurements [5 sessions/subject × (6 subjects × 4 measurements/session + 1 subject × 3 measurements/session)], only three middle-ear pressures appeared to be outside the ±100 daPa range. In 26 of the 35 measurement sessions (7 subjects × 5 sessions per subject) the middle ear pressure varied during the measurement session by less than 100 daPa (i.e., either ±50 or 0–100 daPa); in 7 of the sessions the variation was 100–150 daPa and in the remaining 2 sessions variation was greater than 150 daPa.

F. Statistical analysis

A statistical analysis and model was used to determine whether there were significant changes within the DPOAE magnitude data between positions (90°, 0°, −30°, and −45°) at each of the 14 frequencies. One complication of our analysis involved clustering within subjects because DPOAE magnitudes were measured repeatedly on the same subject. To account for this clustering, random effect (or random coefficient) models were used.[22–24] SAS PROC/MIXED version 9.1 was used to fit these models.

We included the main effects of day (4 df), position (3 df), frequency (13 df), and the interaction between position and frequency (39 df) to model DPOAE magnitudes. We eliminated 59 of the 1890 data points collected because the DPOAE amplitudes were less than 6 dB above the estimated noise floor.

Our approach is similar to a general linear model that models associations between observations (i.e., multivariate analysis of covariance (MANCOVA)). The models assume that the data are approximately normally distributed and specify a structure for the association within the subjects because the observations are clustered within subjects (i.e., non-independent). The residual errors were assumed to be uncorrelated conditional on a random intercept estimated for each subject. We calculated confidence intervals for comparisons between positions for a certain frequency with a least-squares means procedure. These regression models are attractive because they allow for the incorporation of partially observed subjects under the assumption that missing values depend only on observed quantities (missing at random or MAR in the sense of Little and Rubin[25]).

G. Intrasubject variability

Intrasubject variability over a period of minutes was assessed by making five repeated measurements on each of four subjects over the course of 20 minutes. Between each of the measurements, the acoustic probe (ER-10c) was removed and reinserted into the subject's ear canal and a new calibration was performed. Intrasubject variability in the upright (90°) position was assessed over a time period of several days by analyzing the data from the five testing sessions on each of the seven subjects (i.e., all 90° data from Fig. 1).

III. Results

A. DPOAE magnitudes at different postural positions

Repeated measurements of DPOAE magnitudes were made on seven subjects across five measurement sessions on different days. Fig. 1 plots individual session data and Fig. 2 plots the average data for each subject. All subjects had systematic low-frequency changes in DPOAE magnitudes as their position was changed from upright (90°) to $-30°$ and $-45°$. In general, for

f_2 frequencies below 1500 to 2000 Hz, DPOAE magnitudes decreased as posture moved from 90° to −45°.

There was a significant position by frequency interaction ($F_{39,1765} = 3.04$, $p < 0.0001$). This interaction indicates that for f_2 frequencies lower than 1500, the predicted difference in magnitude between upright and −45° were highly significant (all p-values <0.01, see Table 1). However, at higher frequencies, there were minimal differences. Differences between 90° and −30° were highly significant for all f_2 frequencies up to 1000 Hz (all p-values <0.01). A number of pairwise comparisons between 0° and −30° and 0° and −45° were significant at lower frequencies. There were no significant differences between 90° and 0° (all p-values > 0.30). Figure 3 plots the least-square means for the random effects regression model applied to the DPOAE magnitude.

[Table 1 near here.]

B. DPOAE magnitude intrasubject variability

1. Intrasubject variability: Minute-to-minute

Intrasubject variability over a period of minutes was tested by making five repeated measurements on each of four subjects over the course of 20 minutes. The standard deviations across four subjects and 14 frequencies range from 0.1 to 2.4 dB (Fig. 4), and all standard deviations were less than 2 dB for f_2 below 1500 Hz.

2. Intrasubject variability: Day-to-Day

Intrasubject variability in the upright (90°) position was tested over a time period of several days by analyzing the data from the five testing sessions on each of the seven subjects (i.e., all 90° data from Fig. 1). The standard deviations range from 0.3 to 7.6 dB (Fig. 4).

IV. Discussion

A. Summary of results

DPOAE magnitudes changed systematically with posture—and presumably with ICP—for $750 \leq f_2 \leq 1500$ Hz. DPOAE magnitudes generally decreased as posture changed from upright (90°) to $-30°$ and $-45°$ relative to the horizontal. The largest changes occurred at the lowest frequencies.

Multiple DPOAE measurements repeated within minutes of one another showed relatively small standard deviations (generally less than 2 dB and often less than 1 dB). These measurements were made to document the variability associated with inserting and removing the acoustic probe. Variations over several days were larger, with standard deviations ranging from 0.3 to 7.6 dB, with 50% between 2 and 4 dB. The results are comparable to those of Roede et al.,[19] who report standard deviations that range from 0.8 to 4.4 dB SPL with similar stimulus conditions.

B. Effects of middle-ear static pressure

Changes in the static pressure in the middle-ear cavities affect middle-ear sound transmission, modifying low-frequency DPOAE magnitudes.[26,27] Variations in static pressure are thought to modify sound transmission by changing the overall "stiffness" of the middle ear, including the stiffnesses of the tympanic membrane and annular ligament. Since changes induced by increased ICP and those induced by increased middle-ear static pressure have similar effects on middle-ear responses, experiments designed to understand how increased ICP affects DPOAEs must control for middle-ear static pressure changes. Additionally, it has been suggested that postural changes can affect middle-ear static pressure. Thus, it is important to monitor middle-ear static pressure when using postural changes to induce changes in ICP, as the effects of middle-ear static pressure and increased ICP can both affect DPOAE magnitudes.

Knight and Eccles[28] and Tideholm et al.[29] both found that healthy awake patients show no effect on middle-ear pressure between upright and supine positions, and Gaihede and Kjaer[30] found a modest increase of 22 daPa between the upright and supine positions. Thus, the available literature on this subject suggests that middle-ear pressure changes between upright and supine postures are less than ±25 daPa. At the same time, we know of no reports of changes in middle-ear pressure for the postural positions of $-30°$ and $-45°$. We do not have measurements of middle-ear pressure that provide sufficient resolution to determine the effect of posture on changes in middle-ear pressure: while the majority of DPOAE measurements reported here appear to have middle-ear pressures that vary by less than ±50 daPa from the upright position, our measurement resolution does not allow us to determine if the range is the full ±50 daPa or substantially smaller.

The effects of middle-ear pressure on DPOAE magnitudes have been reported for middle-ear pressure changes of ±100 daPa and more. Hauser et al. (1993)[31] demonstrate decreases in DPOAE magnitudes that correspond to static pressure changes in steps of 200 daPa, which are much larger than the middle-ear pressure changes we estimate here (Section II- E). Plinkert et al.[27] (1994) show mean reductions in DPOAE magnitudes at 1000 Hz of about 6 dB when the ear-canal static pressure is reduced from 0 to -100 daPa. Thus, changes in middle-ear static pressure do influence DPOAE magnitudes, and future work should monitor middle-ear pressure with a higher resolution than steps of 25–50 daPa.

Future work in determining how ICP affects DPOAE magnitudes might also equalize ear-canal and middle-ear static pressures prior to DPOAE measurements. Such an approach would require a probe that allows for measurement of both DPOAEs and tympanometry and also has the capability of maintaining a static pressure in the ear canal.

C. Clinical application of monitoring ICP via DPOAE measurements

Measurement of DPOAEs offers a promising noninvasive method to monitor ICP changes in patients with normal hearing. For long-term monitoring, the DPOAE measurement system needs to be supplemented with built-in tympanometric methods to monitor and perhaps compensate for changes in middle-ear pressure. Since the method is sensitive to changes in ICP but not to absolute pressures, long-term monitoring of ICP changes requires a baseline DPOAE measurement in each individual. Although a DPOAE-based system would not be useful for detecting elevated ICP due to acute brain injuries (since no DPOAE baseline is typically available in these cases), specific situations where long-term monitoring with DPOAE magnitudes could be effective include: (1) monitoring patients with brain tumors, (2) long-term monitoring of patients with hydrocephalus, (3) post-surgical monitoring of ICP, and (4) monitoring stable comatose patients with brain injuries (e.g. stroke patients). The next step toward accessing the reliability of changes in DPOAEs to detect changes in ICP is to make DPOAE measurements on individuals with medically-necessary intact ICP monitors so that the two techniques can be compared.

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References

[1] A. Böhmer. Hydrostatic pressure in the inner ear fluid compartments and its effects on inner ear function. *Acta Otolaryngol (Stockh)*, Suppl. 507, 1993.

[2] S. Murakami, K. Gyo, and R. L. Goode. Effect of increased inner ear pressure on middle ear mechanics. *Otolaryngol Head Neck Surg*, 118:703–708, 1998.

[3] B. Büki, P. Avan, J. J. Lemaire, M. Dordain, J. Chazal, and O. Ribari. Otoacoustic emissions: a new tool for monitoring intracranial pressure changes through spates displacements. *Hear. Res.*, 94:125–139, 1996.

[4] S. N. Merchant, M. E. Ravicz, and J. J. Rosowski. Acoustic input impedance of the stapes and cochlea in human temporal bones. *Hear. Res.*, 97:30–45, 1996.

[5] T. J. Lynch, V. Nedzelnitsky, and W. T. Peake. Input impedance of the cochlea in cat. *J. Acoust. Soc. Am.*, 72(1):108–130, 1982.

[6] B. Büki, E. de Kleine, H. P. Wit, and P. Avan. Detection of intracochlear and intracranial pressure changes with otoacoustic emissions: a gerbil model. *Hear. Res.*, 167:180–191, 2002.

[7] B. Büki, A. Chomicki, M. Dordain, J. J. Lemaire, H. P. Wit, J. Chazal, and P. Avan. Middle-ear influence on otoacoustic emissions. II: contributions of posture and intracranial pressure. *Hear. Res.*, 140:202–211, 2000.

[8] A.M. Frank, C. Alexiou, P. Hulin, T. Janssen, W. Arnold, and A. E. Trappe. Non-invasive measurement of intracranial pressure changes by otoacoustic emissions (OAEs) – a report of preliminary data. *Zentralbl Neurochir*, 61:177–180, 2000.

[9] E. de Kleine, H. P. Wit, P. van Dijk, and P. Avan. The behavior of spontaneous otoacoustic emissions during and after postural changes. *J. Acoust. Soc. Am.*, 107:3308–3316, 2000.

[10]E. de Kleine, H. P. Wit, P. Avan, and P. van Kijk. The behavior of evoked otoacoustic emissions during and after postural changes. *J. Acoust. Soc. Am.*, 110:973–980, 2001.

[11]D. T. Kemp. Stimulated acoustic emissions from within the human auditory system. *J. Acoust. Soc. Am.*, 64:1386–1391, 1978.

[12]R. Probst, B. L. Lonsbury-Martin, and G. K. Martin. A review of otoacoustic emissions. *J. Acoust. Soc. Am.*, 89:2027–2067, 1991.

[13]C. A. Shera. Mechanisms of mammalian otoacoustic emission and their implications for the clinical utility of otoacoustic emissions. *Ear Hear*, 25:86–97, 2004.

[14]K. J. Doyle, B. Burggraaff, S. Fujikawa, J. Kim, and C. J. MacArthur. Neonatal hearing screening with otoscopy, auditory brain stem response, and otoacoustic emissions. *Otolaryngol. Head Neck Surg.*, 116:597–603, 1997.

[15]B. A. Prieve. Identification of neonatal hearing impairment: A cornerstone for newborn hearing screening. In *Ear Hear*, volume 21. 2000.

[16]M. Magnano, R. Albera, M. Lacilla, A. Gabini, M. Naddeo, and D. Bruno. Impedance measurement as a noninvasive technique for the monitoring of intracranial pressure variations. *Audiology*, 33:237–243, 1994.

[17]R. J. Marchbanks. Measurement of tympanic membrane displacement arising from aural cardiovascular activity, swallowing, and intraaural muscle reflex. *Acta Oto-Laryngol*, 98:119–129, 1984.

[18]S. E. Voss and C. A. Shera. Simultaneous measurement of middle-ear input impedance and forward/reverse transmission in cat. *J. Acoust. Soc. Am.*, 116:2187–2198, 2004.

[19]J. Roede, F. P. Harris, R. Probst, and L. Xu. Repeatability of distortion product otoacoustic emissions in normally hearing humans. *Audiology*, 32:273–281, 1993.

[20]P. H. Chapman, E. R. Cosman, and M. A. Arnold. The relationship between ventricular fluid pressure and body position in normal subjects and subjects with shunts: A telemetric study. *Neurosurgery*, 26:181–189, 1990.

[21]F. Folowosele. Auditory-based detection of changes in intracranial pressure: Control of middle-ear static pressure. Smith College, 2005. Undergraduate Honors Thesis.

[22]N. M. Laird and J. H. Ware. Random-effects models for longitudinal data. *Biometrics*, 38:963–974, 1982.

[23]H. A. Feldman. Families of lines: random effects in linear regression analysis. *Journal of Applied Physiology*, 64:1721–1732, 1988.

[24]G. M. Fitzmaurice, N. M. Laird, and J. H. Ware. *Applied longitudinal analysis.* John Wiley & Sons, New York, 2004.

[25]R. J. A. Little and D. B. Rubin. *Statistical analysis with missing data, 2nd edition.* John Wiley & Sons, New York, second edition, 2002.

[26]K. B. Huttenbrink. The mechanics of the middle ear at static air pressures. *Act Otolaryngol Suppl*, 451:1–35, 1988.

[27]P. K. Plinkert, F. Bootz, and T. Voßieck. Influence of static middle ear pressure on transiently evoked otoacoustic emissions and distortion products. *Eur Arch Otorhinolaryngol*, 251:95–99, 1994.

[28]L. C. Knight and R. Eccles. The effect of postural change and upper respiratory tract infection on middle ear pressure. *Acta Otolaryngol.*, 111:1075–1082, 1991.

[29]B. Tideholm, M. Brattmo, and B. Carlborg. Middle ear pressure: effect of body position and sleep. *Acta Otolaryngol.*, 119:880–885, 1999.

[30] M. Gaihede and D. Kjaer. Positional changes and stabilization of middle ear pressure. *Auris Nasus Larnyx*, 25:255–259, 1998.

[31] R. Hauser, R. Probst, and F. Harris. Effects of atmospheric pressure variation on spontaneous, transiently evoked, and distortion product otoacoustic emissions in normal human ears. *Hear. Res.*, 69:133–145, 1993.

Figure Captions

1. DPOAE magnitude measurements on seven subjects (one subject per row) repeated on five different days. Data within 6 dB of the noise floor are not plotted. Data are plotted from positions at 90°, $-30°$, and $-45°$. Data from the 0° position are not statistically different from those at the position of 90° (see Table1) and are not shown. Measurements at $-45°$ were not made on Subject 3, who could not tolerate this position.

2. Averaged DPOAE magnitude measurements across five measurement sessions for each of the seven subjects from Fig. 1. To increase visibility, data from the 0° position are not plotted, as these data are not statistically different from those at the position of 90° (Table1). Measurements at $-45°$ were not made on Subject 3, who could not tolerate this position.

3. The least-squares mean values for the DPOAE magnitudes predicted with the random effects model, controlling for day, position, frequency, the interaction between position and frequency, and clustering within subjects. Corresponding standard errors for each value are all between 2 and 2.1 dB.

4. Boxplot of the standard deviations of DPOAE magnitudes in dB for minute-to-minute variations and day-to-day variations. The bottom, middle and upper lines of the box indicate the 25th, 50th and 75th percentiles, respectively. Outlying observations are denoted with a circle.

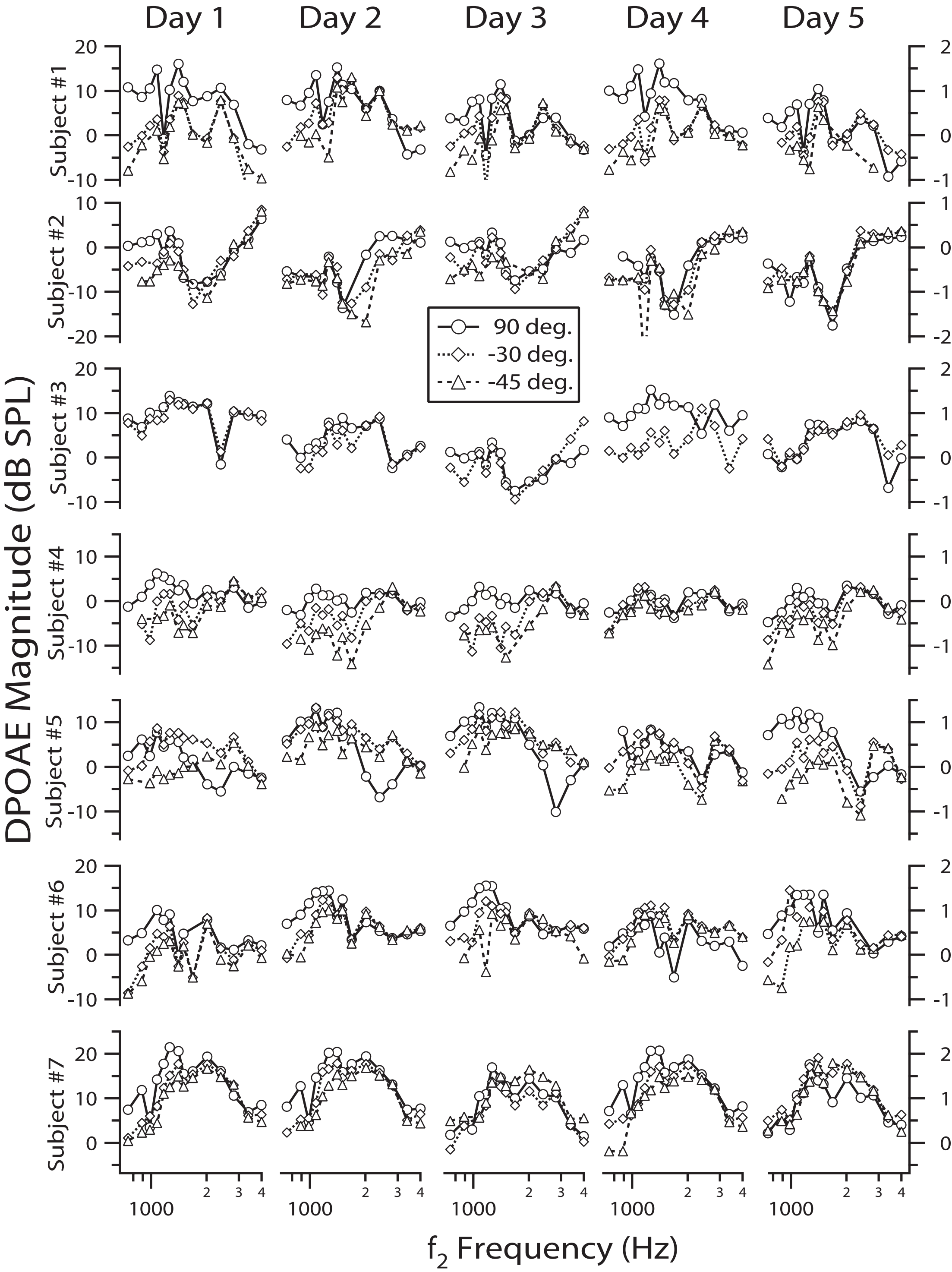
Day 1
Day 2
Day 3
Day 4
Day 5
Subject #1
Subject #2
Subject #3
Subject #4
Subject #5
Subject #6
Subject #7
DPOAE Magnitude (dB SPL)
f2 Frequency (Hz)
1000
2
3
4
90 deg.
-30 deg.
-45 deg.
20
10
0
-10
-20

Figure 1

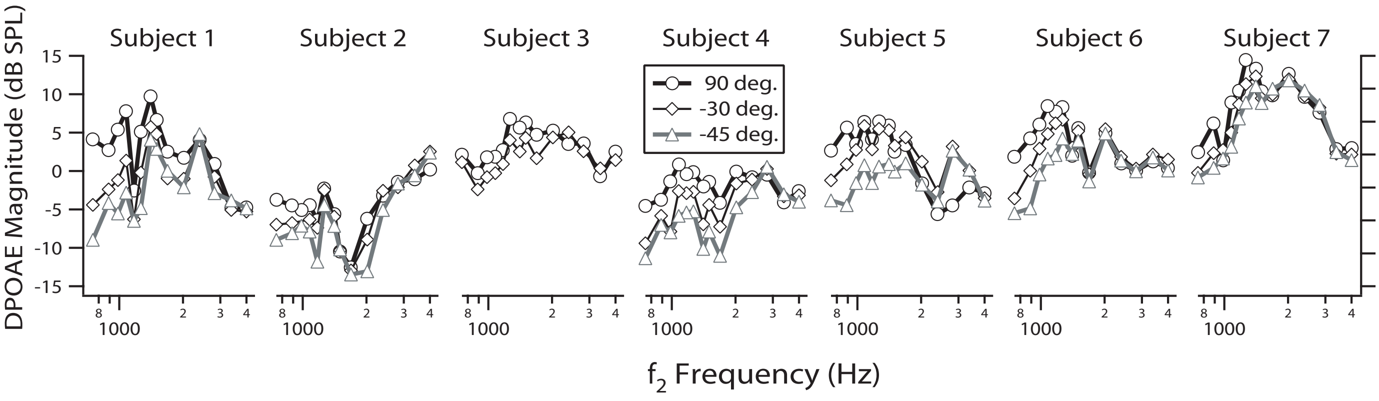
Subject 1
Subject 2
Subject 3
Subject 4
Subject 5
Subject 6
Subject 7
DPOAE Magnitude (dB SPL)
15
10
5
0
-5
-10
-15
20
15
10
5
0
-5
-10
-15
90 deg.
-30 deg.
-45 deg.
8
1000
2
3
4
f$_2$ Frequency (Hz)

Figure 2

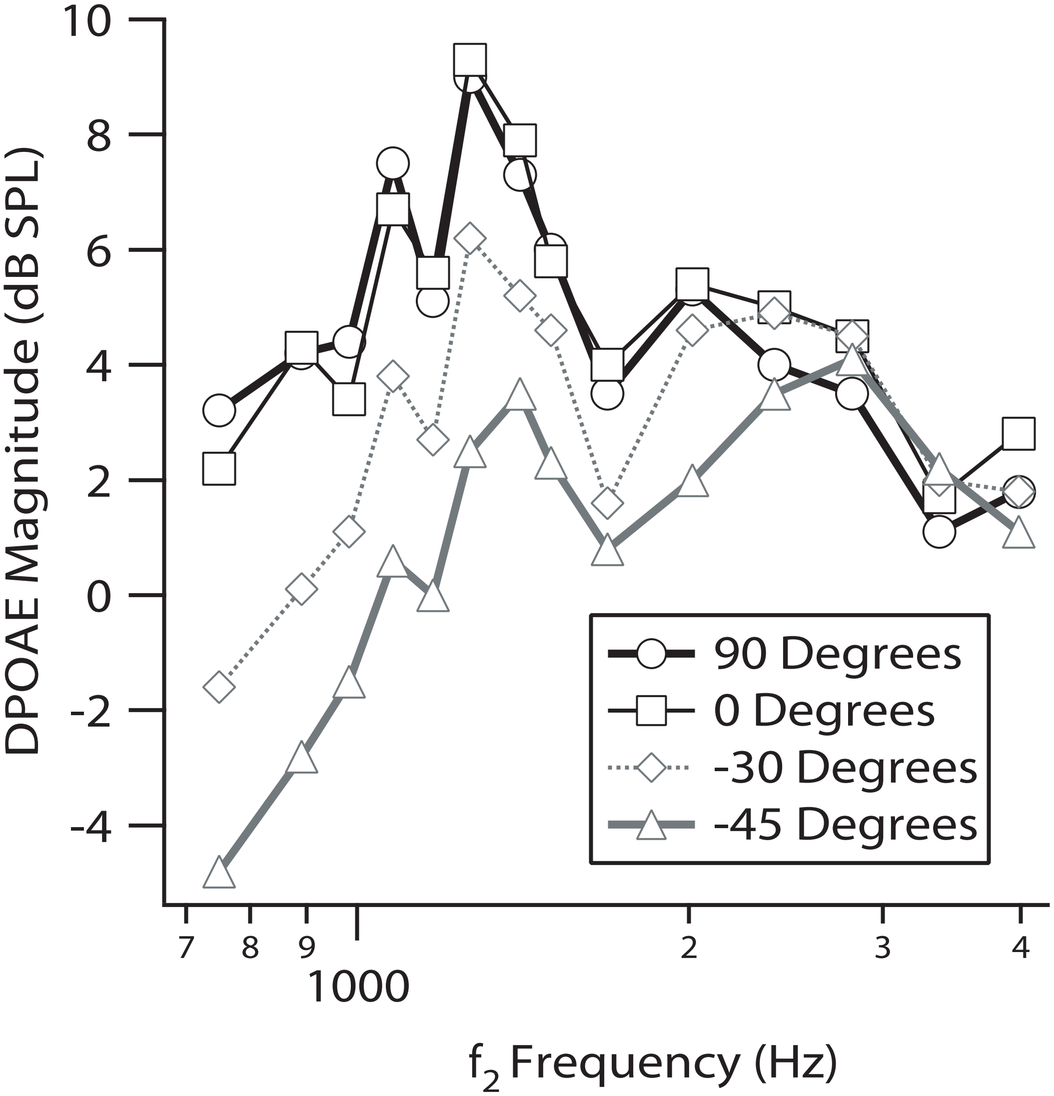
DPOAE Magnitude (dB SPL)
10
8
6
4
2
0
-2
-4
7
8
9
1000
2
3
4
f2 Frequency (Hz)
90 Degrees
0 Degrees
-30 Degrees
-45 Degrees

Figure 3

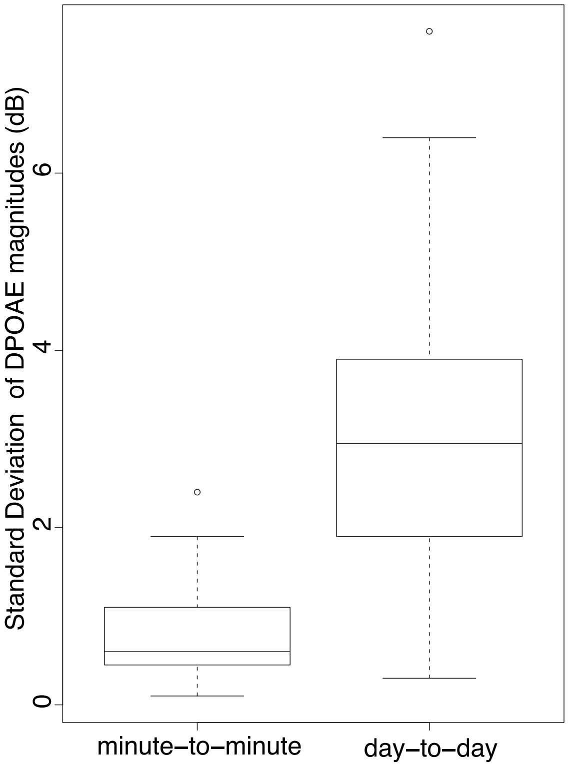
Standard Deviation of DPOAE magnitudes (dB)
0
2
4
6
minute–to–minute
day–to–day

Figure 4

Frequency	90° vs.			0° vs.		−30° vs.
(Hz)	0°	−30°	−45°	−30°	−45°	−45°
750	1.0 (1.1)	*4.8 (1.1)	*8.0 (1.3)	*3.8 (1.1)	*7.0 (1.2)	3.2 (1.3)
891	0.0 (1.1)	*4.1 (1.1)	*7.0 (1.1)	*4.1 (1.1)	*7.0 (1.1)	*2.9 (1.1)
984	1.0 (1.1)	*3.3 (1.1)	*5.9 (1.2)	2.3 (1.1)	*4.9 (1.2)	2.6 (1.3)
1078	0.8 (1.1)	*3.7 (1.1)	*6.9 (1.1)	*2.9 (1.1)	*6.1 (1.1)	*3.2 (1.1)
1172	-0.5 (1.1)	2.4 (1.1)	*5.1 (1.1)	*2.9 (1.1)	*5.6 (1.1)	2.7 (1.1)
1266	-0.3 (1.1)	*2.8 (1.1)	*6.5 (1.1)	*3.1 (1.1)	*6.8 (1.1)	*3.7 (1.1)
1406	-0.6 (1.1)	2.2 (1.1)	*3.9 (1.1)	2.7 (1.1)	*4.5 (1.1)	1.7 (1.1)
1500	0.2 (1.1)	1.4 (1.1)	*3.7 (1.1)	1.2 (1.1)	*3.5 (1.1)	2.3 (1.1)
1688	-0.5 (1.1)	1.9 (1.1)	2.7 (1.2)	2.4 (1.1)	*3.2 (1.2)	0.8 (1.2)
2016	-0.2 (1.1)	0.7 (1.1)	*3.3 (1.1)	0.9 (1.1)	*3.4 (1.1)	2.5 (1.1)
2391	-1.0 (1.1)	-0.9 (1.1)	0.5 (1.1)	0.1 (1.1)	1.5 (1.1)	1.4 (1.1)
2813	-1.0 (1.1)	-1.0 (1.1)	-0.7 (1.1)	0.0 (1.1)	0.3 (1.1)	0.3 (1.1)
3375	-0.6 (1.1)	-1.0 (1.1)	-1.2 (1.1)	-0.4 (1.1)	-0.6 (1.1)	-0.2 (1.1)
3984	-1.0 (1.1)	0.1 (1.1)	0.7 (1.1)	1.1 (1.1)	1.7 (1.1)	0.7 (1.1)

Table 1: Differences in the predicted least-squares means of DPOAE magnitude with standard errors in parentheses for the posture at 90° versus the postures at 0°, −30°, and −45°. The asterisk (*) indicates significance at the $p < 0.01$ level.