

Increased contralateral suppression of otoacoustic emissions indicates a hyperresponsive medial olivocochlear system in humans with tinnitus and hyperacusis

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Knudson IM, Shera CA, Melcher JR. Increased contralateral suppression of otoacoustic emissions indicates a hyperresponsive medial olivocochlear system in humans with tinnitus and hyperacusis. *J Neurophysiol* 112: 3197–3208, 2014. First published September 17, 2014; doi:10.1152/jn.00576.2014.—Atypical medial olivocochlear (MOC) feedback from brain stem to cochlea has been proposed to play a role in tinnitus, but even well-constructed tests of this idea have yielded inconsistent results. In the present study, 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 hyperresponsiveness of the MOC system compared with the group with no tinnitus/high SLT. The results suggest hyperresponsiveness 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 hyperresponsiveness in tinnitus and/or low SLT. The overactivation may develop in each pathway separately. However, a more parsimonious hypothesis is that top-down neuromodulation is the driving force behind ubiquitous overactivation of the auditory brain stem and may correspond to attentional spotlighting on the auditory domain in tinnitus and hyperacusis.

DPOAE; efferent feedback; loudness discomfort level; cochlear efferents; posteroventral cochlear nucleus; anteroventral cochlear nucleus; dorsal cochlear nucleus

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 (Brown et al. 2013a; de Venecia et al. 2005; Horváth et al. 2003; Mulders et al. 2007; Thompson and Thompson 1991).

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 (Guinan 2006; Guinan and Gifford 1988; Warr 1975). 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 (Shargorodsky et al. 2010; Stouffer and Tyler 1990). Despite a large number of studies, however, it remains unclear whether or not there is a relationship between MOC function and tinnitus (Attias et al. 1996, 2005; Ceranic et al. 1998; Chéry-Croze et al. 1993, 1994; Fávero et al. 2006; Fernandes and Santos 2009; Geven et al. 2011, 2012; Graham and Hazell 1994; Hesse et al. 2005, 2008; Hsu et al. 2013; Lalaki et al. 2011; Lind 1996; Paglialonga et al. 2010, 2011; Riga et al. 2007; Riga et al. in press; Urnau and Tochetto 2012). 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 with controls (Geven et al. 2011; Lind 1996; Paglialonga et al. 2010, 2011).

In the present study, 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 with 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 on the basis of 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 hair cells of the opposite ear (Hood

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et al. 1996; Veuillet et al. 1991). 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; Hood et al. 1996; Moulin et al. 1993). In this study, 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 yr, 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 ≤ 25 dB hearing level (HL) at octave intervals from 250 through 4,000 Hz and ≤ 35 dB HL at 8,000 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, 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 mo, 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 eight 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 HDA 200 headphones and either the Interacoustics AC40 audiometer or a custom system calibrated to the same specifications (ANSI S3.6-2004).

Measures of SLT. 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, Natick, MA) and played from a sound card to the tape input of an Interacoustics audiometer (AC33 or AC40). The

Table 1. *Subject characteristics*

	Subject	Age, yr	Sex	Handedness	Depression Score (max = 62)	Anxiety Score (max = 63)	Noise LDL (L, R), dB SPL	SLT Questionnaire Score (max = 1)	DPOAE-Recorded Ear(s)
					<i>No tinnitus</i>				
High SLT	46	47	M	R	0	0	>118, >119	0.83	L, R
	55	47	M	R	12	4	113, 114	0.73	L
	119	43	M	R	0	1	>118, 119	1.0	R
	131	53	M	R	n/a	7	>118, >119	1.0	R
	142	48	M	R	5	3	113, 114	0.9	L, R
	146	43	M	R	6	3	113, 114	0.99	L, R
	348	41	M	L	0	3	113, 117	0.97	R
	409	43	M	R	11	8	115, >117	0.70	R
Low SLT	8	47	M	R	2	0	103, 104	0.93	L, R
	9	53	M	R	0	0	93, 94	0.83	L, R
	125	49	M	R	0	0	96, 94	0.85	L
	135	35	M	R	4	7	>118, >119	0.53	L, R
	137	30	M	R	8	10	68, 69	0.83	L
	148	36	M	R	5	0	116, 107	0.57	L
	338	46	M	R	n/a	n/a	95, 87	1.0	L
	435	40	M	R	0	2	93, 97	1.0	L
				<i>Tinnitus</i>					
High SLT	72	47	M	L	5	5	106, 109	0.8	L, R
	85	54	M	L	0	4	113, 114	0.97	L, R
	109	47	M	R	7	2	116, 114	1.0	L, R
	116	45	M	R	12	16	>118, >119	1.0	L, R
	160	39	M	R	11	12	116, 109	1.0	L, R
Low SLT	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

M, male; L, left; R, right; LDL, loudness discomfort level; SLT, sound-level tolerance; Quest., questionnaire; DPOAE, distortion-product otoacoustic emission; max, maximum; n/a, not available.

Table 2. *Tinnitus characteristics*

	Subject	Tinnitus Duration, yr	Tinnitus Location	Tinnitus Quality	Tinnitus Pitch (L, R), kHz	Tinnitus Loudness (L, R), dB SL	Minimum Masking Level, dB SL	Tinnitus Reaction Questionnaire Score (max = 104)	Residual Inhibition	Somatic Modulation
High SLT	72	15	Both ears, worse in R	Ringling, whistling	>8, >8	25, 25	40	45	No	Yes
	85	"Many"	Both ears, worse in R	Pulsing, hissing, tonal	>12, n/a	18, 15	35	18	Yes	Yes
	109	"Lifelong," worse in past 10–15 yr	In head, center	Ringling, tonal	10, 12	30, 30	45	7	No	Yes
	116	19	Both ears, equally	Ringling	12, 12	15, 10	35	61	No	Yes
	160	2	In head, center	Hissing, electronic	10, 10	25, 15	50	14	No	n/a
Low SLT	23	13	Both ears, worse in L	Tonal	>8, >8	35, 40	45	46	No	Yes
	110	3	Both ears, worse in L	Ringling, buzzing	1–2, 1–2	20, 10	25	61	Yes	Yes
	128	10	R ear*	Ringling, hissing	—, 6	—, 60	55	78	No	Yes
	129	6	R ear†	Ringling	—, 2–3	—, 25	30	5	Yes	Yes
	322	20	R ear*	Ringling, tonal	—, 11	—, 15	70	13	No	n/a
	347	0.5	Both ears, worse in R	Intermittent, ringling	n/a, n/a	n/a, n/a	n/a, n/a	22	No	n/a

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

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 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 scale from 0 (completely disagree) to 100 (completely agree): 1) Many everyday sounds are unbearably loud to me; 2) Sounds that others believe are moderately loud are too loud for me; and 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 min of binaural broadband noise 10 dB re minimum masking level (Table 2). Tinnitus loudness and minimum masking level are 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.

DPOAE measurement with and without contralateral noise. DPOAEs were measured by means of the Mimosa HearID system consisting of measurement probe, input-output card, and acquisition software running on a laptop computer (Mimosa Acoustics, Champaign, IL). 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 (Fig. 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 to 4 kHz at 28 points/octave in noise/no-noise pairs, meaning that broadband noise was played in the contralateral ear during acquisition of one DP-gram, whereas 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 10 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).

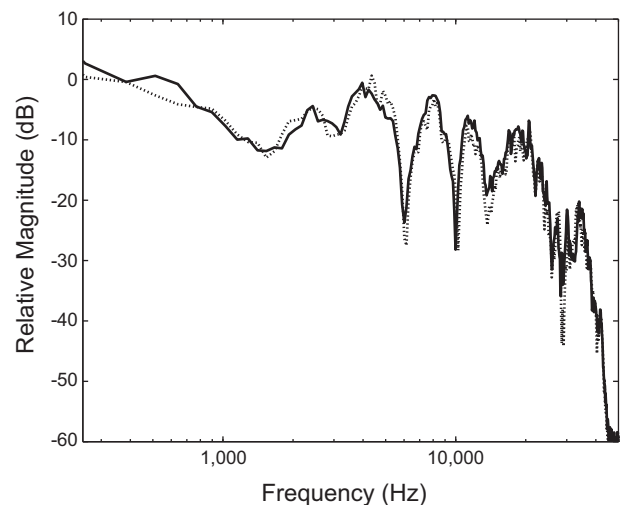


Fig. 1. Magnitude spectrum of noise delivered to ears contralateral to distortion-product otoacoustic emissions (DPOAE) measurement. Spectra were measured at the output of the Sennheiser HDA200 headphones positioned on a Larson-Davis AEC101 artificial ear. Dotted and solid lines correspond to noise delivered to right and left ears, respectively.

DPOAE measurements were made in one or both ears in each subject (Table 1, *far right*). Measurements for a given ear were usually made in a single 3-h session during which subjects reclined, remained awake, and were allowed to read. In 19 instances, measurements for a given ear were distributed over 2 sessions.

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 by 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 to 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).

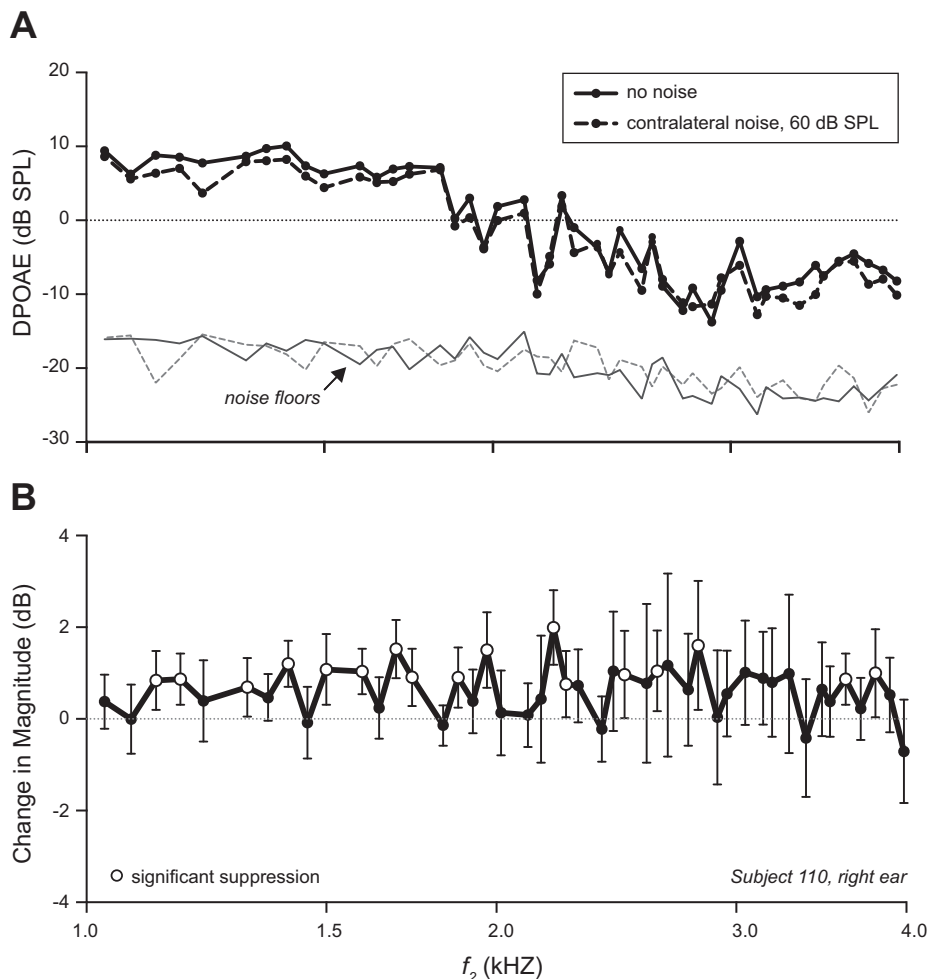
Data analyses. For each DPOAE measurement pair (e.g., Fig. 2A), the change in DPOAE magnitude elicited by contralateral noise was quantified as a magnitude ratio (no noise/noise) and expressed in decibels. The mean change at each frequency was then calculated for each DPOAE-recorded ear. A second analysis identified significant suppression (or facilitation) of DPOAE magnitude at each f_2 value 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 is not 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 Fig. 3A and vs. LDL for the 500-Hz warble tone in Fig. 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 on the basis of tinnitus and the data of Fig. 3A (noise LDL and SLT questionnaire score). Two groups comprised tinnitus subjects with low and high SLT (asterisks and open circles, respectively), whereas 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 that the four groups included similar numbers of subjects and DPOAE-recorded ears. DPOAE-recorded ears with a noise LDL ≥ 105 dB SPL and SLT questionnaire score

Fig. 2. Measures of change in DPOAE magnitude elicited by noise to the contralateral ear. A: typical no-noise/noise pair of DP-grams in 1 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 the same ear as in A. Error bars indicate 95% confidence intervals. For f_2 values showing significant suppression (confidence intervals exclude 0), the data are plotted with open, rather than filled, circles. There was no significant facilitation in this example.



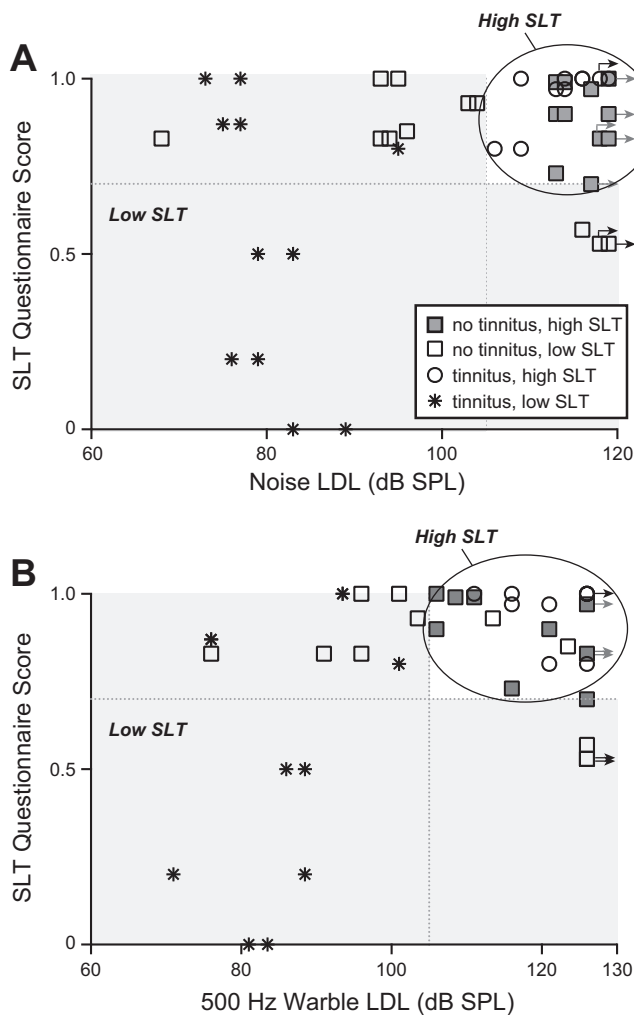


Fig. 3. Categorization based on tinnitus and sound-level tolerance (SLT) assessed via questionnaire and loudness discomfort level (LDL). Plotted is score on an SLT questionnaire vs. LDL for noise stimulus (A) and LDL for 500-Hz warble tone (B). Gray shading indicates SLT questionnaire and LDL range corresponding 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 an SLT questionnaire score of 0.7.

≥ 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 (Fig. 4A). Mean age differed between any pair of groups by 0–6 yr (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 (Fig. 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 Fig. 3A. This change (no-noise/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 and dashed lines), as well as the group with no tinnitus but low SLT (dotted line) tended to show greater suppression than the no-tinnitus/high-SLT group (gray solid line) 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 Fig. 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 compared with 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 with 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, 4) comparisons].

An alternative quantification of the changes in DPOAE magnitude produced by contralateral noise is shown in Fig. 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., Fig. 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); $P = 0.04$ ($f_2 = 2$ –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 1 of 2 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 intergroup differences in mean age and age range. The data were therefore reexamined in two ways taking age into account. The second of these analyses also automatically accounted for the slight differences between groups in high-

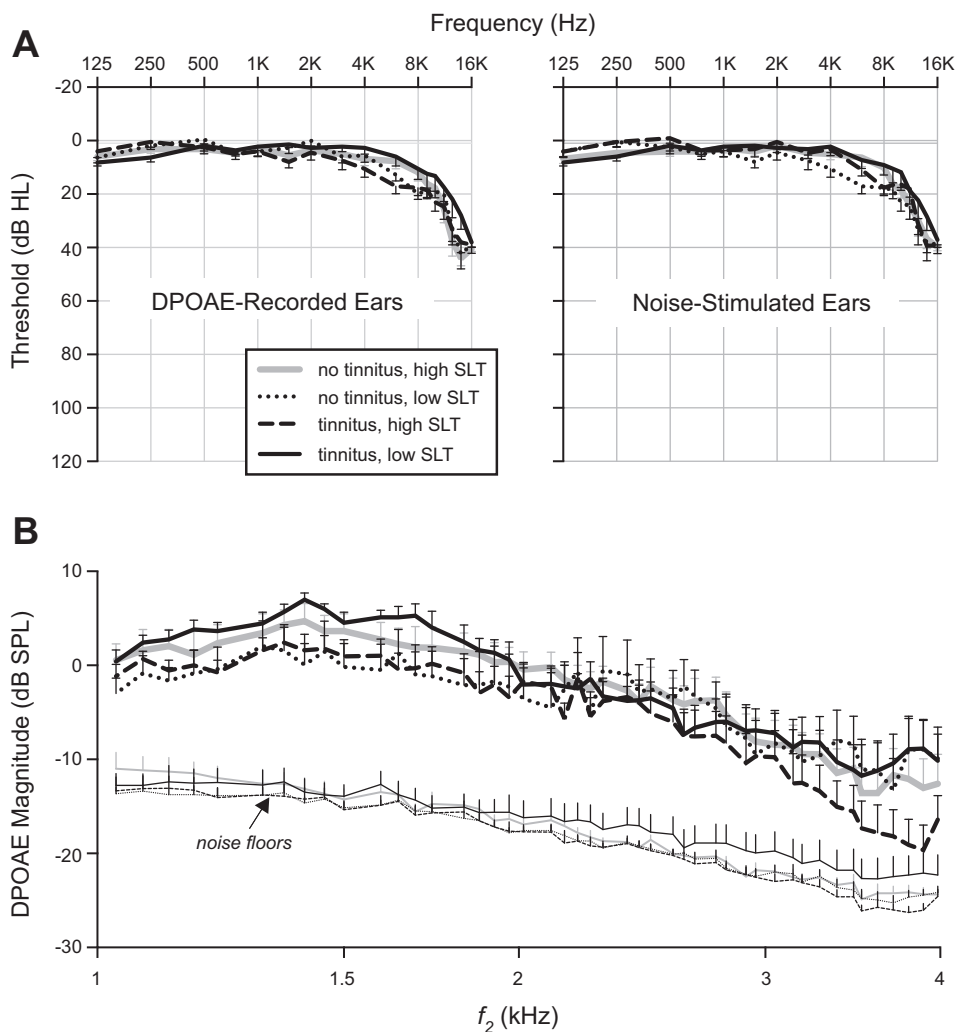


Fig. 4. Audiograms and DP-grams for ears contributing to Fig. 5. *A*: mean audiograms for DPOAE-recorded and noise-stimulated ears of each group. *B*: mean baseline (no noise) DP-grams for each group. Error bars indicate SE.

frequency threshold (≥ 8 kHz, Fig. 4), because high-frequency threshold was correlated with age. In the first analysis, change in DPOAE magnitude over a narrowed age range was examined ($38 \leq \text{age} < 48$ yr). 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 (Fig. 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 (Fig. 7, *A*

Table 3. Group characteristics

	Age, yr	Depression Score	Anxiety Score	Tinnitus Reaction Questionnaire
No tinnitus, high SLT	$46 \pm 1^*$	$5 \pm 1^\dagger$	$3 \pm 1^*$	
No tinnitus, low SLT	$43 \pm 2^*$	$3 \pm 1^\dagger$	$3 \pm 1^\dagger$	
Tinnitus, high SLT	$46 \pm 2^\dagger$	$7 \pm 1^\dagger$	$8 \pm 2^\dagger$	$29 \pm 7^\dagger$
Tinnitus, low SLT	$40 \pm 1^*$	$7 \pm 2^*$	$6 \pm 1^*$	$40 \pm 8^*$

Values are means \pm SE across ears (*11 ears; † 10 ears).

and *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 (Fig. 7*C*). 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 (Fig. 7*D*). The two groups did not differ significantly in any f_2 band ($P \geq 0.08$, all f_2 bands; Mann-Whitney). However, because 1) there was a nonsignificant but nevertheless systematic tendency, across f_2 bands, toward greater DPOAE magnitude in the no-tinnitus/high-SLT group, and 2) 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

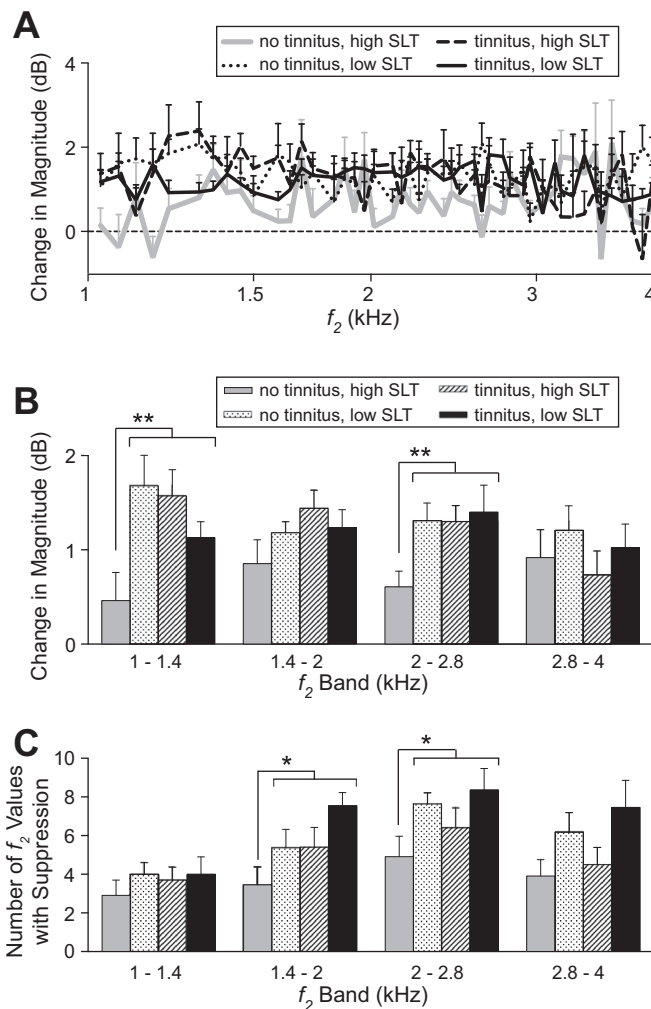


Fig. 5. Effect of contralateral noise on DPOAE magnitude in each of the subject groups defined in Fig. 3A. A: change in magnitude elicited by contralateral noise averaged across DPOAE-recorded ears. B: same as A except that the magnitude change for each ear was first averaged over half-octave bands in 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 SE. Asterisks indicate significance: * $P < 0.05$; ** $P < 0.01$ (not corrected for multiple comparisons). The number of subjects and DPOAE-recorded ears per group are as follows: 8 subjects, 11 ears (no tinnitus, high SLT); 8 subjects, 11 ears (no tinnitus, low SLT); 5 subjects, 10 ears (tinnitus, high SLT); and 6 subjects, 11 ears (tinnitus, low SLT).

by 60-dB contralateral noise, averaged <0.2 dB in any given subject group and f_2 band and averaged <0.1 dB in the frequency ranges showing the greatest difference in DPOAE magnitude change across subject groups ($f_2 = 1\text{--}1.4$, $2\text{--}2.8$ 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 (Fig. 3B). Two ears were reallocated between low and high SLT. Magnitude change remained greater in the group with tinnitus and/or low SLT ($1\text{--}1.4$ kHz, $P = 0.05$; $1.4\text{--}2$, $P = 0.03$; $2\text{--}2.8$, $P = 0.001$). A second analysis assigned ears strictly according to noise LDL (without regard to SLT questionnaire score; high SLT:LDL ≥ 105), which moved three ears from low to high SLT. In both analyses, the main results persisted. Magnitude

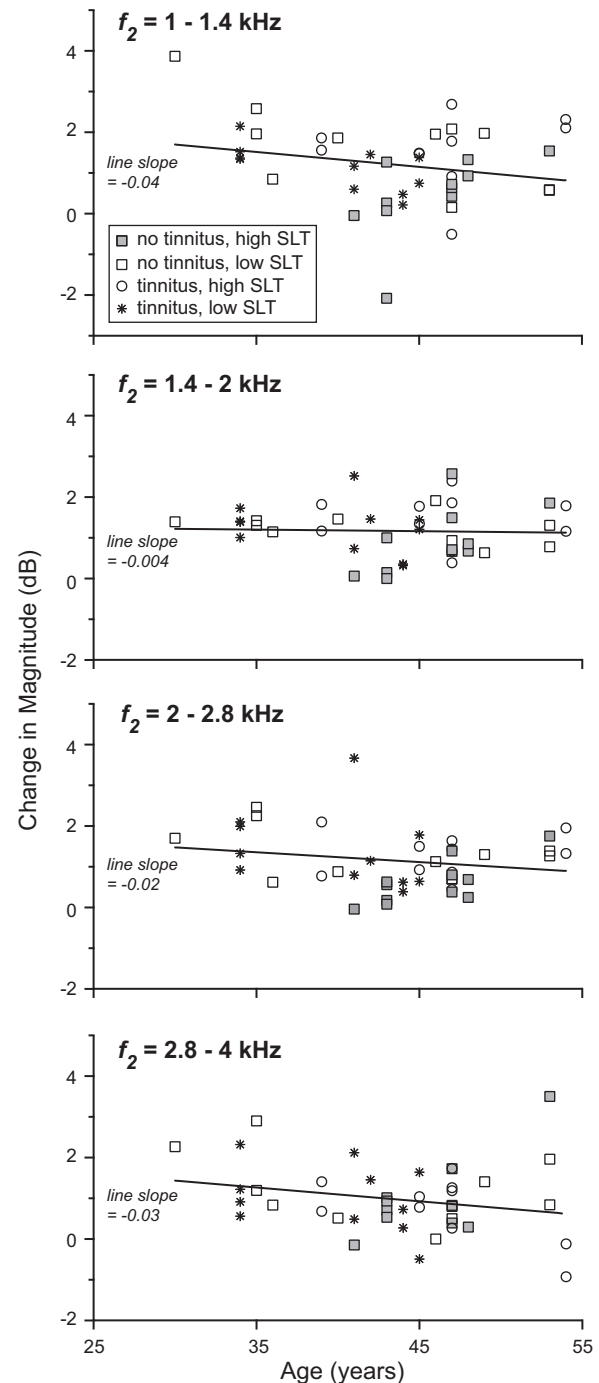
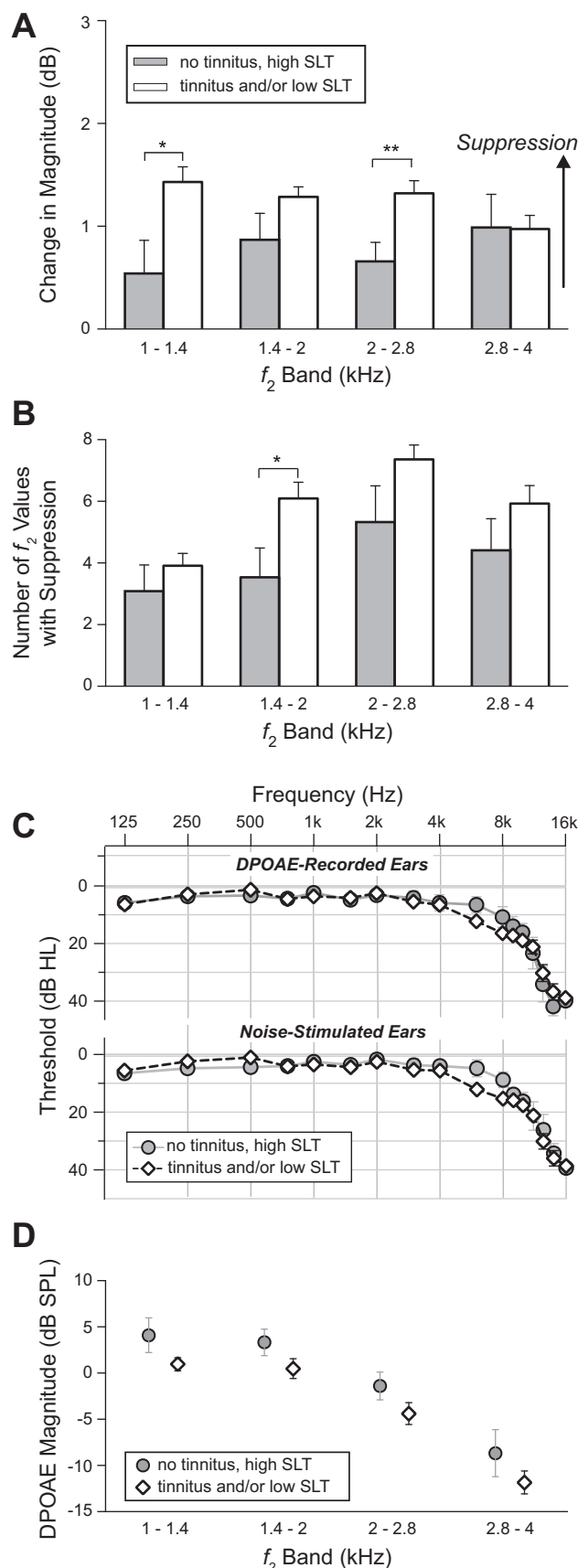


Fig. 6. Change in magnitude vs. age in four f_2 bands. Each point corresponds to a DPOAE-recorded ear. A linear, least mean-square error fit to the data is shown for each band.



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, and 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 ≥ 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 (*subject 110*), suppression in the 2- to 2.8-kHz band was greater than in any other subject. Otherwise, however, the other ear of this subject and that of the other subject with low tinnitus pitch (*subject 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 (*subjects 128* and *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 indexes were calculated for each subject and half-octave band from 1 to 4 kHz. All but one of the asymmetry indexes for the unilateral tinnitus subjects fell within the range for no-tinnitus and bilateral tinnitus subjects. The only exception was for *subject 129* in the 2.8- to 4-kHz band, where the index (3.4) slightly exceeded the maximum for the no-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* and *129* in Table 1). In other words, the tinnitus percept was asymmetric, but (low) SLT was symmetric.

Fig. 7. After age correction. A: the change in DPOAE magnitude remains greater in the combined tinnitus and/or low-SLT group compared with the no-tinnitus/high-SLT group. 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 2 groups are even more closely matched. D: baseline (no noise) DPOAE magnitude shows no significant difference between groups. * $P < 0.05$; ** $P < 0.01$ (not corrected for multiple comparisons). Exact P values are as follows: A, 1–1.4 kHz, $P = 0.01$, uncorrected; A, 2–2.8 kHz, $P = 0.004$; B, 1.4–2 kHz, $P = 0.02$.

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 supraclinical (>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, although 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 with 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. However, 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; Geven et al. 2011; Lind 1996; Paglialonga et al. 2010, 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 also could have 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 underestimation of MOC hyperresponsiveness 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 suprathreshold 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 with threshold-matched no-tinnitus subjects (Gu et al. 2012; Schaette and McAlpine 2011). 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 underrepresent the degree of MOC hyperresponsiveness actually present. In other words, hyperresponsiveness of the MOC system could actually be greater in tinnitus subjects than that reported here.

Possible neural bases for hyperresponsiveness 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 hyperresponsiveness of the portion of the MOC system activated by noise stimulation in the present experiments. The exact basis for the measured hyperresponsiveness 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 hyperresponsiveness 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 Fig. 7, A 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 because 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; Darrow et al. 2012; Mulders et al. 2007; Oertel et al. 2011). These animal data demonstrate that hyperactivity can indeed develop within certain elements of the MOC system.

MOC hyperresponsiveness and tinnitus/low SLT: cause-and-effect relationship? Neither hyperactivity nor hyperresponsiveness 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 hyperresponsiveness), 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, 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). 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/hyperresponsiveness 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., Mishra

and Lutman 2014; Smith et al. 2012). 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 (Brown et al. 2013b; Mellott et al. 2011; Mulders et al. 2000a, 2000b; Schofield et al. 2011). 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 brain stem hyperresponsiveness/hyperactivity associated with tinnitus and low sound tolerance: a result of top-down neuromodulation? The present results add to previous data indicating brain stem hyperresponsiveness 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 brain stem 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, in the present study, 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 hyperresponsiveness 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/hyperresponsiveness is ubiquitous in the auditory brain stem of people with tinnitus and/or low sound tolerance.

Prior to the present study, when hyperactivity/hyperresponsiveness 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/hyperresponsiveness 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 overactivation in tinnitus and low sound tolerance. In light of the existing data, it is worth considering a more parsimonious hypothesis, that overactivation of the auditory brain stem arises from forebrain-mediated neuromodulation broadly distributed throughout the brain stem, and for which

there is evidence (Schofield et al. 2011; see also Geven et al. 2014; Roberts et al. 2013). We propose that the patterns of activity in ascending auditory brain stem 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.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

I.M.K., C.A.S., and J.R.M. conception and design of research; I.M.K. performed experiments; I.M.K. and J.R.M. analyzed data; I.M.K., C.A.S., and J.R.M. interpreted results of experiments; I.M.K. prepared figures; I.M.K., C.A.S., and J.R.M. edited and revised manuscript; I.M.K., C.A.S., and J.R.M. approved final version of manuscript; J.R.M. drafted manuscript.

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