

The spatial percept of tinnitus is associated with hearing asymmetry: subgroup comparisons

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Abstract

The spatial percept of tinnitus is hypothesized as an important variable for tinnitus subtyping. Hearing asymmetry often associates with tinnitus laterality, but not always. One of the methodological limitations for cross-study comparisons is how the variables for hearing asymmetry and tinnitus spatial perception are defined. In this study, data from two independent datasets were combined (n= 833 adults, age ranging from 20 to 91 years, 404 males, 429 females) to investigate characteristics of subgroups with different tinnitus spatial perception focusing on hearing asymmetry. Three principle findings emerged. First, a hearing asymmetry variable emphasizing the maximum interaural difference most strongly discriminated unilateral from bilateral tinnitus. Merging lateralized bilateral tinnitus (perceived in both ears but worse in one side) with unilateral tinnitus weakened this relationship. Second, there was an association between unilateral tinnitus and ipsilateral asymmetric hearing. Third, unilateral and bilateral tinnitus were phenotypically distinct, with unilateral tinnitus being characterized by older age, asymmetric hearing, more often wearing one hearing aid, older age at tinnitus onset, shorter tinnitus duration, and higher percentage of time being annoyed by tinnitus. We recommend that careful consideration is given to the definitions of hearing asymmetry and tinnitus spatial perception in order to improve the comparability of findings across studies.

Keywords

Hearing loss, tinnitus, unilateral, bilateral, symmetric, localization, lateralization, laterality, classification

1 Introduction

2 There is emerging evidence indicating that tinnitus percepts with different spatial profiles
3 might represent subtypes with different mechanisms (Maas et al., 2017, Vanneste et al.,
4 2011, Cuny et al., 2004). In addition, it has been shown that tinnitus laterality tends to
5 associate with hearing asymmetry (Cahani et al., 1984, Tsai et al., 2012), however, this is
6 not always the case (Lee et al., 2019).

7 One of the methodological limitations for cross-study comparisons is how hearing
8 asymmetry and tinnitus spatial perception are operationally defined. There is no single
9 established method for defining asymmetric hearing. Asymmetry can be based on the
10 average interaural difference (ID) of specific audiometric frequencies or a frequency range,
11 the value of the maximum difference in one or more frequencies, or a combination of
12 characteristics. Many different approaches have been documented (Cahani et al., 1984,
13 Caldera and Pearson, 2000, Cheng and Wareing, 2012, Hendrix et al., 1990, Hojjat et al.,
14 2017, Jeffery et al., 2016, Mangham, 1991, Margolis and Saly, 2008, National Guideline
15 Centre UK, 2018, Tsai et al., 2012, Urben et al., 1999). Examples from clinical practice also
16 differ. In the UK, the British Academy of Audiology considers a diagnosis of asymmetric
17 hearing when there is an interaural difference of 20 dB or more in at least two consecutive
18 frequencies at 0.5, 1, 2, 4 and 8 kHz (Jeffery et al., 2016). However, also in the UK, the
19 National Institute for Health and Care Excellence (NICE) recommendation considers an
20 onward referral for Magnetic Resonance Imaging (MRI) when there is an interaural
21 difference of 15 dB or more in two consecutive frequencies at 0.5, 1, 2, 4 and 8 kHz
22 (National Guideline Centre UK, 2018). Based on 1490 audiograms from military personnel,
23 Caldera and Pearson (2000) showed that the prevalence of hearing asymmetry could have a
24 more than 100-fold variation (varying from 543 to 77,242 per 100,000) depending on the
25 definition used for asymmetry. The task becomes even more complicated when the
26 audiometric profile is sampled more comprehensively at mid-octave frequencies and
27 extended high frequencies above the conventional cut-off at 8 kHz, as is often the case in
28 research settings. One proposed solution could be to measure the area under the audiogram
29 curve after interpolating in-between frequencies (König et al., 2006). For research purposes,
30 some have sought to define the optimum asymmetry metric depending on the hypothesis.
31 For example, Tsai et al. (2012) investigated how different asymmetry metrics can predict
32 tinnitus laterality. They concluded that a maximum threshold difference averaged to the
33 adjacent second maximum of at least 15 dB difference was the optimum predictor. However,
34 this has not been independently verified. Examples of different definitions for hearing
35 asymmetry reported in the literature, and their application are shown in Supplementary Table
36 1 and 2 respectively. Importantly, none of these measures included extended high frequency
37 audiometric thresholds.

38 As in asymmetric hearing, there is no standard method for defining the spatial percept of
39 tinnitus. Tinnitus can be perceived anywhere in space (Searchfield et al., 2015), but to
40 localize the percept of tinnitus requires psychophysical testing procedures. Instead, studies
41 more often rely on self-report and limit inquiry to whether tinnitus is perceived in one or both
42 ears or in the head. Many studies use a binary classification of unilateral and bilateral
43 tinnitus, although response options can be extended to include: in the right ear, in the left
44 ear, in both ears equally, in both ears but worse in the right or left ear, and inside the head or

45 elsewhere (Langguth et al., 2007, Nuttall et al., 2004). The challenge here is how to pool
46 such response options to form characteristics that define meaningful subgroups.

47 Table 1 proposes four potential summary variables for tinnitus spatial perception. These
48 discriminate the percept of tinnitus that is clearly restricted to one ear (unilateral) from that
49 where tinnitus is perceived equally in both ears (bilateral). They also consider cases that are
50 less distinct; where tinnitus is in both ears but more on one side than the other or is
51 somewhere inside the head. The characterization of being lateralized or non-lateralized is
52 used to discriminate percepts based on whether there is a dominance in one side (left or
53 right) or not. There is some degree of subjectivity in determining whether the less distinct
54 lateralized bilateral cases should be categorized with unilateral or bilateral tinnitus.
55 Reasonable justifications could be made to categorize a participant who experiences tinnitus
56 in both ears but worse on one side, either as a case of bilateral tinnitus or unilateral tinnitus.

57 In this study, we combined two independent datasets to address the following research
58 questions.

59 1. Which definition of hearing asymmetry reliably discriminates unilateral from bilateral
60 tinnitus? We also explored whether participants reporting tinnitus in both ears but worse in
61 one ear should be classified as unilateral or bilateral tinnitus cases.

62 2. Does the pattern of hearing asymmetry differ between tinnitus and non-tinnitus cases,
63 and across different spatial tinnitus percepts in those reporting tinnitus?

64 3. What are phenotypic characteristics of subgroups with unilateral or bilateral tinnitus?

65 **Table 1.** Summary labelling of response options for tinnitus spatial perception.

Summary labelling for tinnitus laterality	Self-reported description
(lateralized) unilateral	<ul style="list-style-type: none">• left ear• right ear
non-lateralized bilateral	<ul style="list-style-type: none">• both ears equally
(non-lateralized) central	<ul style="list-style-type: none">• inside the head
lateralized bilateral	<ul style="list-style-type: none">• both ears, worse in left• both ears, worse in right

66 **Methods**

67 **Dataset description**

68 The two independent datasets were from the Swedish Tinnitus Outreach Project (STOP)
69 Sweden and the NIHR Nottingham Biomedical Research Centre (BRC) UK. The STOP
70 dataset analyzed was a subset from a population-based tinnitus specific database (Swedish
71 Tinnitus Outreach Project, 2015). The BRC dataset analyzed was a collection of published
72 data from three previous tinnitus clinical studies conducted by some of the authors (Davies
73 et al., 2014, Hoare et al., 2012, Hoare et al., 2014). Each of these studies had received

74 ethical approval from the National Research Ethics Committee (Nottingham or Derby, UK).
75 For the STOP project, ethical approval was granted by the local ethics committee “*Regionala*
76 *etikprövningsnämnden*” in Stockholm (2015/2129-31/1). The two datasets included a number
77 of common variables and were composed of phenotypical information (both general and
78 tinnitus specific) that had been collected using various hearing tests and questionnaires,
79 including the Tinnitus Sample Case History Questionnaire (TSCHQ; Langguth et al., 2007)
80 and the Hyperacusis Questionnaire (HQ; Khalfa et al., 2002). For the BRC dataset, pure
81 tone audiometry was conducted manually by an examiner using a Siemens Unity 2 system
82 and Sennheiser HDA 200 headphones. For the STOP dataset, fixed frequency Bekesy
83 audiometry was done using the Astera 2 audiometer (Otometrics) and Sennheiser HDA 200
84 headphones. In both cases, frequencies from 0.125 kHz to 14 kHz were tested in sound-
85 proofed conditions. Thresholds greater than the audiometer limit were given a standardized
86 value of 110 dB HL. Details of all the included variables can be found in Supplementary
87 Table 3.

88 Data for participants without pure tone audiometry (n=10) were excluded from further
89 analyses. Data for participants with missing responses to the question ‘Where do you
90 perceive your tinnitus?’ (n=19), and cases reporting tinnitus ‘elsewhere’ (n=12) were also
91 excluded. From an initial sample of 612 tinnitus cases, this left 571 for analysis (n=382 from
92 the STOP and n=189 from the BRC databases). Data from 262 non-tinnitus cases were also
93 available from the STOP database. The mean age from the total sample (n=833) was 53
94 years, ranging from 20 to 91. There were 404 males and 429 females.

95 Participants with tinnitus across datasets differed significantly in terms of age, mean
96 audiometric hearing thresholds, hearing aid use, presence of headaches and balance
97 disorders, tinnitus duration and age at onset, spatial perception of tinnitus, stress influence
98 on tinnitus and percentage of time being annoyed by tinnitus. This information is shown in
99 Supplementary Table 4. These observations fall within the variability that would be expected,
100 considering the differences in the populations and sampling methodology. We therefore
101 considered it reasonable to combine the two datasets for our analyses. This created a more
102 diverse sample, and from a practical point of view also boosted the number of cases
103 reporting unilateral tinnitus.

104 **Variables for hearing asymmetry**

105 A benchmark’ variable for asymmetric hearing was defined according to Jeffery et al. (2016)
106 as an interaural difference of 20 dB or more in at least two consecutive frequencies at 0.5, 1,
107 2, 4 and 8 kHz. Four additional variables, which additionally quantify the *degree* of hearing
108 asymmetry, were also calculated:

- 109 1. **MaxDiff**: the maximum mean interaural threshold difference of two adjacent
110 frequencies (including thresholds at the frequency with the maximum interaural
111 difference), spanning the range of thresholds at 0.5, 1, 2, 4 and 8 kHz as in Tsai,
112 Sweetow et al. (2012).
- 113 2. **MaxDiffExt**: calculated as MaxDiff, spanning the range of thresholds at 0.125, 0.25,
114 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 kHz, and including the mean difference from the
115 available extended high frequencies (10, 12.5, and 14 kHz for the STOP dataset and
116 9, 10, 11.2, 12.5, and 14kHz for the BRC dataset). Thresholds at 0.75 and 1.5 kHz
117 were not available for the STOP dataset and were calculated as the mean of the
118 adjacent frequencies.

- 119 3. **AUCDiff**: the interaural difference of the area under the audiogram curve (integral)
120 after logarithmically transforming frequencies to obtain equal distance per octave and
121 interpolating in-between thresholds (including all available thresholds at 0.125-14
122 kHz).
123 4. **PTADiff**: the interaural difference of the mean threshold at 0.5, 1, 2, 4, and 8 kHz.

124 MaxDiff and MaxDiffExt emphasize the informational content of the two frequencies with the
125 maximum interaural difference. In contrast, AUCDiff and PTADiff emphasize the overall
126 average of the interaural difference. Another key difference is that MaxDiffExt and AUCDiff
127 incorporate information from all available thresholds, whereas MaxDiff and PTADiff are
128 limited to the mid-frequency octaves.

129 **Variables for tinnitus spatial perception**

130 For both datasets the question ‘Where do you perceive your tinnitus?’ was asked, and
131 response options were (a) in the right ear, (b) in the left ear, (c) in both ears equally, (d) in
132 both ears but worse in the right or left ear, (e) inside the head, or (f) elsewhere (Langguth et
133 al., 2007). Following Table 1, our variables for summarizing tinnitus spatial perception were:

- 134 1. (lateralized) unilateral
135 2. lateralized bilateral
136 3. non-lateralized bilateral

137 Throughout this report, the term ‘laterality’ is used to describe subgroups of unilateral and
138 bilateral tinnitus, regardless of how the classification was done.

139 **Analysis**

140 All analyses were conducted in R version 3.6.1 (R Core Team, 2019). R packages used
141 included pROC (Robin et al., 2011), caret (Kuhn, 2015), glmnet (Friedman et al., 2010),
142 missForest (Stekhoven, 2015, Stekhoven and Bühlmann, 2012), FSA (Ogle, 2017), and
143 viridis (Garnier, 2018). Alpha level was set to 0.05 and for multiple comparisons p-values
144 were adjusted using Holm’s method (Holm, 1979).

145 To address question 1, Receiver Operating Characteristic (ROC) curves were used to
146 assess performance of hearing asymmetry variables for discriminating unilateral tinnitus
147 (defined as the positive condition) from bilateral tinnitus (Robin et al., 2011). ROC curves are
148 plots of the true positive rate (or sensitivity; proportion of correctly classified as positive of all
149 positives) on the y-axis and the false positive rate (or $1 - \text{specificity}$; proportion of wrongly
150 classified as positive of all negatives) on the x-axis for different thresholds of a predictor. The
151 area under the ROC curve (ROC AUC) takes values from 0 to 1, with 1 indicating excellent
152 discrimination and 0.5 no discrimination capacity. The 95% confidence intervals for ROC
153 AUCs were calculated using stratified bootstrapping (R package pROC; Robin et al., 2011).
154 Delong’s method was used for comparison of ROC curves (DeLong et al., 1988), as
155 implemented in the roc.test function from the pROC package (Robin et al., 2011). Results
156 present the p-values for the pair-wise tests for statistically significant differences. Further, the
157 ROC curve was used to define a cut off value to transform a numerical hearing asymmetry
158 variable into a binary categorical variable. The best cut off was defined as the value that
159 maximized the sum of sensitivity and specificity from the ROC curve (J-Index; Youden,
160 1950).

161 A further exploratory analysis compared performance of different operational definitions of
162 binary categorical variables for hearing asymmetry in predicting tinnitus laterality. To do this,
163 we calculated the specificity (proportion of being correctly classified as negative of all
164 negatives), accuracy (fraction of all instances that are classified correctly), positive predictive
165 value (proportions of being correctly classified as positive of all classified as positive), and
166 negative predictive values (proportion of being correctly classified as negative of all
167 classified as negative). Higher value for all these metrics indicates better performance.

168 To address question 2, box plots and frequency distributions were used to explore the
169 relationship between hearing asymmetry and tinnitus spatial perception. Kruskal-Wallis test
170 and post-hoc Dunn's test were used to compare the distribution of hearing asymmetry
171 across the different tinnitus spatial perception subgroups.

172 To address question 3, the associations between tinnitus laterality and various other
173 phenotypic variables were assessed using Fisher's exact tests and Wilcoxon tests. In
174 addition, a multivariable logistic regression was used to assess the simultaneous effect of
175 selected phenotypic variables in predicting tinnitus laterality. To avoid overfitting, the
176 following protocol was applied for variable selection. First, a set of variables was selected by
177 the authors. Then, univariable logistic regression models were fitted and the variables found
178 significant were subsequently considered simultaneously into a multivariable logistic
179 regression. The latter was fitted using least absolute shrinkage and selection operator
180 (LASSO) (R package glmnet; Friedman et al., 2010). LASSO is a method for fitting linear
181 models that includes a penalization for the sum of the absolute coefficients (Tibshirani,
182 1996). The method shrinks some coefficients to zero, allowing selection of the most relevant
183 variables. Performance of the method was assessed using a 5-fold cross validation in an
184 outer loop. The parameter lambda, which defines the penalty for the coefficients, was
185 selected using 5 fold cross-validation in an inner loop (nested cross validation; see for
186 example Varma and Simon, 2006), choosing the largest value for which error was within 1
187 standard error from the minimum (Breiman et al., 1984, Friedman et al., 2010). Cases with
188 more than 20% missing values were excluded. Otherwise missing values were imputed
189 using a random forest algorithm (R package missForest; Stekhoven, 2015, Stekhoven and
190 Bühlmann, 2012).

191 **Results**

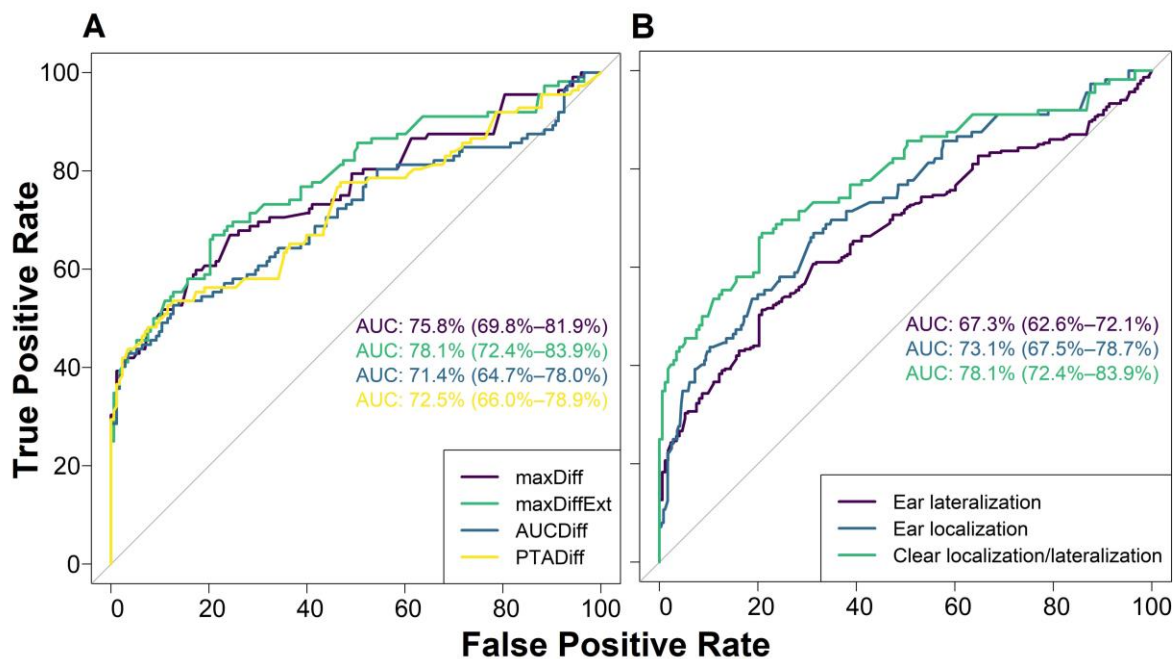
192 **A hearing asymmetry emphasizing the maximum interaural difference across the full** 193 **audiometric range most strongly discriminated unilateral from bilateral tinnitus**

194 For the 571 cases reporting tinnitus, the four hearing asymmetry variables (MaxDiff,
195 MaxDiffExt, AUCDiff and PTADiff) were compared to one another in their ability to predict
196 tinnitus laterality. For each variable, the absolute values for hearing asymmetry were used
197 as a marker for the degree of asymmetry. Only participants whereby tinnitus could be clearly
198 discriminated as unilateral (left or right ears) or bilateral (both ears equally) (Table 1) were
199 included in this analysis to avoid any difficulties in interpreting the findings which could be
200 attributed to categorization bias.

201 For these data, ROC curves were plotted with each of the hearing asymmetry variables as
202 predictors and tinnitus laterality as the outcome (Panel A, Figure 1), while Table 2 shows p-
203 values from ROC AUC pairwise comparisons using DeLong's test for correlated ROC
204 curves. From visual inspection, differences between the ROC curves appeared to be

205 marginal, and this was supported by the DeLong's results which were mostly non-significant.
206 A notable exception was that of the maxDiffExt metric which performed significantly better
207 than AUCDiff in classifying tinnitus laterality (Table 2).

208 We therefore conclude that the maxDiffExt metric was the preferred hearing asymmetry
209 variable for subsequent subgrouping analyses. Not only did it perform best on the ROC
210 evaluation, but also incorporated all available information obtained from the pure tone
211 audiometry.



212

213 **Figure 1.** ROC Curves and AUCs using: A) the four hearing asymmetry variables (absolute values) as
214 predictors and tinnitus laterality as outcome, and B) absolute MaxDiffExt as predictor and each of the
215 different binary variables for tinnitus laterality as outcome. Unilateral tinnitus (versus bilateral) was
216 coded as the positive outcome. MaxDiff: maximum interaural threshold difference mean of two
217 adjacent frequencies including thresholds at 0.5-8 kHz; maxDiffExt: same as MaxDiff including
218 thresholds at lower frequencies, half-octave frequencies and extended high frequencies; AUCDiff:
219 interaural difference of the area under the audiometric curve including all available thresholds at
220 0.125-14 kHz; PTADiff: interaural difference of the mean threshold at 0.5-8 kHz; Ear lateralization:
221 lateralized unilateral and bilateral versus non-lateralized bilateral; Ear localization: (lateralized)
222 unilateral versus (lateralized and non-lateralized) bilateral; Clear localization/lateralization:
223 (lateralized) unilateral versus non-lateralized bilateral.

224 **Table 2.** Pairwise comparison of AUCs of ROC curves
 225 for the four hearing asymmetry variables.

	maxDiffExt	AUCDiff	PTADiff
maxDiff	0.781	0.481	0.481
maxDiffExt		0.032	0.184
AUCDiff			0.781

P-values from Delong's test for correlated ROC curves (adjusted for multiple comparisons; Holm 1979).

226 As used so far, the MaxDiffExt variable quantifies the degree of hearing asymmetry on an
 227 numerical scale. But for clinical decision making, a binary classification (akin to a 'diagnosis')
 228 is preferred as this clearly discriminates a person with symmetric hearing from a person with
 229 asymmetric hearing. The best cut off value for MaxDiffExt to define such a binary hearing
 230 asymmetry variable was found to be 14.54 dB (value that maximized sum of sensitivity and
 231 specificity). For practical purposes, 14.54 dB was rounded up to the nearest integer giving a
 232 recommended cut off of 15 dB. We therefore ascribed the label 'symmetric hearing' in all
 233 cases where the absolute maxDiffExt was <15 dB and 'asymmetric hearing' when the
 234 absolute maxDiffExt was ≥15 dB. This newly derived variable was called Asym15.

235 The performance of Asym15 in discriminating tinnitus laterality was compared to the
 236 performance of the Jeffery et al. (2016) benchmark. The latter showed high specificity and
 237 positive predictive value, but this contrasted with its rather poor sensitivity. Although Asym15
 238 did not perform with the same specificity, it was a much more sensitive metric, performing
 239 better at correctly classifying positive cases (unilateral tinnitus) as true positive (Table 3).

240 **Table 3.** Performance of Asym15 and Jeffery et al. (2016) binary classification variables for
 241 hearing asymmetry.

	Specificity	Sensitivity	Accuracy	Negative predictive value	Positive predictive value
Asym15	79.77	65.18	74.04	77.97	67.59
Jeffery et al. (2016) benchmark	98.27	37.50	74.39	70.83	93.33

242 In summary, for cases where the tinnitus spatial percept is unambiguous, we conclude that a
 243 hearing asymmetry variable emphasizing the maximum interaural difference across the full
 244 audiometric range appears able to most reliably discriminate unilateral from bilateral tinnitus.

245 **Merging lateralized bilateral tinnitus with unilateral tinnitus weakened the association**
 246 **with hearing asymmetry**

247 Our analysis so far excluded cases where the laterality of the tinnitus spatial percept was
 248 somewhat ambiguous (i.e. cases of lateralized bilateral tinnitus in both ears, but worse on
 249 one side). But since these cases represent 32.9% (188/571) of the full tinnitus dataset, they
 250 should preferably not be ignored. A follow-on analysis was therefore conducted to
 251 investigate the effect of adding these participants into the ROC computation. The exploratory

252 question that we asked was how would adding these participants affect the good
253 performance of the maxDiffExt in discriminating unilateral from bilateral tinnitus?

254 The benchmark was the previous dataset comprising only participants whereby tinnitus
255 could be clearly discriminated as unilateral (left or right ears) or bilateral (both ears equally).
256 This condition is termed 'clear ear localization/lateralization'. Two comparator datasets were
257 created. One discriminated unilateral (tinnitus in left or right ears) from bilateral (tinnitus in
258 both ears equally, plus tinnitus in both ears but worse on one side). This condition is termed
259 'ear localization'. Another discriminated lateralized (tinnitus in left or right ears, plus tinnitus
260 in both ears but worse on one side) from non-lateralized (tinnitus in both ears equally). This
261 condition is termed 'ear lateralization'.

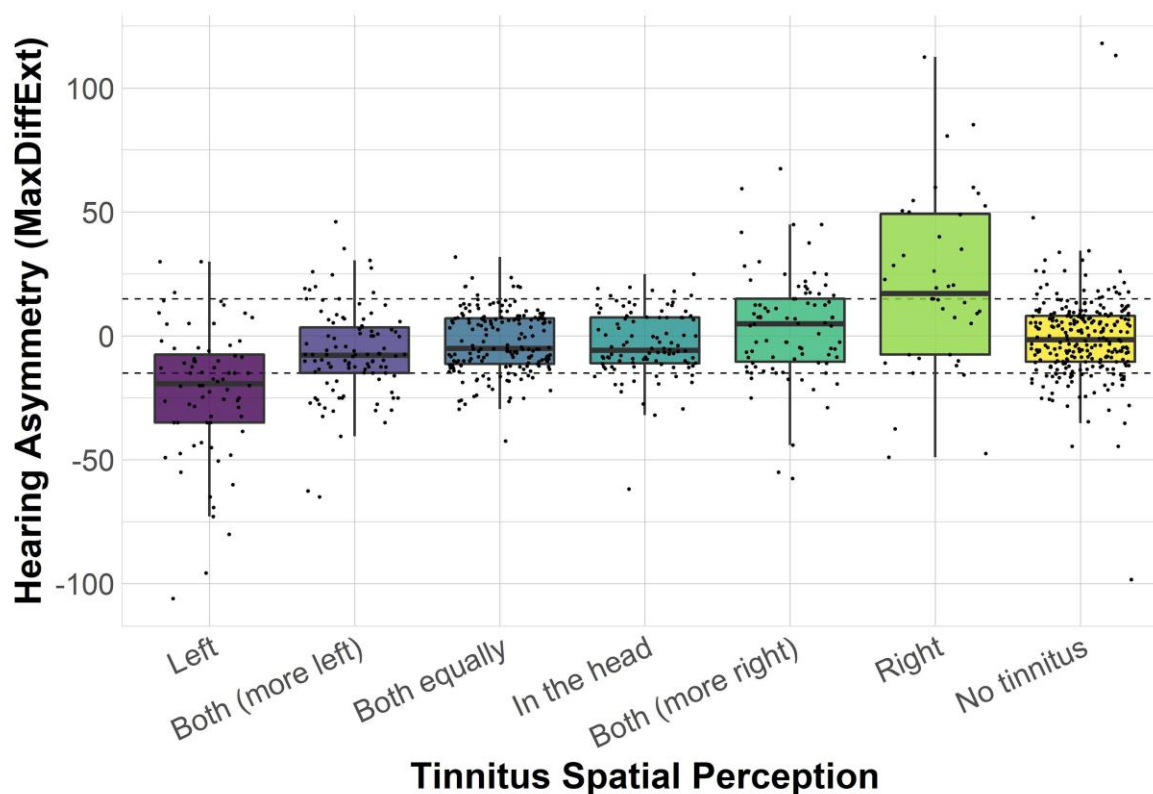
262 ROC curves were plotted with the maxDiffExt as the predictor and each of the three different
263 conditions defining tinnitus laterality as the outcome (Panel B, Figure 1), while Table 4
264 shows p-values from ROC AUC comparisons using DeLong's test for uncorrelated ROC
265 curves. From visual inspection, differences between the ROC curves appeared to be
266 marginal, but notably the DeLong's results indicated that ear lateralization performed
267 significantly worse than the benchmark condition in classifying tinnitus laterality. Ear
268 localization did not significantly differ from the benchmark condition.

269 **Table 4.** Pairwise comparison of AUCs of ROC curves for the different binary variables for
270 tinnitus spatial perception.

	Ear localization	Clear localization/lateralization
Ear lateralization	0.2534	0.014
Ear localization		0.253

P-values from DeLong's test for uncorrelated ROC curves (adjusted for multiple comparisons).

271 We therefore conclude that one should not consider participants who report their tinnitus in
272 both ears but worse on one side, as being equivalent to participants who report a unilateral
273 tinnitus clearly in the left or right ear. Doing so reduced the discriminative power of hearing
274 asymmetry for tinnitus laterality subgroups.



275

276 **Figure 2.** Box plots of MaxDiffExt (right minus left thresholds) for tinnitus cases reporting different
277 tinnitus spatial perceptions, and for the non-tinnitus cases. The dashed line shows the 15 dB
278 asymmetry threshold, defining Asym15.

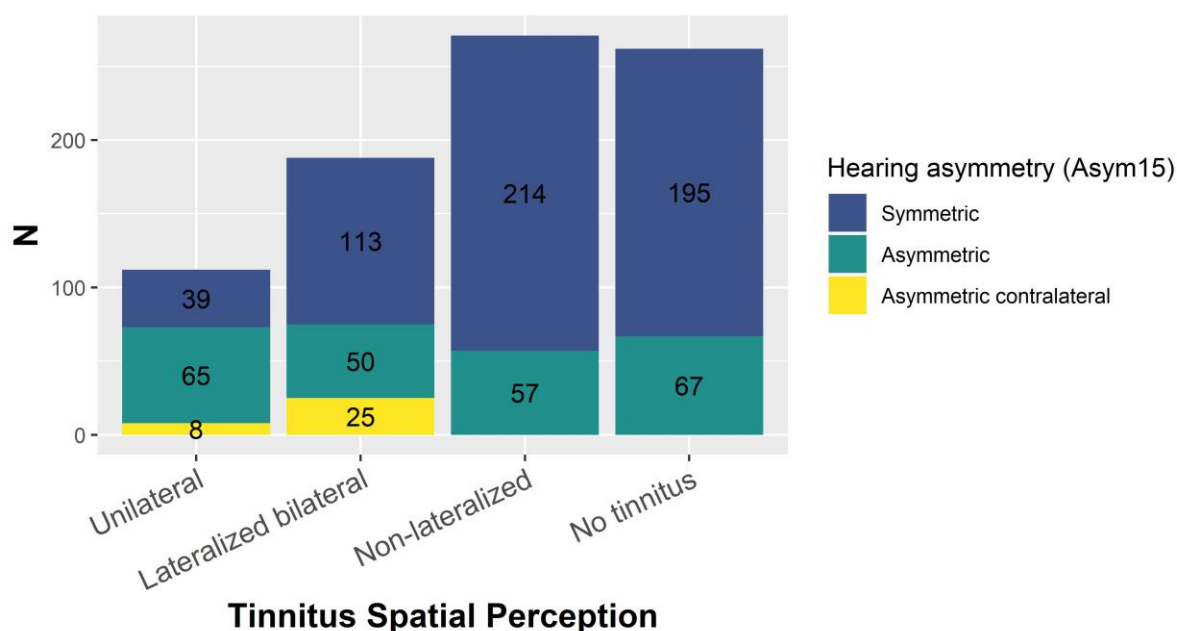
279 **Association between asymmetric hearing and a unilateral tinnitus reported on the**
280 **side of the worse hearing ear**

281 Question 2 addressed how the pattern of hearing asymmetry differed between tinnitus and
282 non-tinnitus cases, and for those reporting tinnitus, across different spatial tinnitus percepts.
283 The MaxDiffExt data computed for all participants in the full dataset (n=833) were displayed
284 using box plots (Figure 2); data points falling between the dashed lines indicate symmetric
285 hearing (Asym15). On visual inspection, there was a trend towards an association between
286 asymmetric hearing and unilateral tinnitus on the side of the worse ear. Nevertheless, many
287 unilateral tinnitus cases had symmetric hearing. The remaining tinnitus cases all showed a
288 similar pattern to one another, tending towards symmetric hearing. The same was also true
289 for the non-tinnitus cases, albeit with some extreme deviations. Distributions of hearing
290 asymmetry differed across different tinnitus spatial percepts (Kruskal-Wallis chi-squared =
291 84, degrees of freedom = 5, p-value < 0.001). The Dunn post-hoc tests showed that
292 lateralized bilateral tinnitus was heterogeneous, with 'both, more left' tinnitus being
293 significantly different to 'both, more right' tinnitus (Supplementary Table 5).

294 Data were displayed in an alternative format by using Asym15 to categorize individuals into
295 symmetric or asymmetric hearing (Figure 3). The majority of participants (67.3%) in the full
296 dataset had symmetric hearing. The non-tinnitus group and the group reporting a non-
297 lateralized tinnitus (both ears equally or in the head) had the highest proportion of symmetric
298 hearing. Many of these had clinically normal hearing (no threshold higher than 20 dB,
299 Supplementary Figure 1). Asymmetric hearing was present in 35.9% of tinnitus cases and
300 25.6% of non-tinnitus cases. The unilateral tinnitus group had the highest percentage of

301 asymmetric hearing (58.0% with ipsilateral asymmetric hearing). This frequency distribution
302 confirmed the association between asymmetric hearing and unilateral tinnitus on the side of
303 the worse ear. Nevertheless, there were also many cases with unilateral tinnitus and
304 symmetric hearing (34.8%). Notably, there were some cases with contralateral hearing
305 asymmetry in the lateralized bilateral tinnitus (13.3%) and the unilateral tinnitus (7.1%)
306 subgroups (Figure 3).

307 In summary, we observed a trend towards an association between hearing asymmetry and
308 tinnitus spatial perception; specifically between asymmetric hearing and a unilateral tinnitus
309 reported on the side of the worse hearing ear. This indicates a potential criterion for
310 subgrouping people with tinnitus.



311 **Tinnitus Spatial Perception**
312 **Figure 3.** Frequency of symmetric and asymmetric hearing for unilateral, lateralized bilateral, and
313 non-lateralized tinnitus, and non-tinnitus cases. Contralateral asymmetry is presented separately for
314 lateralized cases.

315 **Spatial tinnitus perception is an important variable for tinnitus phenotyping**

316 Question 3 compared unilateral (left or right ears) and bilateral (both ears equally) tinnitus on
317 a number of phenotypic variables, investigating whether any of these might be informative
318 for predicting tinnitus laterality. Compared to bilateral tinnitus, participants with unilateral
319 tinnitus were older, with older age at tinnitus onset, and shorter tinnitus duration (Table 5). In
320 addition, they had higher hearing asymmetry, more often used a hearing aid unilaterally, and
321 were annoyed by tinnitus for a higher percentage of time. The multivariable LASSO logistic
322 regression model identified hearing asymmetry, hearing aid use, and age at tinnitus onset as
323 predictors of tinnitus laterality. The 5-fold cross-validated ROC AUC of the regression
324 method was 84.2%, indicating very good predictive power.

325 In summary, unilateral and bilateral tinnitus groups differed in a number of statistically
326 significant ways. The modelling work confirmed a relationship between hearing asymmetry
327 and tinnitus spatial perception and suggested that spatial tinnitus perception may be
328 informative as a criterion for subgrouping people with tinnitus.

329 **Table 5.** Comparison of unilateral (left or right ears) and bilateral (both ears equally) tinnitus.

	All	Unilateral	Bilateral	Statistics
All	285	112	173	-
<i>General individual characteristics</i>				
Age (y)	54.7, 13.56, n=284	58.85, 12.61, n=111	52.03, 13.51, n=173	W=6991, p=0.001 ^z
Gender (male/female)	131/154	55/57	76/97	p=1
Handedness (both/left/right)	4/23/257	1/9/101	3/14/156	p=1
<i>Hearing function and other comorbidities</i>				
Absolute maxDiffExt (dB)	17.8, 17.74, n=285	28.63, 23.22, n=112	10.79, 6.77, n=173	W=4235.5, p<0.001*
Hearing aid use (both sides/unilateral/none)	19/14/221	6/14/76	13/0/145	p=0.006*
TMJ disorder (no/yes)	236/32	91/17	145/15	p=1
Balance disorder (no/yes)	188/82	70/38	118/44	p=1
Headaches (no/yes)	203/70	76/32	127/38	p=1
HQ score (0-42)	15.07, 8.2, n=279	14.32, 7.77, n=106	15.53, 8.44, n=173	W=9778, p=1
<i>Tinnitus-related characteristics</i>				
Age at tinnitus onset (y)	39.08, 17.7, n=206	45.87, 16.13, n=94	33.38, 16.99, n=112	W=3155.5, p<0.001*
Tinnitus duration (y)	14.98, 13.09, n=207	12.38, 12.66, n=95	17.17, 13.11, n=112	W=6759.5, p=0.009 ^z
Tinnitus annoyance (%)	24.43, 25.83, n=278	29.27, 26.4, n=110	21.26, 25.02, n=168	W=7247, p=0.022 ^z
Tinnitus loudness rating (0-100)	42.9, 22.7, n=274	43.22, 20.24, n=109	42.69, 24.24, n=165	W=8619, p=1
Pulsatile tinnitus (no/yes)	258/21	104/6	154/15	p=1
Tinnitus influenced by stress (no effect/reduces/worsens)	103/57/118	44/17/48	59/40/70	p=0.244

Table presents frequencies for categorical variables and mean, standard deviation and sample size for numerical variables. Statistical tests: Fisher's exact tests for categorical variables and Wilcoxon tests for numerical variables. P-values are adjusted for multiple comparisons. ^zSignificant coefficient in simple regression and zero coefficient in LASSO regression; *Significant coefficient in simple regression and non-zero coefficient in LASSO regression; HQ: Hyperacusis Questionnaire; TMJ: Temporomandibular joint.

330 **Discussion**

331 The principle findings of this study were:

- 332 1. A hearing asymmetry variable emphasizing the maximum interaural difference across
333 the full audiometric range most reliably discriminated unilateral and bilateral tinnitus.
334 Grouping lateralized bilateral tinnitus with unilateral tinnitus weakened this
335 discrimination.
- 336 2. There was an association between asymmetric hearing and a unilateral tinnitus
337 reported on the side of the worse hearing ear.
- 338 3. Unilateral and bilateral tinnitus were phenotypically different.

339 The strength of the study is in using data drawn from two distinct sampling populations (i.e.
340 from people participating in tinnitus clinical trials and from people with tinnitus recruited from
341 a population-based cohort) and two countries (i.e. UK and Sweden). Combining the two
342 datasets for our study led to a large and diverse sample that allowed us to statistically
343 explore tinnitus heterogeneity focusing on the relationship between tinnitus spatial
344 perception and hearing asymmetry. We expect that the large and diverse sample would
345 make our findings generalizable to other datasets, and we greatly encourage attempts of
346 replication.

347 **Hearing asymmetry and tinnitus spatial perception**

348 Examining different variables for hearing asymmetry, there was a similar performance in
349 discriminating tinnitus laterality. Nevertheless, a variable emphasizing the maximum
350 interaural difference (mean difference of two adjacent frequencies), using all available
351 thresholds, demonstrated the best performance. The optimum threshold for asymmetric
352 hearing was 15 dB. This finding is in agreement with Tsai et al. (2012) who also investigated
353 how different hearing asymmetry variables associated with tinnitus spatial perception.
354 Specificity, sensitivity, and positive predictive value were 80, 65 and 68% respectively, as
355 compared to 71, 59, and 76% in Tsai et al. (2012). The higher specificity in our study could
356 be due to the exclusion of the non-lateralized bilateral cases and the additional frequencies
357 used for calculation of the asymmetry variable.

358 Regarding the ambiguous cases in which tinnitus is reported in both ears but greater on one
359 side, to our knowledge, only one previous study has reported their hearing asymmetry
360 profile, presenting only the mean thresholds for each ear per tinnitus subgroup (Nuttall et al.,
361 2004). In our study, hearing asymmetry for individual cases and frequency of symmetric and
362 asymmetric hearing were assessed. We showed that lateralized bilateral cases represent a
363 large proportion of the tinnitus population and, although the majority had symmetric hearing,
364 asymmetric hearing was common. This should be considered in future studies when
365 deciding to group this type of tinnitus with either unilateral or non-lateralized bilateral tinnitus.

366 It is not clear why for some tinnitus cases hearing asymmetry is not predictive of tinnitus
367 laterality. One possibility is that pure tone audiometry at specific frequencies is not enough,
368 and that more detailed hearing assessment would reveal hearing loss corresponding to the
369 spatial perception of tinnitus (Xiong et al., 2019). One recent study analyzed characteristics
370 of 62 unilateral tinnitus cases with better mean hearing threshold on the tinnitus side (Lee et
371 al., 2019). About one fourth of these cases were shown to be associated with fluctuating
372 hearing loss and in seven cases there were indications of somatic tinnitus.

373 **Tinnitus laterality subgroups**

374 When we examined phenotypical characteristics differentiating unilateral from bilateral
375 tinnitus, the most robust differences were in hearing asymmetry, hearing aid use, and age at
376 tinnitus onset. In addition to these, subgroups differed in age, tinnitus duration, and
377 percentage of time being annoyed by tinnitus. At least seven other studies with sample sizes
378 larger than 50 have compared characteristics of unilateral and bilateral tinnitus (Gabr, 2011,
379 Hallam et al., 1984, Koning and Koning, 2018, Pan et al., 2009, Vanneste et al., 2011, Yang
380 et al., 2015, Zagólski and Stręk, 2017). Interestingly, none of these reported hearing
381 asymmetry across groups.

382 Comparing our results with other studies, a common finding is that unilateral tinnitus
383 corresponds to shorter tinnitus duration than bilateral tinnitus (Pan et al., 2009, Zagólski and
384 Stręk, 2017). One interpretation is that unilateral tinnitus might evolve to bilateral tinnitus with
385 time (Pan et al., 2009). In our study, unilateral tinnitus was also characterized by older age at
386 tinnitus onset. This is in agreement with the findings of Maas et al. (2017), who showed that
387 in a twin cohort heritability was much higher for bilateral tinnitus (0.56) than unilateral tinnitus
388 (0.27). Considering this, another potential explanation for the difference in tinnitus duration is
389 the earlier onset of the more genetically influenced bilateral tinnitus. In addition, bilateral
390 tinnitus was shown to be associated with a higher percentage of prolonged exposure to
391 excessive noise than unilateral tinnitus (Zagólski and Stręk, 2017), suggesting that a
392 combination of genetic and environmental factors might trigger an earlier onset.

393 Yang et al. (2015) found that bilateral tinnitus cases were older with a higher tinnitus burden.
394 In contrast, in our study, as in Zagólski and Stręk (2017), unilateral cases were older. With
395 regards to tinnitus impact, unilateral cases in our dataset were annoyed by their tinnitus for a
396 greater percentage of time. A higher burden of tinnitus for the unilateral tinnitus cases was
397 also found by Song et al. (2018). The discrepancies with the findings from Yang et al. (2015)
398 could be due to differences in the sampling population characteristics. For example, in Yang
399 et al. (2015) there was a high percentage of normal hearing, especially for unilateral tinnitus
400 (63.8%). In our dataset, only a few tinnitus cases had normal hearing and these were mainly
401 non-lateralized tinnitus cases (Supplementary Figure 1).

402 Overall, there is evidence suggesting that subgroups of tinnitus with different spatial
403 perception might be associated with different underlying mechanisms. Tinnitus spatial
404 perception is associated with hearing asymmetry, but further research is needed to
405 understand why hearing asymmetry is not always predictive of tinnitus laterality. In addition,
406 unilateral tinnitus compared to bilateral, seems to have an earlier onset age and has been
407 repeatedly shown to have a shorter duration than bilateral tinnitus. This evidence supports
408 the recommendation that tinnitus spatial perception should be used to define phenotypically
409 more homogeneous tinnitus subgroups for tinnitus research and clinical practice.

410 **Limitations and future considerations**

411 The main limitation of our study is that, although the sample size was relatively large
412 compared to previous studies, it is still small considering the high dimensionality of tinnitus.
413 In addition, our combined dataset did not include some potentially important variables, such
414 as family history of tinnitus or self-reported tinnitus severity, because they were collected
415 using different measures across the two datasets. Pure tone audiometry methodology was
416 also different in the STOP and BRC datasets. We do not expect this to influence our results

417 as automated audiometry has been shown to be comparable to manual methods (Mahomed
418 et al., 2013), and any systematic difference would be eliminated in the asymmetry indices
419 because these reflect a difference between two measurements. Nevertheless, we refrained
420 from comparing overall hearing thresholds across unilateral and bilateral subgroups,
421 because participants in each subgroup were not balanced across the STOP and BRC
422 datasets. Other information missing from our datasets that would be important for
423 characterizing subgroups of tinnitus is brain imaging and genetic profiling.

424 Previous efforts to standardize tinnitus research has allowed us to combine independent
425 datasets for this analysis (Langguth et al., 2007). Such efforts should be reinforced to allow
426 the creation of even larger datasets with a broader spectrum of information per participant, to
427 further understand tinnitus heterogeneity (Schlee et al., 2018).

428 **Declaration of conflicting interests**

429 All authors declare that there is no conflict of interest.

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