Increased Contralateral Suppression of Otoacoustic Emissions Indicates
a Hyper-responsive Medial Olivocochlear System in Humans with
Tinnitus and Hyperacusis

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Running Head: MOC Efferents in Tinnitus and Hyperacusis

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Abstract

Atypical medial olivo-cochlear (MOC) feedback from brainstem to cochlea has been proposed to play a role in tinnitus, but even well-constructed tests of this idea have yielded inconsistent results. Here, it was hypothesized that low sound tolerance (mild to moderate hyperacusis), which can accompany tinnitus or occur on its own, might contribute to the inconsistency. Sound-level tolerance (SLT) was assessed in subjects (all men) with clinically normal or near-normal thresholds to form threshold-, age-, and sex-matched groups: (1) no tinnitus/high SLT, (2) no tinnitus/low SLT, (3) tinnitus/high SLT, and (4) tinnitus/low SLT. MOC function was measured from the ear canal as the change in magnitude of distortion-product otoacoustic emissions (DPOAE) elicited by broadband noise presented to the contralateral ear. The noise reduced DPOAE magnitude in all groups (“contralateral suppression”), but significantly more reduction occurred in groups with tinnitus and/or low SLT, indicating hyper-responsiveness of the MOC system compared to the group with no tinnitus/high SLT. The results suggest hyper-responsiveness of the interneurons of the MOC system residing in the cochlear nucleus and/or MOC neurons themselves. The present data, combined with previous human and animal data, indicate that neural pathways involving every major division of the cochlear nucleus manifest hyperactivity and/or hyper-responsiveness in tinnitus and/or low SLT. The over-activation may develop in each pathway separately. However, a more parsimonious hypothesis is that top-down neuromodulation is the driving force behind ubiquitous over-activation of the auditory brainstem and may correspond to attentional spotlighting on the auditory domain in tinnitus and hyperacusis.
Keywords: DPOAE, efferent feedback, loudness discomfort level, cochlear efferents, posteroventral cochlear nucleus, anteroventral cochlear nucleus, dorsal cochlear nucleus
Introduction

The medial olivocochlear (MOC) system is one of two efferent systems that exert descending control over the cochlea (e.g., see Guinan 2006 for review). In the MOC system, auditory-nerve fibers project to a subpopulation of multipolar neurons in the posteroventral cochlear nucleus (PVCN), which in turn project to MOC neurons of the superior olivary complex (Thomson and Thompson 1991; de Venecia et al. 2005; Horváth et al. 2003; Mulders et al. 2007; Brown et al. 2013a). MOC neurons then collectively project bilaterally to the outer hair cells of the cochleae, thus controlling cochlear gain and enabling modulation of auditory-nerve activity (Warr 1975; Guinan and Gifford 1988; Guinan 2006). MOC feedback to the cochlea is believed to play roles in deciphering signals such as speech in noisy environments and protecting the cochlea from traumatizing exposures to sound (Liberman et al. 2014; Mishra and Lutman 2014).

Anomalous MOC function has been hypothesized, and tested for, in a variety of clinical conditions, including tinnitus, a prevalent and often-disruptive condition in which sound is perceived in the absence of actual sound (Stouffer and Tyler 1990; Shargorodsky et al. 2010). Despite a large number of studies, however, it remains unclear whether or not there is a relationship between MOC function and tinnitus (Chéry-Croze et al. 1993, 1994; Graham and Hazell 1994; Attias et al. 1996; Lind 1996; Ceranic et al. 1998; Attias et al. 2005; Fávero et al. 2006; Riga et al. 2007; Hesse et al., 2005, 2008; Fernandes and Santos 2009; Pagliagonga et al. 2010, 2011; Geven et al. 2011, 2012; Lalaki et al. 2011; Urnau and Tochetto 2012; Hsu et al. 2013; Riga et al. 2014). Results differ even among the more carefully controlled studies of this issue, with some reporting reduced MOC function in tinnitus (Attias et al. 1996; Riga et al. 2007) and others reporting no
difference compared to controls (Lind 1996; Pagliagonga et al. 2010, 2011; Geven et al. 2011).

Here, it was hypothesized that the inconsistent findings of previous MOC/tinnitus studies might be due to a particular uncontrolled variable: the degree to which sound is tolerated or not, based on its level (sound-level tolerance, SLT). Extreme intolerance, or very low SLT, corresponds to clinical hyperacusis, where even moderate-level sounds are considered uncomfortable (Baguley 2003; Tyler et al. 2003). SLT tends to be reduced in people with tinnitus compared to threshold-matched controls without tinnitus, although the ranges of SLT for those with and without tinnitus are overlapping (Gu et al. 2010; Hébert et al. 2013). SLT is a potentially important variable here because the MOC system, as a controller of cochlear gain, is positioned to influence loudness and therefore SLT.

The present study examined MOC function in threshold-, age-, and sex-matched subject groups defined based on tinnitus (having it chronically or not) and SLT (low or high). A widely used test of MOC function was employed that measures the effect of sound to one ear on the otoacoustic emissions (OAE) produced by outer hairs cells of the opposite ear (Veuillet et al. 1991; Hood et al. 1996). When measured in normal human subjects using common protocols, the effect is generally suppressive; that is, the magnitude of the OAE – for instance, distortion-product OAE (DPOAE) - is reduced by contralaterally-presented sound (commonly broadband noise; Moulin et al. 1993; Hood et al. 1996). Here, DPOAE suppression was found in all subject groups, but it was greater in the groups with tinnitus and/or low SLT, indicating increased responsiveness of the MOC system.
Materials and methods

Twenty-seven men (30 – 54 yrs., 24 right-handed) were recruited through advertisements and Massachusetts Eye and Ear clinics. Eleven subjects had chronic, subjective tinnitus. All subjects had clinically normal or near-normal audiograms defined as threshold $\leq 25$ dB hearing level (HL) at octave intervals from 250 through 4000 Hz and $\leq 35$ dB HL at 8000 Hz. Subjects had no known neurological problems except for subject 129 who had an MRI suggesting a possible telangiectasia in the right pons near the superior olivary complex and trapezoid body. Subject 347 was notable for only intermittent tinnitus (mainly noticeable at night) and a flapping sensation in the right ear in response to certain sounds. No subject had severe depression or anxiety according to standard inventories (Beck et al. 1961; Beck et al. 1988; scores in Table 1). None of the subjects was a professional musician in whom MOC reflex strength might be stronger than in the general population (Perrot and Collet 2014). In a questionnaire asking about musical training, only 4 subjects reported regularly playing musical instruments or singing in the previous 6 months, and they were distributed across subject groups.

Tinnitus subjects completed questionnaires assessing tinnitus-related distress (Tinnitus Reaction Questionnaire; Wilson et al., 1991) and general tinnitus characteristics such as the location and quality of the tinnitus percept. Tinnitus was bilateral or “in the head” for 8 of the 11 tinnitus subjects. The remaining three subjects reported unilateral tinnitus during testing, but had a history of occasional tinnitus in the other ear as well. The tinnitus of 8 subjects could be modulated somatically, that is altered in loudness or pitch by contractions of head and/or neck muscles (Levine et al. 2003). Additional tinnitus characteristics are given in Table 2.
Subjects provided informed written consent prior to participation. The study was approved by the Human Studies Committee at the Massachusetts Eye and Ear Infirmary. All of the following testing was performed in a double-walled sound-attenuating booth.

* Audiograms

Pure tone thresholds were measured from 0.125 through 8 kHz at half-octave intervals and at 9, 10, 11.2, 12.5, 14, and 16 kHz. Thresholds for 8 kHz and below were measured using TDH-39P headphones and an Interacoustics audiometer (AC33 or AC40). Thresholds above 8 kHz were measured using Sennheiser HDA200 headphones and either the Interacoustics AC40 audiometer or a custom system calibrated to the same specifications (ANSI S3.6-2004).

* Measures of sound-level tolerance

Two measures of sound tolerance were used: loudness discomfort level (LDL) and a questionnaire assessment of SLT. LDL was determined for broadband noise and 500 Hz warble tone stimuli as follows (Cox et al. 1997). Each sound was presented monaurally over headphones (TDH-39P) at progressively higher levels beginning at 35 dB SPL. The noise was generated in MATLAB® (The MathWorks, Inc., Natick, MA, USA) and played from a sound card to the tape input of an Interacoustics audiometer (AC33 or AC40). The 500 Hz warble tone (i.e., frequency modulated tone) was produced by the audiometer. As sound level was incremented in 5 dB steps, subjects rated the perceived loudness from 1 (very soft) to 7 (uncomfortably loud). Sound level at “7” was
the LDL for the stimulated ear. If a subject’s rating never reached “7”, the highest

testable level served as a lower bound on the LDL.

The sound-level tolerance questionnaire (SLT questionnaire) consisted of three
items about sound tolerance in everyday life (Gu et al. 2010; Tyler et al. 2003). Subjects
rated their agreement with the following statements on a 0 (completely disagree) to 100
(completely agree) scale:

(1) Many everyday sounds are unbearably loud to me.
(2) Sounds that others believe are moderately loud are too loud for me.
(3) I hear very soft sounds that others with normal hearing do not hear.

Ratings were averaged across statements and normalized to yield a score between 0 (low
tolerance) and 1 (high tolerance).

Measures of tinnitus

In tinnitus subjects, the following were measured: tinnitus pitch, tinnitus loudness,
the minimum level of binaural broadband noise needed to fully mask the tinnitus percept
(minimum masking level), and residual inhibition following 1 minute of binaural
broadband noise 10 dB re minimum masking level (Table 2). Tinnitus loudness and
minimum masking level were expressed relative to the detection threshold of the
broadband noise (that is, in dB sensation level; dB SL). Residual inhibition was defined
as a reduction in volume or absence of tinnitus for any length of time following cessation
of the masking noise.
DPOAEs were measured by means of the Mimosa HearID® system consisting of measurement probe, I/O card and acquisition software running on a laptop (Mimosa Acoustics, Champaign, IL, USA). The probe, consisting of a measurement microphone and two earphones for primary tone delivery, was coupled to the ear canal via a foam ear tip (Etymotic Research ER10C-14A). Quadratic distortion products ($2f_1 - f_2; f_2/f_1 = 1.2$) were measured with and without 60 dB SPL broadband noise presented to the contralateral ear (Figure 1). Primary levels known to allow for robust contralateral suppression were used ($L_1 = 55$, $L_2 = 40$ dB SPL; Williams and Brown 1997), and were verified by in-ear calibration.

The contralateral noise stimulus was delivered via Sennheiser® HDA 200 headphones. Subjects wore the full HDA 200 headset with an extra earmuff cushion added to the headphone over the DPOAE-recorded ear to prevent contact between headphone and DPOAE measurement probe. Noise was delivered to the opposite headphone. The noise was generated by MATLAB® software controlling a laptop sound card. The sound card output was fed to the tape input of the audiometer, which was then used to control the noise level.

DP-grams, consisting of DPOAE magnitude vs. frequency, were measured from 1 - 4 kHz at 28 pts/octave in noise/no-noise pairs, meaning that broadband noise was played in the contralateral ear during acquisition of one DP-gram, while the contralateral ear was unstimulated during the other DP-gram. During the first half of a recording session, the no-noise DP-gram of each pair was measured first and the noise DP-gram second. In the second half, after the subject was allowed to stretch, the order was
reversed. At least ten no-noise/noise pairs were obtained during a session. Primary levels were calibrated prior to each pair of no-noise/noise DP-grams. In cases with primary level fluctuations > 3 dB from baseline at any frequency, the entire DP-gram was discarded. This yielded an average of 13 usable DP-gram pairs per ear (range 3-20).

DPOAE measurements were made in one or both ears in each subject (far right column in Table 1). Measurements for a given ear were usually made in a single 3-hour session during which subjects reclined, remained awake, and were allowed to read. In 19 instances measurements for a given ear were distributed over two sessions.

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*Stapedial Reflex*

The noise level used (60 dB SPL) was less than typically required to activate a stapedial reflex, but each DPOAE-recorded ear was nonetheless tested for stapedius muscle contractions in response to the same contralaterally presented noise used during the noise/no-noise DPOAE measurements. This was done using the DPOAE recording system and tones as close to one another in frequency as the system allowed ($f_2/f_1 = 1.05$). Tone levels were the same as for DPOAE measurement, which is low enough to avoid contributions from stimulus-frequency OAE ($L_1 = 55$ dB SPL and $L_2 = 40$ dB SPL). Tone magnitude in the ear canal was measured for frequencies from 0.5 – 4 kHz at half-octave intervals, alternately with and without noise presented to the contralateral ear. Stapedial reflex strength was quantified at each frequency as the change in primary tone magnitude (ratio of no-noise to noise, expressed in dB).
Data analyses

For each DPOAE measurement pair (e.g., Figure 2A), the change in DPOAE magnitude elicited by contralateral noise was quantified as a magnitude ratio (noISE/noISE) and expressed in dB. The mean change at each frequency was then calculated for each DPOAE-recorded ear. A second analysis identified significant suppression (or facilitation) of DPOAE magnitude at each \( f_2 \) in individual ears. Mean magnitude changes were considered significant when their 95% confidence intervals excluded zero. Positive changes are referred to as suppression, negative as facilitation. Figure 2B illustrates with open circles instances of significant suppression in a representative subject. In a third analysis, the difference was taken between the complex DPOAE pressures (real and imaginary parts) recorded with contralateral noise and without. The magnitude of the resulting difference provided a measure of noise-elicited changes in either the magnitude or phase of the DPOAE (or both). This measure showed no significant differences between groups and will not be discussed further.

Results

Figure 3 shows, for both tinnitus and no-tinnitus subjects, the SLT data for each ear in which DPOAE recordings were made. Score on the SLT questionnaire is plotted vs. LDL for noise in Figure 3A and vs. LDL for the 500 Hz warble tone in Figure 3B. Noise LDLs, 500 Hz warble tone LDLs, and SLT questionnaire scores each had a range of values that overlapped between tinnitus subjects (asterisks and circles) and no-tinnitus subjects (open and shaded squares). For the primary analysis below, DPOAE-recorded
ears were divided into four groups based on tinnitus and the data of Figure 3A (noise
LDL and SLT questionnaire score). Two groups comprised tinnitus subjects with low and
high SLT (asterisks and open circles, respectively), while the remaining two groups
comprised no-tinnitus subjects with low and high SLT (open and shaded squares,
respectively). The division between low and high SLT was set so the four groups
included similar numbers of subjects and DPOAE-recorded ears. DPOAE-recorded ears
with a noise LDL $\geq$ 105 dB SPL and SLT questionnaire score $\geq$ 0.7 were designated high-
SLT, and the rest were designated low-SLT. Supplementary analyses, also described
below, examined the sensitivity of the results to grouping criteria (e.g., using the LDL
data for 500 Hz warble tones).

The groups formed for the primary analysis were closely matched: Mean
threshold for the DPOAE-recorded ears, and for the noise-stimulated ears, of each group
differed by 7 dB or less at any given frequency below 4 kHz and by 16 dB or less at 4
kHz and above (Figure 4A). Mean age differed between any pair of groups by 0 – 6 yrs.
(Table 3). Sex was automatically matched between groups because all subjects were
male. Mean baseline DPOAE magnitude (no contralateral noise) was well above the
mean noise floor in all groups for all but the highest $f_2$ values (Figure 4B).

Change in DPOAE magnitude with contralateral noise: primary analysis

Figure 5A shows the average change in DPOAE magnitude produced by
contralateral noise for each subject group defined in Figure 3A. This change (no-
oise/noise magnitude ratio in dB) was generally positive for all groups, indicating a
reduction in DPOAE magnitude by the contralateral noise (suppression). However, the
two groups with tinnitus (black solid, dashed), as well as the group with no tinnitus but low SLT (dotted) tended to show greater suppression than the no-tinnitus/high-SLT group; gray) over much of the $f_2$ range (1 – 3 kHz). This tendency for greater suppression (that is, greater magnitude change) can also be seen in Figure 5B where the data for individual DPOAE-recorded ears were first averaged over half-octave $f_2$ bands and then across ears. The difference in mean magnitude change between the two no-tinnitus groups suggested that the data for the two groups, which differed in SLT, came from different underlying populations. This was confirmed by a Kolmogorov-Smirnov test, which demonstrated significantly greater magnitude change in the no-tinnitus/low-SLT group in two $f_2$ bands (1-1.4 kHz, $p = 0.02$; 2-2.8 kHz, $p = 0.02$). At the same time, the no-tinnitus/low-SLT group showed no significant differences in any $f_2$ band when compared to each of the two groups with tinnitus (1-1.4 kHz, $p = 0.08$, tinnitus/low SLT; all other comparisons, $p \geq 0.34$). Thus the no-tinnitus/low-SLT group bore greater similarity to the tinnitus groups than to the other no-tinnitus group and has been combined with the tinnitus groups in subsequent analyses. The no-tinnitus/low-SLT group, combined with the two tinnitus groups, showed significantly greater magnitude change (greater suppression) compared to the no-tinnitus/high-SLT control group in two $f_2$ bands (1-1.4 kHz, $p = 0.003$; 2-2.8 kHz, $p = 0.001$; Mann-Whitney; uncorrected for multiple (that is, four) comparisons).

An alternative quantification of the changes in DPOAE magnitude produced by contralateral noise is shown in Figure 5C. The alternative analysis separately analyzed each DPOAE-recorded ear to identify each $f_2$ value at which significant suppression (or facilitation) occurred along the DP-gram (e.g., Figure 2B). Thus, the analysis took into
account the fact that the effect of contralateral noise varies across frequency (i.e., along
the DP-gram) in a manner related to the specific DPOAE fine structure of individual ears
(Abdala et al. 2009). Figure 5C plots, for each subject group, the average number of $f_2$
values showing significant suppression in half-octave $f_2$ bands from 1 to 4 kHz.

Collectively, the three groups with tinnitus and/or low SLT showed more instances of
significant suppression than the no-tinnitus, high-SLT group ($p = 0.01$ ($f_2 = 1.4-2$kHz), $p$
= 0.04 (2 – 2.8)). Significant facilitation of DPOAE magnitude also occurred, but far less
often than significant suppression, averaging between 0 and 0.73 depending on octave
band and subject group. One interpretation is that the same underlying mechanism
accounts for both suppression and facilitation (reduced magnitude of one of two
underlying DPOAE sources; e.g., see Abdala et al. 2009), in which case instances of
facilitation should be added to those of suppression. When this was done, the main result
was unchanged and indicated that contralateral noise had a greater effect on DPOAE
magnitude in the groups with tinnitus and/or low SLT than in the group with no tinnitus
and high SLT.

Although the subject groups were close in age, there were still some inter-group
differences in mean age and age range. The data were therefore re-examined in two ways
taking age into account. The second of these analyses also automatically accounted for
the slight differences between groups in high-frequency threshold ($\geq 8$ kHz, Figure 4)
because high-frequency threshold was correlated with age. In the first analysis, change in
DPOAE magnitude over a narrowed age range was examined (38 $\leq$ age $< 48$ yrs.). As for
the full age range, change in DPOAE magnitude over the narrowed range was greater in
the tinnitus and/or low-SLT groups than in the no-tinnitus/high-SLT group in $f_2$ bands
from 1 to 2.8 kHz. In a second analysis, a correction for age was made to the data covering the full age range of subjects. Based on plots of magnitude change vs. age, correction via linear regression was determined to be appropriate (Figure 6). Figure 7 shows the age-corrected results. Magnitude change remained greater for the tinnitus and/or low-SLT groups across $f_2$ bands from 1-2.8 kHz, as did the number of $f_2$ values showing significant suppression (Figure 7A, B). There was almost no difference in age-corrected hearing threshold between the no-tinnitus/high-SLT group and the combined tinnitus and/or low-SLT group (Figure 7C). Therefore, neither age nor hearing threshold accounts for the greater magnitude change present, on net, in subjects with tinnitus and/or low SLT.

Age-corrected baseline (no noise) DPOAE magnitude was also compared between the no-tinnitus/high-SLT group and the combined tinnitus and/or low-SLT group (Figure 7D). The two groups did not differ significantly in any $f_2$ band ($p \geq 0.08$, all $f_2$ bands, Mann-Whitney). However, because (a) there was a non-significant, but nevertheless systematic tendency, across $f_2$ bands, toward greater DPOAE magnitude in the no-tinnitus/high-SLT group, and (b) there was a weak linear relationship between change in magnitude and baseline DPOAE magnitude (decreasing magnitude change with increasing DPOAE magnitude), age-corrected magnitude change was further corrected for DPOAE magnitude via linear regression, as was the number of $f_2$ values showing suppression. The main result again remained: change in magnitude was greater in the combined tinnitus and/or low-SLT group (magnitude change, 2 - 2.8 kHz: $p = 0.02$; number of $f_2$ values, 1.4 - 2 kHz: $p = 0.02$).
Negligible effect of the stapedial reflex

Stapedial reflex strength, measured as a change in ear-canal tone level elicited by 60 dB contralateral noise, averaged less than 0.2 dB in any given subject group and \( f_2 \) band, and averaged less than 0.1 dB in the frequency ranges showing the greatest difference in DPOAE magnitude change across subject groups (\( f_2 = 1 – 1.4, 2 – 2.8 \) kHz). Tone frequencies tested were at approximately half-octave intervals over the frequency range of DPOAE measurement (from 1 through 4 kHz), and also at lower frequencies (515 and 750 Hz), where one would expect the greatest effects of stapedius muscle contraction. These measurements indicate that noise-induced stapedius muscle contractions made little or no contribution to the noise-induced changes in DPOAE magnitude reported in this study.

Test of sensitivity to SLT criterion

One last pair of analyses was conducted to test the robustness of the main results. These analyses tested for sensitivity to the criterion for grouping ears into low vs. high SLT. A first analysis still used LDL and SLT questionnaire score to divide low from high SLT, but used LDL for a 500 Hz warble tone instead of noise (Figure 3B). Two ears were reallocated between low and high SLT. Magnitude change remained greater in the group with tinnitus and/or low SLT (1 - 1.4 kHz, \( p = 0.05 \); 1.4 – 2, \( p = 0.03 \); 2 - 2.8, \( p = 0.001 \)). A second analysis assigned ears strictly according to noise LDL (without regard to SLT questionnaire score; high SLT: \( LDL \geq 105 \)), which moved three ears from low to high SLT. In both analyses, the main results persisted. Magnitude change again remained
greater in the group with tinnitus and/or low SLT (1 - 1.4 kHz, $p = 0.04$; 2 - 2.8, $p = 0.02$).

Comparison with depression, anxiety, and tinnitus variables

Mean depression and mean anxiety differed across subject groups, but the trend across groups did not parallel that of magnitude change (Table 3).

For the tinnitus subjects, each of the following variables from Table 2 was cross-correlated with magnitude change to test for relationships: minimum masking level, tinnitus loudness, score on Tinnitus Reaction Questionnaire. There were no significant correlations for any $f_2$ band (minimum masking level: $|r| \leq 0.36$, $p \geq 0.13$; tinnitus loudness: $|r| \leq 0.44$, $p \geq 0.07$; Tinnitus Reaction Questionnaire score: $|r| \leq 0.16$, $p \geq 0.50$; Spearman correlation, $p$-values uncorrected for multiple comparisons).

For most tinnitus subjects (8 of 10), tinnitus pitch exceeded the frequency range over which suppression was measured (Table 2; tinnitus pitch: $\geq 6$ kHz). Therefore, increased suppression was not limited to tinnitus frequency(s). In one ear of one of the two subjects with lower tinnitus pitch (110), suppression in the 2-2.8 kHz band was greater than in any other subject. Otherwise, however, the other ear of this subject and the other subject with low tinnitus pitch (129) showed suppression that was well within the range of the other tinnitus subjects. Thus, there was no obvious relationship between tinnitus pitch and the degree to which contralateral suppression was increased in tinnitus subjects.

To test for a relationship between magnitude change and lateralization of the tinnitus percept, an index of magnitude change asymmetry was calculated for all subjects.
in which both the right and left ears served as a DPOAE-recorded ear, including two
subjects with unilateral tinnitus (128, 129). The index was calculated as the absolute
value of the difference in magnitude change between the right and left ears, divided by
the average magnitude change for the two ears. Using the age-corrected magnitude
change data, asymmetry indices were calculated for each subject and half-octave band
from 1 to 4 kHz. All but one of the asymmetry indices for the unilateral tinnitus subjects
fell within the range for non-tinnitus and bilateral tinnitus subjects. The only exception
was for subject 129 in the 2.8 – 4 kHz band where the index (3.4) slightly exceeded the
maximum for the non-tinnitus/ bilateral tinnitus subjects (3.2). Thus, the data showed no
clear relationship between magnitude change in the right vs. left ear and tinnitus laterality.
The lack of asymmetry in magnitude change may reflect the fact that the unilateral
tinnitus subjects had low SLT that was equally reflected in the two ears (note similarly
low LDLs for the left and right ears of subjects 128, 129 in Table 1). In other words, the
tinnitus percept was asymmetric, but (low) SLT was symmetric.

Discussion

The results demonstrated that, on net, noise delivered to one ear had a greater
effect on DPOAE magnitude in the other ear in subjects with tinnitus and/or low SLT.
The nature of the effect was suppressive; that is, DPOAE magnitude was reduced with
delivery of contralateral noise (contralateral suppression). Importantly, the experimental
design included crucial controls that have not generally been incorporated into tests of
contralateral suppression in tinnitus. For instance, possible effects of middle ear muscles
were tested for and found to be negligible. Additionally, hearing threshold at both clinical
and supra-clinical (> 8 kHz) frequencies was controlled in both the DPOAE-recorded and noise-stimulated ears, as was baseline DPOAE magnitude. Mean threshold, DPOAE magnitude, and also age were highly similar across groups to begin with. (Sex was identical.) Nevertheless, the data were corrected via linear regression for remaining differences to test whether the differences, while small, might still account for the greater contralateral suppression in subject groups with tinnitus and/or low SLT. They did not. The main result – greater contralateral suppression in subjects with tinnitus, and in subjects without tinnitus but with low SLT – remained.

**Importance of considering SLT and closely matching subject groups**

The present data demonstrate the importance of factoring SLT into the design of any study examining contralateral suppression in tinnitus. If SLT had been ignored, and the two tinnitus groups (high and low SLT) had been compared to the two no-tinnitus groups, little or no difference in contralateral suppression would have been found. An important point is that lowered tolerance of sound was not usually reported spontaneously by the low-SLT subjects of the present study (see also Gu et al. 2010, 2012). Lower tolerance only became apparent through questionnaire responses and LDL measurement. In other words, it is easy to see how low- and high-SLT subjects could have been mixed together in the no-tinnitus groups of previous reports without the investigators realizing it, resulting in little or no difference between tinnitus and no-tinnitus groups. To our knowledge, no previous examination of contralateral suppression and tinnitus has taken SLT into account while also incorporating crucial controls needed to prevent the
enhancements in contralateral suppression from being obscured (see following paragraph).

One might expect that at least some previous studies comparing tinnitus and no-tinnitus subjects would have, by chance, included a majority of high-SLT subjects in the no-tinnitus group and thus observed elevated contralateral suppression in the tinnitus group. But this has not been the case, most likely because of a second issue: inadequate control of hearing threshold, particularly in the noise-stimulated ear. With some exceptions (Attias et al. 1996; Lind 1996; Pagliagonga et al. 2010, 2011; Geven et al. 2011; Riga et al. 2007), the previous work leaves room for a systematic offset in hearing threshold between tinnitus subjects and no-tinnitus controls because subjects were screened for clinically normal thresholds without ensuring that mean threshold was matched between tinnitus and no-tinnitus control groups. Screening without matching does not prevent substantial (e.g., 10 dB) threshold differences between groups extending over the entire audiometric frequency range. Given the general tendency for tinnitus and poor hearing to go hand-in-hand, mean threshold, left unconstrained, is likely to be poorer for any given group of tinnitus subjects with clinically normal thresholds than for a given group of no-tinnitus subjects meeting the same minimum threshold criteria. Systematically poorer thresholds in the noise-stimulated ears of tinnitus subjects would result in lower effective noise stimulation levels, lessening any noise-induced suppression (because suppression decreases with decreasing noise level; Veuillet et al. 1991) and thus counteracting any enhancement of suppression that would have been apparent otherwise. Note that similar logic suggests that some counteraction of enhanced suppression could have also occurred in studies that matched mean threshold for noise-stimulated ears up to
8 kHz, but not beyond, if the noise spectrum as well as significant hearing in the noise-stimulated ears extended to those higher frequencies.

Possible under-estimation of MOC hyper-responsiveness in the present study

Even in the present study, where mean threshold was closely matched across subject groups, effective levels of noise stimulation may have been less in the groups with tinnitus because of supra-threshold diminishment of auditory-nerve responsiveness. This suggestion follows from previous data demonstrating lower ABR wave I amplitude (indicating less sound-evoked auditory-nerve activity) in tinnitus subjects compared to threshold-matched no-tinnitus subjects (Schaette and McAlpine 2011; Gu et al. 2012). If auditory-nerve activity were similarly diminished in the noise-stimulated ears of the present study, the reported levels of contralateral suppression in the tinnitus groups would under-represent the degree of MOC hyper-responsiveness actually present. In other words hyper-responsiveness of the MOC system could actually be greater in tinnitus subjects than that reported here.

Possible neural bases for hyper-responsiveness of the MOC system

The greater DPOAE suppression found in subject groups with tinnitus and/or low SLT (relative to no tinnitus, high SLT) indicates a net hyper-responsiveness of the portion of the MOC system activated by noise stimulation in the present experiments. The exact basis for the measured hyper-responsiveness is unclear, but may involve the following: (1) increased responsiveness of MOC interneurons, that is, planar multipolar cells (T stellate cells) of the PVCN, which receive auditory-nerve input from the noise-
stimulated ear and provide excitatory input to MOC neurons, which are located in the superior olivary complex (Darrow et al. 2012), (2) increased responsiveness of MOC neurons themselves, as might be mediated by the large, presumably excitatory endings onto these cells that may represent descending inputs from auditory cortex (Brown et al. 2013), (3) increased efficacy of any or all of the synapses in the chain of MOC feedback to the DPOAE-recorded cochlea, including between MOC terminals and outer hair cells.

Some of these bases for hyper-responsiveness might also underlie a secondary observation of the present study, namely the slight negative correlation between DPOAE magnitude and noise-induced DPOAE suppression. Specifically, if mechanisms leading to increased responsiveness of the MOC system also lead to increased spontaneous activity within the system (hyperactivity), a predicted consequence would be tonic DPOAE suppression. In other words, greater noise-induced DPOAE suppression would co-occur with lower DPOAE magnitude, which is what the present data showed (compare Figure 7A and D). Relevant to the proposal of a spontaneously hyperactive MOC system are animal data indicating the development of elevated spontaneous activity in ventral cochlear nucleus unit types following acoustic trauma, a known inducer of tinnitus (Vogler et al. 2011). The elevated activity that develops in onset choppers and transient choppers has particular relevance since there is evidence that both of these unit types (or subgroups thereof) are part of the MOC system, either projecting to MOC neurons (transient choppers, which correspond to T stellate cells) or receiving MOC input (both onset and transient choppers; Mulders et al. 2007; Oertel et al. 2011; Darrow et al. 2012). These animal data demonstrate that hyperactivity can indeed develop within certain elements of the MOC system.
MOC hyper-responsiveness and tinnitus/low SLT: Cause and effect relationship?

Neither hyperactivity nor hyper-responsiveness of the MOC system provides an obvious way to account for the tinnitus percept or for low SLT as defined in the present study. In contrast to afferent spontaneous hyperactivity, for instance, efferent hyperactivity is not in a position to be carried to more rostral centers for subsequent interpretation as sound in the absence of sound (tinnitus). Also, the frequency range of any hyperactivity, as manifest in reduced DPOAEs, extends well below the tinnitus pitch. Lastly, hyperactivity (or hyper-responsiveness), at first glance, seems to be opposite what would be needed to account for the lowered LDLs of most subjects in the present study’s low-SLT group, since it implies greater MOC-mediated reductions in cochlear gain and auditory-nerve activity than would occur normally. Reduced auditory-nerve activity in response to sound in turn implies reduced loudness, not the enhanced loudness that characterizes low SLT.

However, there are many unknowns, so the possibility of a direct role for the MOC system in tinnitus and/or low SLT, cannot be dismissed. One major question is how the central auditory system is informed of, and takes into account, MOC-mediated cochlear gain changes. It is known that MOC axons, in addition to projecting to the cochlea, also project to the cochlear nucleus (especially the edges, where they likely terminate on dendrites of T stellate cells), thus providing the central auditory system with a copy of the control signals sent to the outer hair cells (Brown 1993; Brown 2011). A direct indicator of what the outer hair cells actually do (i.e. reduce cochlear gain) may be conveyed centrally by type II auditory-nerve fibers acting in a manner akin to
proprioceptive neurons in muscular motor control (Jagger and Housley 2003). But regardless of which neural elements report the action of the outer hair cells to the central auditory system, if the neural elements are damaged or destroyed, there is an opportunity for a mismatch between the actual gain of the cochlea and what the central auditory system thinks the gain is. In the event of a mismatch, there is the potential for sound-evoked (or spontaneous) auditory-nerve input to the brain to be misinterpreted such that the level of sound (and ultimately its loudness) is incorrectly perceived (for example, leading to low SLT), or the level of spontaneous activity is misconstrued to be great enough to come from sound (leading to tinnitus).

Instead of MOC hyperactivity/ hyper-responsiveness leading to tinnitus/ low SLT, the opposite is equally possible - that tinnitus/ low SLT leads to changes in the MOC system. In humans, auditory discrimination, signal detection in noise, and stimulus-counting tasks, for instance, have been reported to result in increased activation of the MOC system (e.g., Smith et al. 2012; Mishra and Lutman 2014). The increase may be mediated by known descending projections: directly from inferior colliculus or auditory cortex to MOC neurons, or indirectly from auditory cortex to cochlear nucleus (Mulders et al. 2000a, 2000b; Mellott et al. 2011; Schofield et al. 2011; Brown et al. 2013b). These same pathways and mechanisms may be responsible for increasing MOC activity in tinnitus and low SLT. Specifically, tinnitus and/or low sound tolerance may heighten arousal or draw attention to the auditory domain, either overtly or covertly, triggering top-down-mediated activity increases in the MOC system.
Ubiquitous brainstem hyper-responsiveness/ hyperactivity associated with tinnitus and low sound tolerance: A result of top-down neuromodulation?

The present results add to previous data indicating brainstem hyper-responsiveness and/or hyperactivity associated with tinnitus and/or lowered sound tolerance: Elevated responses to sound in the inferior colliculi of people with low SLT have been demonstrated with functional magnetic resonance imaging (Melcher et al. 2009; Gu et al. 2010); Wave V of the auditory brainstem response, which is generated by pathways originating in the anteroventral cochlear nucleus (AVCN), has been found to be elevated in people with tinnitus compared to those without (Gu et al. 2012); Acoustic startle, also likely mediated through AVCN in humans, is elevated in people with tinnitus (Fournier and Hébert 2013; Knudson and Melcher 2014); There have been numerous reports of elevated spontaneous and sound-driven activity in the dorsal cochlear nucleus (DCN) in animal models of tinnitus (for review, see Kaltenbach and Godfrey 2008); And finally, here, in people with tinnitus and/or low sound tolerance, we found elevated responsiveness of the MOC system which involves neuronal types in yet another division of the cochlear nucleus, the PVCN. In other words, there is evidence for hyperactivity and/or hyper-responsiveness associated with tinnitus and low sound tolerance in structures ranging from the cochlea (efferent feedback; present study) to inferior colliculus (Bauer et al. 2008; Gu et al. 2010; Vogler et al. 2014) and in neural pathways distributed across every major division of the cochlear nucleus, the source of all ascending signals in the central auditory pathway. We propose that hyperactivity/ hyper-responsiveness is ubiquitous in the auditory brainstem of people with tinnitus and/or low sound tolerance.
Prior to the present study, when hyperactivity/hyper-responsiveness had only been demonstrated within the highly plastic, cerebellum-like circuitry of the DCN (Tzounopoulos 2008), and more recently in evoked responses mediated by a subset of neurons of the AVCN (Gu et al. 2012), it seemed plausible that excesses of activity or responsiveness, triggered by cochlear damage, might develop independently in each of the involved neural populations, presumably via different mechanisms given their very different circuitries. And this may be true. However, in our view, the plausibility of this scenario, in which hyperactivity/hyper-responsiveness develops separately in different neuronal pathways, is diminished by the present data, which add another (PVCN-mediated) neural system with distinct innervation and neurochemistry to the list of those manifesting over-activation in tinnitus and low sound tolerance. In light of the existing data, it is worth considering a more parsimonious hypothesis: that over-activation of the auditory brainstem arises from forebrain-mediated neuromodulation broadly distributed throughout the brainstem, and for which there is evidence (Schofield et al. 2011; see also Roberts et al. 2013; Geven et al. 2014). We propose that the patterns of activity in ascending auditory brainstem pathways (e.g., spontaneous activity distribution across characteristic frequency) determine what tinnitus will sound like once heard, but for the tinnitus to be heard, those ascending activity patterns must have an attentional spotlight shone on them via top-down neuromodulation.
The authors wish to thank M. Christian Brown for many helpful discussions and comments on the manuscript, John Guinan Jr. for suggesting the method used to measure the stapedius muscle reflex and comments on the manuscript, Barbara Norris and Jianwen Wendy Gu for assistance with data-taking, and Barbara Norris for assistance with the figures. Support was provided by the Tinnitus Research Consortium and NIH/NIDCD P30DC005209.


51. Paglialonga A, Fiocchi S, Del Bo L, Ravazzani P, Tognola G. Quantitative analysis of transient evoked otoacoustic emissions and contralateral


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781 57. **Schofield BR, Motts SD, Mellott JG.** Cholinergic cells of the pontomesencephalic tegmentum: Connections with auditory structures from cochlear nucleus to cortex. *Hear Res* 279: 85-95, 2011.


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Figure Captions

**Figure 1:** Magnitude spectrum of noise delivered to ears contralateral to DPOAE measurement. Spectra were measured at the output of the Sennheiser HDA200 headphones positioned on a Larson-Davis AEC101 artificial ear. Dotted and solid lines correspond to noise delivered to right and left ears, respectively.

**Figure 2:** Measures of change in DPOAE magnitude elicited by noise to the contralateral ear. (A) Typical no noise/noise pair of DP-grams in one ear. (B) Change in magnitude (i.e., magnitude without noise/magnitude with noise expressed in dB) averaged over all 18 of the no-noise/noise pairs for same ear as (A). Error bars indicate 95% confidence intervals. For \( f_2 \) values showing significant suppression (confidence intervals exclude zero), the data are plotted with open, rather than filled, circles. There was no significant facilitation in this example.

**Figure 3:** Categorization based on tinnitus and sound-level tolerance (SLT) assessed via questionnaire and loudness discomfort level (LDL). Score on a SLT questionnaire vs. (A) LDL for noise stimulus, and (B) LDL for 500 Hz warble tone. Gray shading indicates SLT questionnaire and LDL range corresponding to “low SLT”. Unshaded region corresponds to “high SLT”. In both (A) and (B), each point corresponds to a particular subject and DPOAE-recorded ear. Right-pointing arrows next to some points indicate that LDL exceeded the upper limit of stimulation. Vertical and horizontal dashed lines correspond, respectively, to an LDL of 105 dB SPL and SLT questionnaire score of 0.7.
Figure 4: Audiograms and DP-grams for ears contributing to Figure 5. (A) Mean audiograms for DPOAE-recorded and noise-stimulated ears of each group. (B) Mean baseline (no-noise) DP-grams for each group. Error bars indicate one standard error of the mean.

Figure 5: Effect of contralateral noise on DPOAE magnitude in each of the subject groups defined in Figure 3A. (A) Change in magnitude elicited by contralateral noise averaged across DPOAE-recorded ears. (B) Same as (A) except that the magnitude change for each ear was first averaged over half-octave bands in $f_2$ and then averaged across ears. (C) Number of $f_2$ values showing significant suppression in half-octave bands averaged across ears. Error bars indicate one standard error of the mean. Asterisks indicate significance: *, $p < 0.05$; **, $p < 0.01$ (not corrected for multiple comparisons).

The number of subjects and DPOAE-recorded ears per group is as follows: 8 subjects, 11 ears (no tinnitus/ high SLT); 8, 11 (no tinnitus/low SLT); 5, 10 (tinnitus, high SLT); 6, 11 (tinnitus, low SLT).

Figure 6: Change in magnitude vs. age in four $f_2$ bands. Each point corresponds to a DPOAE-recorded ear. A linear, least mean-square error fit to the data is shown for each band.

Figure 7: After age-correction: (A) Change in DPOAE magnitude remains greater in the combined tinnitus and/or low SLT group (white bars) compared to the no-tinnitus/ high
SLT group (gray bars). (B) The number of $f_2$ values showing suppression also remains greater in the tinnitus and/or low SLT group. (C) Mean audiograms for the two groups are even more closely matched. (D) Baseline (no noise) DPOAE magnitude shows no significant difference between groups. Asterisks indicate significance: *, p < 0.05; **, p < 0.01 (not corrected for multiple comparisons). Exact p-values are as follows: panel A, 1 – 1.4 kHz, $p = 0.01$ uncorrected; A, 2 – 2.8 kHz, $p = 0.004$; B, 1.4 – 2 kHz, $p = 0.02$. 
Figure 2

A. Change in Magnitude (dB) DPOAE (dB SPL)

- **no noise**
- **contralateral noise, 60 dB SPL**

Noise floors

B. Change in Magnitude (dB) $f_2$ (kHz)

- **significant suppression**

Subject 110, right ear

Figure 2
SLT Questionnaire Score vs. Noise LDL (dB SPL) for 500 Hz Warble LDL (dB SPL):

A. No tinnitus, high SLT
B. No tinnitus, low SLT
C. Tinnitus, high SLT
D. Tinnitus, low SLT

Figure 3
Figure 4

A. Frequency (Hz)

-20 0 20 40 60 80 100 120

DPOAE-Recorded Ears

-20 0 20 40 60 80 100 120

Noise-Stimulated Ears

DPOAE-Recorded Ears

no tinnitus, high SLT

no tinnitus, low SLT

tinnitus, high SLT

tinnitus, low SLT

B. DPOAE Magnitude (dB SPL)

-30 -20 -10 0 10

f2 (kHz)

noise floors
A. Change in Magnitude (dB)

B. Change in Magnitude (dB)

C. Number of $f_2$ Values with Suppression

Figure 5
$f_2 = 1 - 1.4 \text{ kHz}$

- No tinnitus, high SLT
- No tinnitus, low SLT
- Tinnitus, high SLT
- Tinnitus, low SLT

Line slope = -0.04

$\text{Change in Magnitude (dB)}$

$\text{Age (years)}$

$f_2 = 1.4 - 2 \text{ kHz}$

Line slope = -0.004

$\text{f}_2 = 2 - 2.8 \text{ kHz}$

Line slope = -0.02

$\text{f}_2 = 2.8 - 4 \text{ kHz}$

Line slope = -0.03

Figure 6
DPOAE Magnitude (dB SPL)

\[
\begin{array}{c|c|c|c|c}
\hline
f_2 \text{ Band (kHz)} & 1 - 1.4 & 1.4 - 2 & 2 - 2.8 & 2.8 - 4 \\
\hline
\text{Threshold (dB HL)} & \text{no tinnitus, high SLT} & \text{tinnitus and/or low SLT} \\
\hline
125 & 10 & 15 & 20 & 25 \\
250 & 15 & 20 & 25 & 30 \\
500 & 20 & 25 & 30 & 35 \\
1k & 25 & 30 & 35 & 40 \\
2k & 30 & 35 & 40 & 45 \\
4k & 35 & 40 & 45 & 50 \\
8k & 40 & 45 & 50 & 55 \\
16k & 45 & 50 & 55 & 60 \\
\hline
\end{array}
\]

A.

![Graph of Change in Magnitude (dB) with Suppression](image)

- **no tinnitus, high SLT**
- **tinnitus and/or low SLT**

B.

![Graph of Number of f2 Values with Suppression](image)

C.

![Graph of Frequency (Hz) and Threshold (dB HL) for DPOAE-Recorded Ears and Noise-Stimulated Ears](image)

D.

![Graph of DPOAE Magnitude (dB SPL) with no tinnitus, high SLT and tinnitus and/or low SLT](image)

Figure 7
Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Handed-ness</th>
<th>Depression (max = 62)</th>
<th>Anxiety (max = 63)</th>
<th>Noise LDL (dB SPL)</th>
<th>SLT Quest. Score (max = 1)</th>
<th>DPOAE-Recorded Ear(s)</th>
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<tr>
<td>72</td>
<td>47</td>
<td>M</td>
<td>L</td>
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<td>5</td>
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<td>L, R</td>
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<td>54</td>
<td>M</td>
<td>L</td>
<td>0</td>
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<td>0.97</td>
<td>L, R</td>
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<td>M</td>
<td>R</td>
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<td>2</td>
<td>116, 114</td>
<td>1.0</td>
<td>L, R</td>
</tr>
<tr>
<td>116</td>
<td>45</td>
<td>M</td>
<td>R</td>
<td>12</td>
<td>16</td>
<td>&gt;118, &gt;119</td>
<td>1.0</td>
<td>L, R</td>
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<tr>
<td>160</td>
<td>39</td>
<td>M</td>
<td>R</td>
<td>11</td>
<td>12</td>
<td>116, 109</td>
<td>1.0</td>
<td>L, R</td>
</tr>
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| 23      | 34  | M   | R           | 0                     | 11                | 83, 89            | 0                         | L, R                   |
| 110     | 41  | M   | R           | 8                     | 7                 | 83, 79            | 0.5                       | L, R                   |
| 128     | 44  | M   | R           | 20                    | 6                 | 76, 79            | 0.2                       | L, R                   |
| 129     | 45  | M   | R           | 0                     | 1                 | 73, 77            | 1.0                       | L, R                   |
| 322     | 42  | M   | R           | 0                     | 1                 | >110, 95          | 0.8                       | R                      |
| 347     | 34  | M   | R           | 2                     | 8                 | 75, 77            | 0.87                      | L, R                   |

**Non-Tinnitus**

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<th>Anxiety (max = 63)</th>
<th>Noise LDL (dB SPL)</th>
<th>SLT Quest. Score (max = 1)</th>
<th>DPOAE-Recorded Ear(s)</th>
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<td>53</td>
<td>M</td>
<td>R</td>
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**Tinnitus**

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<th>Depression (max = 62)</th>
<th>Anxiety (max = 63)</th>
<th>Noise LDL (dB SPL)</th>
<th>SLT Quest. Score (max = 1)</th>
<th>DPOAE-Recorded Ear(s)</th>
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<td>M</td>
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<td>46</td>
<td>M</td>
<td>R</td>
<td>&gt;110, 95</td>
<td>0</td>
<td>75, 77</td>
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</tr>
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</table>

LDL: loudness discomfort level
SLT: sound level tolerance
n/a: not available
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<tr>
<th>Subject</th>
<th>Tinnitus Duration (yrs.)</th>
<th>Tinnitus Location</th>
<th>Tinnitus Quality</th>
<th>Tinnitus Pitch L, R (kHz)</th>
<th>Tinnitus Loudness L, R (dB SL)</th>
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</tr>
</tbody>
</table>

¹Subject also has occasional episodes of left ear tinnitus that are distinct from the right ear tinnitus.
²Subject's tinnitus was bilateral when first noticed, and then became unilateral.

n/a: not available
Table 3. Group Characteristics: Mean Across Ears ± SEM

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Depression Score</th>
<th>Anxiety Score</th>
<th>Tinnitus Reaction Quest.</th>
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<tr>
<td>No Tinnitus,</td>
<td>46 ± 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 ± 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 ± 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>High SLT</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No Tinnitus,</td>
<td>43 ± 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 ± 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 ± 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—</td>
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<tr>
<td>Low SLT</td>
<td></td>
<td></td>
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<tr>
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<td>46 ± 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 ± 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 ± 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>29 ± 7&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>7 ± 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 ± 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40 ± 8&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Low SLT</td>
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<sup>a</sup>11 ears; <sup>b</sup>10 ears