

Residual Inhibition Functions in Relation to Tinnitus Spectra and Auditory Threshold Shift

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Abstract

Conclusions. Psychoacoustic functions relating the depth and duration of tinnitus suppression (“residual inhibition”) to the center frequency of band-passed noise masking sounds appear to span the region of hearing loss, as do psychoacoustic measurements of the tinnitus spectrum. The results (1) suggest that cortical map reorganization induced by hearing loss is not the principal source of the tinnitus sensation and (2) provide a necessary baseline for optimizing residual inhibition in individual cases. **Objective.** To measure residual inhibition functions and tinnitus spectra using sounds spanning the region of hearing loss. **Material and Methods.** Three subject-driven, computer-based tools were developed and applied to measure psychoacoustic properties of tinnitus and residual inhibition in 32 subjects with chronic tonal, ringing, or hissing tinnitus. Residual inhibition functions were measured with band-passed noise sounds varying in center frequency up to 12.0 kHz. **Results.** The depth and duration of residual inhibition increased with the center frequency of the band-passed noise stimuli. Near-elimination of tinnitus for up to 45 seconds was reported by 8/24 (33%) subjects at center frequencies above 3 kHz (these cases distributed across tinnitus types). Tinnitus spectra covered the region of hearing loss with no preponderance of frequencies near the audiometric edge of normal hearing.

Keywords: Tinnitus, residual inhibition, tinnitus pitch matching, neural basis of sound

Introduction

Animal studies have shown that hearing impairment induced by noise exposure leads to a reorganization of the tonotopic map in primary auditory cortex, such that sound frequencies near the edge of the region of hearing impairment come to be over-represented at the expense of sound frequencies in the affected region [1-5]. Cortical reorganization has been linked directly with human tinnitus, which is also usually associated with hearing loss. According to this hypothesis, neurons at the edge of the region of hearing loss come to express the tuning preferences of their unaffected neighbors, thereby enhancing neural activity in this frequency region which is perceived as the tinnitus sensation [6]. Alternatively, map reorganization and tinnitus may be parallel outcomes of changes in dynamic neural activity that occur throughout the deafferented auditory cortex after hearing injury [7]. According to this view, cortical maps are altered when neurons which have lost their principal thalamocortical input respond to input from their unaffected neighbors via horizontal connections in the neocortical laminae, or to input from unaffected neighboring thalamocortical projections. Tinnitus, on the other hand, is a consequence not of map reorganization, but of spontaneous synchronous activity that forms among neurons in the deafferented region and is perceived in accordance with the location of the constituent neurons in the cortical place map. Increased synchronous activity in the affected region has been demonstrated in

animal models of hearing loss [8-9] and is believed to reflect loss of surround inhibition following diminished input from thalamocortical pathways.

Psychoacoustic measurements are relevant to the question of the relation of cortical map reorganization to the mechanism of tinnitus [7, 10-13]. Models that link tinnitus with cortical map reorganization predict that psychoacoustic assessments of tinnitus will localize the tinnitus sensation to frequencies at or near the edge of the audiometric threshold shift [6]. Models that link tinnitus with spontaneous synchronous activity in the deafferented frequency region, on the other hand, predict that the tinnitus spectrum spans the region of hearing loss in accordance with the depth of loss expressed in the audiogram, with no necessary preponderance of edge frequencies [7]. Norena et al. [14] assessed the tinnitus spectrum in a sample of 10 subjects using pure tones covering a range of frequencies including the region of hearing loss. Although two subjects reported tinnitus spectra peaking near the region of the audiometric edge, the majority of cases gave spectra spanning the region of hearing loss. The latter results are more consistent with the idea that tinnitus reflects altered neural activity in the region of hearing loss and not map reorganization which reflects tuning shifts to the audiometric edge.

In this paper we describe computer-based tools designed to evaluate tinnitus spectra using narrow band noise stimuli with center frequencies covering the audiogram. Audiograms were measured up to 20 kHz

where warranted. In addition, we extended the analysis to “residual inhibition” (RI, a temporary suppression of tinnitus by masking sounds which outlasts the duration of the masker) [12]. Eggermont and Roberts [7] suggested that RI occurs when masking sounds presented at supra-threshold levels inject inhibition into the deafferented region of the tonotopic map, briefly segregating the synchronous activity underlying the tinnitus sensation. If so, RI functions relating the depth and duration of RI to masking sounds of different center frequencies should show optimal tinnitus suppression covering the range of hearing loss in the audiogram, provided that the masking sounds can be heard. In this preliminary report application of tools for measuring tinnitus spectra and RI functions to a baseline sample of 32 tinnitus cases is described.

Material and Methods

Subjects Thirty-two adults (mean age 55.8 ± 18.0 years, range 33-74 years, 19 male) were recruited from the ENT clinic at McMaster University Medical Center or by advertisements in the local newspaper. Subjects reported chronic stable tinnitus persisting an average of 10.6 ± 7.4 years (range 0.4 – 30.1 years) and gave a mean loudness rating for their tinnitus of 42.0 ± 17.9 (range 10-80) which corresponds to the midpoint between “moderate” to “strong” on a logarithmic Borg CR100 psychophysical scale known to relate subjective loudness to sound pressure level as a power function in normal hearing subjects [15]. Subjects signed a consent form and were reimbursed for their parking fees but not otherwise remunerated. All study procedures were approved by the McMaster University Office of Research Ethics.

Apparatus and Procedure Assessment tools were three adaptive, subject-directed computerized procedures (Familiarization Program, Tinnitus Tester, and RI Tester, see below) programmed in Visual Basic. All sounds were prepared in Matlab and delivered by a sound card (Creative Audigy 2) through a programmable attenuator (Tucker-Davis PA5) using Sennheiser HDA-200 headphones. Behavioral responses were recorded by a Powermate USB Multimedia controller (Griffin Technologies) which allowed subjects to turn and then depress a bidirectional dial to record their decisions.

In their first visit to the laboratory subjects were interviewed to obtain information about their tinnitus and completed the Tinnitus Handicap Inventory. Audiograms were measured to 20 kHz using a GSI-61 audiometer. Subjects completed the Familiarization Program and then the Tinnitus Tester which assessed psychoacoustic properties of tinnitus. The session lasted about two hours. In a second visit one week later RI functions were measured by the RI Tester.

(1) *Familiarization Programme* This programme introduced subjects to the graphical user interface used for all procedures. By proceeding stepwise through a brief series of tasks, subjects learned how the computer program responded to their input from the dial by changing the sounds they heard and the images seen on the screen. The tasks also familiarized subjects with the concepts of loudness and pitch, which changed on separate trials as subjects manipulated dial settings. The Familiarization Programme required about 15 minutes for completion.

(2) *Tinnitus Tester* This computerized procedure assessed the quality of the tinnitus sensation (ear, loudness, bandwidth, and frequency spectrum to limit of the subjects’ audiogram) and gave a brief test for RI. The following steps were completed in the order indicated. (1) *Localize your tinnitus sensation.* Subjects used the dial to select one of three options, left ear, right ear, or both ears. (2) *Adjustment of sound intensity.* Subjects used the dial to adjust the loudness of a 0.5 kHz pure tone to a comfortable level. This level was used in steps (3) and (4) to present sound clips for tinnitus assessment. (3) *Bandwidth of tinnitus.* Subjects indicated whether their tinnitus was “tonal”, “ringing”, or “hissing”. Three sound clips were presented to illustrate these choices, consisting of a 5 kHz pure tone (“tonal” tinnitus) and two Gaussian band-pass noise maskers with a center frequency (CF) of 5 kHz differing in bandwidth. The two bandwidths were approximately $\pm 5\%$ of CF @ -20dB (called BPN5 herein) and the other $\pm 15\%$ of CF @ -20dB (called BPN15 herein; these two bandwidths illustrated “ringing” and “hissing” tinnitus, respectively). Subjects used the dial to sample the sounds and indicate their choice. (4) *Temporal properties.* Subjects indicated whether their tinnitus was steady or pulsing. Sound clips controlled by the dial illustrated their two choices. (5) *Tinnitus loudness rating.* Subjects rated the perceived loudness of their tinnitus using the dial to select a position on a Borg CR100 scale with the following quasi-logarithmic anchors: 0 “extremely weak”, 30 “moderate”, 50 “strong”, 70 “very strong”, and 100 “extremely strong” [15]. (6) *Tinnitus loudness matching.* Subjects were presented with sound clips with center frequencies ranging from 0.5 to 12.0 kHz. Bandwidth was determined by the selection made in step 3 (pure tone, BPN5, or BPN15). Subjects adjusted the loudness of each sound to match the loudness of their tinnitus, up to a maximum sound pressure level (SPL) of 95 dB. (7) *Tinnitus likeness ratings.* Subjects rated the pitch of each of the sounds presented in step (6) for similarity to the pitch of their tinnitus using a Borg CR100 scale (0 = not at all, 30 = not very similar, 50 = somewhat similar, 70 = very similar, 100 = identical). A profile of the tinnitus spectrum was thus generated. (8) *Sound threshold at*

1.0 kHz. Subjects increased the loudness of a 1.0 kHz tone until it was just audible. 65 dB was added to this level. Subjects then matched the loudness of each of three maskers to this stimulus. Two masking stimuli were PBN15 noise maskers with centre frequencies of 0.5 and 5.0 kHz. The third masking stimulus was a custom masker generated by the computer program according to the spectrum of the tinnitus measured in step (7). (9) *Brief RI test.* The three masking stimuli of Step 8 were tested for RI. On trials of 90 sec duration subjects listened to their tinnitus for 30 seconds followed by a masker for 30 seconds and then 30 seconds of silence. During the silence subjects adjusted the dial to indicate whether their tinnitus had increased (+5 maximum), decreased (-5 meant tinnitus was eliminated), or had not changed (0). Ratings were given separately for each ear, if bilateral tinnitus was indicated in step 1. After their tinnitus had returned subjects pressed the dial to initiate the next trial. Each masking stimulus was tested three times by this procedure in a mixed order. The Tinnitus Tester required about one hour for completion.

(3) *Residual Inhibition Tester.* The RI tester measured “RI functions” which related the magnitude and duration of RI to a standardized set of eleven BPN15 maskers differing in CF and a 12th stimulus which was white noise (WN). The stepwise progression of the RI Tester was as follows. (1) *Threshold at 1.0 kHz.* Using the dial, subjects completed a staircase procedure measuring the threshold of a 1.0 kHz pure tone. (2) *Loudness matching.* Subjects adjusted the loudness of each of 12 masking stimuli to match the loudness of a 1 kHz tone presented at 65 dB SL, up to a limit of 95 dB SPL. The CFs of the PBN15 maskers were 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, and 12.0 kHz. Stimuli were presented three times each in a random order. (3) *RI Function.* Subjects listened to each of the 12 masking stimuli (11 PBN15 stimuli and 1 WN stimulus) three times on discrete trials given in a random order. On each trial subjects listened to their tinnitus for 30 seconds followed by a masker for 30 seconds; an RI rating was then given using the same procedure of Step 9 in the Tinnitus Tester. After the rating was given, subjects depressed the dial to indicate when their tinnitus had returned to normal (thus giving a measure of RI duration). Following the dial press or 45 seconds (whichever came first), the next trial commenced. The RI test required about one hour for completion.

Data Analysis Mean audiograms, tinnitus spectra (the likeness ratings from step 7 of the Tinnitus Tester), and RI functions (RI depth and duration, from step 3 of the RI tester) are reported for groups of subjects reporting tonal, ringing, and hissing tinnitus. RI functions reported by subjects with bilateral tinnitus were similar for the two ears and were therefore

collapsed over ears. Between-subject variability was depicted by overlaying individual tinnitus spectra and RI functions within each group. These descriptive analyses were supplemented by nonparametric statistical tests (Friedman Analyses of Variance by Ranks or sign tests) as described herein.

Results

Hearing Function and Properties of Tinnitus

All subjects showed some degree of hearing loss (thresholds >25 dB HL) at frequencies ≤ 16 kHz. In 13/32 cases (40.6%) hearing thresholds were normal in both ears to 4 kHz and in 8/32 cases (25.0%) to 8 kHz. Hence 25% of our sample showed normal hearing in both ears up to 8 kHz but varying degrees of impairment at higher frequencies.

Using sound clips in the Tinnitus Tester as examples, 43.8% (14/32) of subjects described their tinnitus as “tonal”, 34.4% (11/32) as “ringing”, and 21.9% (7/32) as “hissing”. Thirty subjects reported a stable tinnitus and the remaining 2 cases a steady pulsating tinnitus. Twenty-four subjects reported bilateral tinnitus and eight subjects unilateral tinnitus (6 right ear). All forms of tinnitus (tonal, ringing, and hissing) were represented within the bilateral and unilateral groups. We present results from the 24 subjects reporting bilateral tinnitus herein, which conveys the overall picture while simplifying the graphical presentation.

Relation of Tinnitus Spectra and RI Functions to Hearing loss

The mean audiogram, tinnitus spectrum (likeness ratings), and RI functions (depth and duration) are presented for all bilateral cases in Figure 1, broken out by whether tinnitus was described as tonal, ringing, or hissing. The edge of normal hearing (threshold >25 dB) is demarcated by a broken line in the audiograms (Panel A) and projected onto the tinnitus spectra in Panel B and the RI function for depth in Panel C. Mean likeness ratings increased with CF in each subgroup (overall Friedman $\chi^2 = 63.0$, $p < 0.000$), reaching asymptote and spanning the region of hearing loss with no apparent diminution except at the highest frequency tested (12 kHz, which some subjects with tonal or ringing tinnitus could not hear). When the subgroups were considered separately, the effect of CF on likeness ratings was significant for hissing ($p < 0.0027$) and tonal ($p < 0.0001$) subjects but not within the ringing subgroup considered alone. RI functions for depth and duration (presented in Panels C and D, respectively) resembled the tinnitus spectra, with RI depth and duration increasing at higher CFs within the

hissing and tonal groups but showing a shallow trend in ringing tinnitus. When the tinnitus groups were considered as a whole the effect of CF was significant for RI depth ($\chi^2 = 23.3$, $p < 0.0096$) as well as for RI duration ($\chi^2 = 26.2$, $p < 0.004$). When the groups were considered separately, the effect of CF was significant only for RI depth in hissing tinnitus ($p < 0.022$). Mean RI depth reached a rating of -2.7 (54%) at 8 kHz within the hissing group where masker bandwidth most closely matched the subject's tinnitus. At this frequency RI duration was approximately 20 seconds in these subjects. Overall, 17/24 (70.8%) of subjects reported at least some degree of RI at 8 kHz and 12 kHz. RI depth averaged -1.46 (29%) at 8 kHz when averaged over all subjects.

Panel B of Figure 1 also reports the sound pressure levels that subjects matched to the loudness of their tinnitus in Step 6 of the Tinnitus Tester, and Panel C the sound pressure levels that equalized the perceived loudness of the maskers in Step 2 of the RI Tester (right ordinates in both cases). Because our subjects had high frequency hearing loss, the sound pressure levels chosen by the subjects tended to be higher for sounds of high CF. This effect was more pronounced for the tinnitus loudness matches (Panel B, particularly for tonal and ringing tinnitus) than for the masker level adjustments (Panel C), because the bandwidth of the sounds that subjects matched to the loudness of their tinnitus in Panel B differed between groups in order to approximate the bandwidth of their tinnitus. The sounds used to measure the RI functions in Panel C (and D) were BPN15 sounds in all groups, which may have permitted some off-frequency listening. SPL differed among the masking sounds used for the RI test ($\chi^2 = 84.9$, $p < 0.0001$), being lowest at 1.0 kHz and highest at 5.0 kHz and relatively stable above 5.0 kHz where some auditory recruitment may have occurred. RI duration correlated weakly with masker SPL within subjects (mean $r = 0.154$, $p = 0.047$) but RI depth did not (mean $r = -0.091$, $p = 0.323$).

Figure 2 shows tinnitus spectra (Panel A) and RI functions (Panels B and C) overlaid for individual subjects, separately for the tonal, ringing, and hissing groups. Although considerable individual variability was evident in the tinnitus spectra within each group (Panel A), overall 21 of 24 bilateral cases showed likeness ratings reaching asymptotes for stimuli with CFs covering the region of hearing loss. These 21/24 subjects ($p < 0.002$, sign test) gave maximum likeness ratings at CFs above 4.0 kHz followed in most cases by a decrease at 12.0 kHz (a stimulus that was not well matched for loudness to the other stimuli owing to hearing impairment). The three subjects that gave decreased likeness ratings for CFs above 4.0 kHz had hearing thresholds ≥ 60 dB above 2.0 or 3.0 kHz where the perceived loudness of the stimuli may also have

been a problem. RI functions for depth and duration (Panels B and C, respectively) were also variable between subjects in each tinnitus group. Although most subjects reporting RI indicated modest suppression, near-elimination of tinnitus (a scale rating ≥ -4.0) was reported by 8/24 (33%) subjects at CFs > 3.0 kHz for up to 45 seconds, with no apparent relation of such cases to tinnitus type. For two of these subjects sounds with lower CF were also effective. RI depth and duration produced by the WN masker is shown to the left of RI functions for each subject in Figure 2, and also in Figure 1 for the averaged data. WN was generally as effective at inducing RI as BPN15 sounds in each group. However, for two subjects in the hissing group RI duration was markedly greater for BPN15 with CFs > 4.0 kHz than for WH. Inspection of RI functions for depth shows that BPN15 maskers with CFs below 4.0 kHz made tinnitus worse in ringing and particularly in tonal tinnitus (5/19 subjects in these groups combined), but not for hissing tinnitus. However, the depth and duration of RI induced by BPN15 sounds of the highest CF did not differ among the tinnitus types.

It will be recalled that 25% of our total sample of 32 tinnitus cases showed normal audiograms at or below 8.0 kHz but hearing loss at higher frequencies. The tinnitus spectra and RI functions for these subjects were similar to subjects with hearing loss below 4.0 kHz, with both groups showing the deepest and most persistent RI to BPN15 maskers with CFs > 4.0 kHz. Compared to the clinically impaired hearing group, subjects with clinically "normal" hearing tended to experience a worsening of tinnitus when the CF of the maskers was < 4.0 kHz.

Discussion

Our findings corroborate the results of Norena et al. [14] in showing that tinnitus spectra extend well into the region of hearing loss without a preponderance of frequencies at or near the edge of the region of auditory threshold shift. The tinnitus spectra described in Figure 1 were assessed with sounds resembling the bandwidth of each subject's tinnitus (pure tonal, ringing, or hissing tinnitus) and did not differ appreciably as a function of tinnitus type. For tonal and ringing tinnitus a roll-off occurred in the likeness matches at the highest frequency tested (12 kHz), probably because loudness matching of the sounds to tinnitus was less successful at this frequency for these subjects where pure tones or BPN5 sounds were used to assess the tinnitus spectrum. The results suggest that the sensation of tinnitus reflects changes in neural dynamics occurring throughout the region of hearing loss [7] rather than an over-representation of edge frequencies known to occur after noise-induced hearing

impairment [6].

RI functions which are described here for the first time point to a similar conclusion. Based on psychoacoustic measurements of tinnitus [10] and studies of animal models of hearing loss [8-9], Eggermont and Roberts [7] suggested that tinnitus occurs when increased synchronous neural activity forms in the region of hearing impairment following a decrease in surround inhibition consequent on hearing injury. Synchronous neural activity may be the basis of the normal perception of sound, but in tinnitus such activity is unconstrained by surround inhibition and thus may spread over more frequencies and occur without acoustic input. This hypothesis implies that presentation of supra-threshold sounds in the affected frequency region should segregate synchronous neural activity by restoring intracortical inhibition, thereby dampening the tinnitus sensation. Our RI functions, which generally paralleled tinnitus spectra and the region of audiometric threshold shift, are consistent with this view. The mean duration of RI at the asymptote of RI depth was about 20 seconds which is consistent with earlier reports [12] and implies a physiological time constant for a process the details of which are unknown.

Some features of the RI functions are noteworthy. Although RI depth and duration were significantly greater for BPN15 sounds of higher CF in the averaged data, considerable variability was present between subjects. At the group level RI functions for depth and duration tended to be most pronounced for subjects with hissing tinnitus where the bandwidth of the BPN15 masking sounds most closely resembled the bandwidth of their tinnitus. Nevertheless, subjects reporting RI depth approaching tinnitus elimination for up to 45 seconds (the maximum duration that we assessed) were seen in all tinnitus groups (8/24 subjects overall). WN maskers were generally as effective at inducing RI as BPN15 maskers, although tinnitus elimination was more commonly reported following maskers with high CFs. The effect of high frequency BPN15 sounds on RI duration may have been greater had subjects been permitted to assess their tinnitus for longer than 45 seconds. BPN15 maskers and WH maskers made tinnitus worse for 5/19 tonal and ringing subjects, but this outcome was not reported by hissing cases. The presence of so much variability among our subjects leads one to ask whether we can identify variables and procedures that may optimize RI for individual cases. The present findings provide a necessary baseline for answering this question.

The sounds used to measure tinnitus spectra and RI functions in the present study were equated for sensation level for each subject by our computer-based tools. Because subjects had high frequency hearing loss, sounds of high CF were generally presented at

higher sound pressure levels, particularly when tinnitus spectra were measured for tonal and ringing tinnitus where the bandwidth of the sounds was narrower (pure tones or BPN5 stimuli respectively) than in hissing cases (BPN15 stimuli). All subjects were presented with BPN15 maskers when RI functions were measured. During RI testing within-subject correlations between SPL and RI variables were weak or non-significant, suggesting that CF influenced the shape of the RI functions. Nevertheless the bandwidth of the frequency response of the basilar membrane at high sound pressure levels is likely to be broad [16]. RI induced by maskers of high CF might profit from enhanced segregation of synchronous neural activity consequent on spectral splatter at these frequencies. Another contributing factor could be that more neurons become refractory at high sound pressure levels.

Eight of our total sample of 32 subjects (25%) would have been judged to have normal hearing by clinical audiometry to 8 kHz. However, all eight of these subjects showed high frequency hearing losses, had tinnitus, and experienced RI at high frequencies. To fully appreciate the meaning of these data age-matched control subjects without tinnitus need to be assessed audiometrically. Were control subjects without tinnitus to show normal hearing above 12 kHz, the role of high frequency hearing loss in tinnitus would be suggested. This could have implications for the prevention of tinnitus and for the design of hearing devices aimed at reducing tinnitus sensations [7, 17].

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Acknowledgements This research was supported by grants from the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, and the American Tinnitus Association. We thank Lawrence Ward for calling our attention to Borg CR100 scaling procedures.

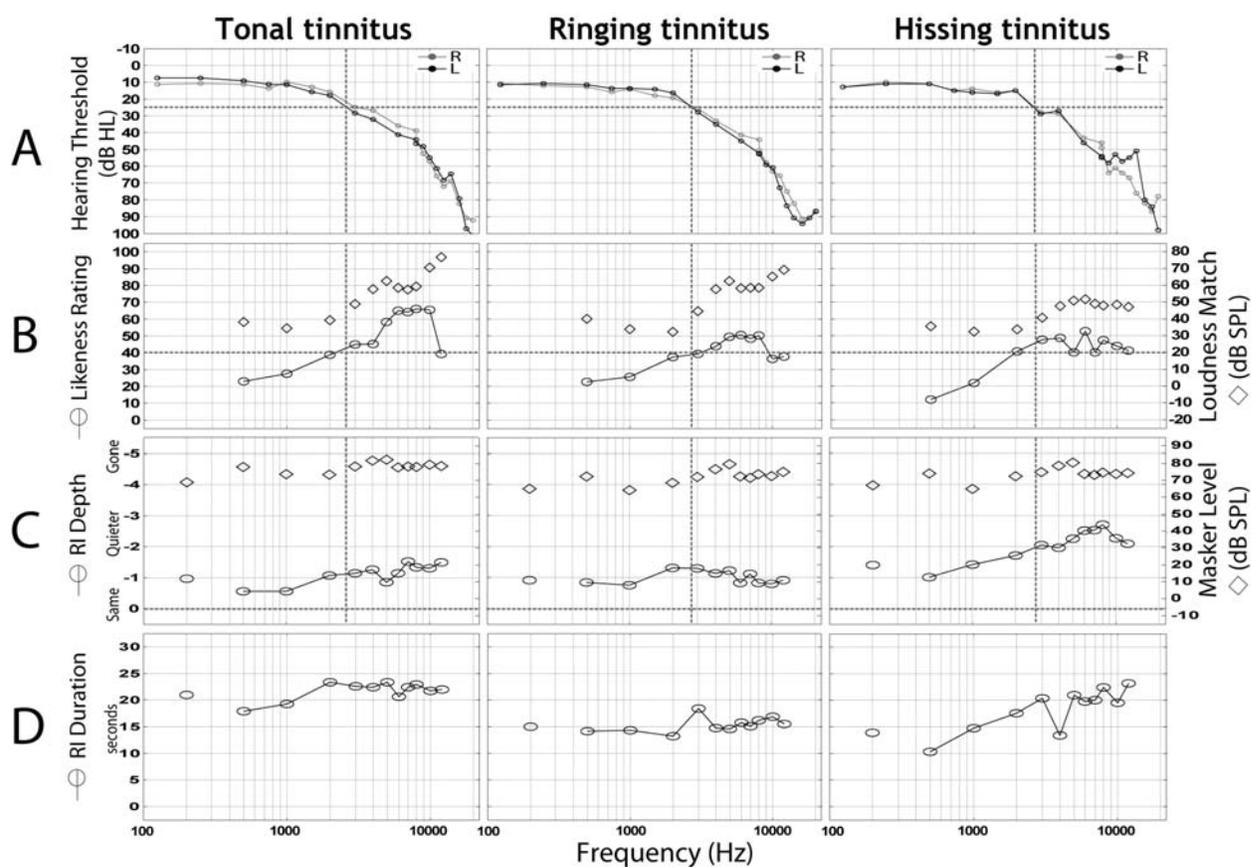


Figure 1. Averaged data are presented separately for subjects reporting tonal, ringing, or hissing tinnitus. (A) Audiogram. The region of hearing loss is identified by a broken line and projected into Panels B and C. (B) Tinnitus spectrum determined from likeness ratings (left ordinate) and intensity of the sound stimuli used in the likeness rating procedure (intensity adjusted by each subject to match the loudness of their tinnitus, right ordinate). The horizontal broken line at a likeness rating of 40 corresponds to the region where subjects reported that the center frequency of the sounds was beginning to resemble their tinnitus. (C) RI depth (left ordinate) and intensity of the stimuli used to measure the RI function (right ordinate). Subjects adjusted the intensity of each stimulus to equal that of a 1.0 kHz tone at 65 dB SL. The broken horizontal line denotes no reported change in the tinnitus sensation (-5, tinnitus gone). (D) RI duration. In Panels C and D, the data points to the left are for the WH stimulus.

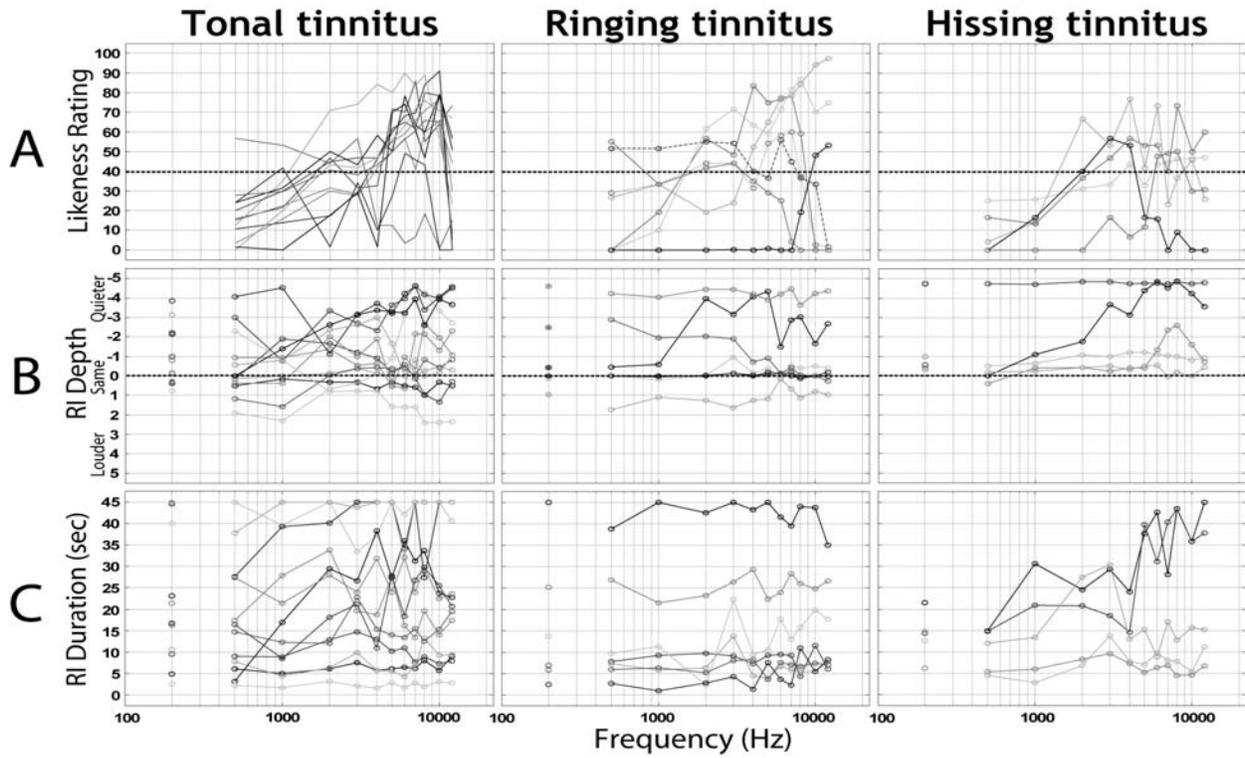


Figure 2. Tinnitus spectra (Panel A) and RI functions (Panels B and C, depth and duration respectively) are overlaid for each subject in the three tinnitus groups. The broken horizontal line in Panel A denotes a likeness rating of 40, where subjects reported that the tinnitus sensation began to resemble their tinnitus. The broken horizontal line in Panel B denotes no change in the tinnitus sensation (-5, tinnitus gone). The data points to the left in Panels B and C are for the WN masker.