Investigating the relation between minimum masking levels and hearing thresholds for tinnitus subtyping

Santacruz, Jose L; de Kleine, Emile; van Dijk, Pim

Published in:
TINNITUS - AN INTERDISCIPLINARY APPROACH TOWARDS INDIVIDUALIZED TREATMENT: RESULTS FROM THE EUROPEAN GRADUATE SCHOOL FOR INTERDISCIPLINARY TINNITUS RESEARCH

DOI:
10.1016/bs.pbr.2021.04.011

Publication date:
2021

CHAPTER

Investigating the relation between minimum masking levels and hearing thresholds for tinnitus subtyping

4

Jose L. Santacruz[a,b,*], Emile de Kleine[a,b], and Pim van Dijk[a,b]

[a]*Department of Otorhinolaryngology/Head and Neck Surgery, University of Groningen, University Medical Center Groningen, Groningen, Netherlands*

[b]*Graduate School of Medical Sciences (Research School of Behavioral and Cognitive Neurosciences), University of Groningen, Groningen, Netherlands*

**Corresponding author: Tel.:+31-633316550, e-mail address: j.lopez.santacruz@umcg.nl*

Abstract

Heterogeneity of tinnitus imposes a challenge for its treatment. Identifying tinnitus subtypes might help to establish individualized diagnosis and therapies. The minimum masking level (MML) is a clinical tool defined as the minimum intensity of a masking sound required to cover tinnitus. Understanding the differences among masking patterns in patients could facilitate the task of subtyping tinnitus. Here, we studied the variability of hearing thresholds and MMLs among patients with tinnitus to identify tinnitus subgroups.

A population of 366 consecutive patients from a specialized tinnitus clinic were included in the analysis. Hearing thresholds and MMLs were determined for octave frequencies from 0.25 to 8 kHz, as well as for 3 and 6 kHz. Subjects were divided into two groups according to whether their tinnitus was maskable (M, 329 subjects) or non-maskable (NM, 37 subjects). Hearing thresholds and tinnitus loudness did not differ significantly between both groups. The dimensionality of the data was reduced by means of principal component analysis (PCA), and the largest resulting components were used for clustering the data. The cluster analysis resulted in five clusters with differences in tinnitus pitch, lateralization, hearing thresholds and MML, as well as on age and gender. Clusters differed in contours of hearing thresholds and MML, describing patterns of low or high thresholds in combination with low or high MML. The clustering solution presented a low silhouette value (0.45), implying that the clustering is weak and could be artificial. The analysis pointed out the diversity across tinnitus patients. Our results suggest that there might be a continuum of patients' characteristics rather than discrete subgroups.

Progress in Brain Research, Volume 263, ISSN 0079-6123, https://doi.org/10.1016/bs.pbr.2021.04.011

Keywords

Tinnitus, Minimum masking levels, MML, Subtyping, Cluster analysis

1 Introduction

Tinnitus is a widespread phenomenon affecting up to 18% of the population in industrialized societies (Savage and Waddell, 2013). The etiology of tinnitus is frequently heterogeneous (Zagólski and Stręk, 2014) and its characteristics differs among patients. Possibly, several subtypes of tinnitus exist, each of them requiring a specific treatment. Subtyping different forms of tinnitus might be useful to find a homogeneous response to a treatment (Landgrebe et al., 2010). Several authors have suggested the importance of a personalized rehabilitation, attainable with an effective classification that is based on the physiological mechanism underlying the individual symptoms (Baguley et al., 2013; Ward et al., 2015).

Despite the literature about its underlying mechanisms has increased during the last years, the effectiveness of most of the existing treatment therapies has not followed the same trend. There is still a lack of high-quality evidence to support most of the available treatments for tinnitus. The limited available data makes it difficult to prove the benefit of sound therapies, but several studies using self-assessment tools like the Tinnitus Handicap Inventory (Newman et al., 1996) suggested that the effect might be better than a placebo when sound devices such as maskers, hearing aids or combination instruments are part of the therapy (Hobson et al., 2007). The exposure to acoustic stimulation like masking sounds can reduce or even temporarily suppress tinnitus (Feldmann, 1971; Hazell, 1981). Patients seem to best benefit from acoustic treatments when tinnitus is easily masked (Vernon, 1977), therefore psychoacoustical measures that assess more directly the tinnitus sensations such as masking might be helpful to improve the accuracy of the diagnosis and further treatment.

The minimum masking level (MML) is defined as the minimum intensity of a masking sound required to mask tinnitus, and it is a way to measure the intrusiveness of tinnitus and the acceptance of masking (Andersson, 2003; Vernon et al., 1990). There are only a few studies on MML, most of which tried to discriminate tinnitus subtypes. Feldmann (1971) described six types of masking pattern, defined according to the masking attainability and frequency contours of the maskers and hearing thresholds. Mitchell (1983) found similar classifications using Feldmann's congruence and convergence types of contours, characterized by thresholds running parallel to MML contours or crossing them, respectively. Unlike Feldman, no divergent pattern was reported in this study. Tyler and Conrad-Armes (1984) obtained heterogeneous results in a similar study, suggesting the existence of more masking patterns than observed by Mitchell, and the lack of an apparent relation between the frequency contours of maskers and hearing thresholds. Zagólski and Stręk (2014) reported differences in mean MML values in relation to different tinnitus etiologies by using broadband noise. Particularly, the authors obtained lower MML values in acute acoustic trauma and congenital hearing loss cases, and higher MML values in patients after a stroke and with presbycusis. Etiology-dependent masking characteristics may be of value for patients whose etiology is doubtful. Despite the fact that MML is a widely used psychoacoustical technique in screening tinnitus patients, the relationship between hearing thresholds and MML remains unclear.

In this paper, we address an analysis of patients' masking patterns from the tinnitus database of the University Medical Center Groningen ($n = 366$ patients). As a first step, we studied the relation between the hearing thresholds and the MMLs across frequencies. Next, we performed a principal component and cluster analysis to identify possible subgroups within the patients in the dataset.

The motivation to perform a cluster analysis stems from the large heterogeneity of tinnitus patients (Langguth et al., 2017; Tyler et al., 2008; van den Berge et al., 2017). Patients differ with respect to many parameters, such as the degree of hearing loss, the underlying etiologies of the hearing loss itself, the factors that influence the tinnitus or their psychological response to the tinnitus. Often, these parameters are grouped in the literature according to several dimensions such as perception, causal risk factors, distress and treatment responses (Cederroth et al., 2019). The advantage of a cluster analysis is that it may recognize groups that are not evident upon superficial observation of the various variables. Clustering may serve the purpose of tailoring a treatment to the members of a particular cluster. Possibly, the members of a particular cluster are sensitive to a particular treatment. This treatment may be based on knowledge of the etiology of the tinnitus in that cluster, or on the symptoms of the tinnitus, such as the psychological response of a patient.

2 Methods

2.1 Participants

The study was conducted at the Otorhinolaryngology Department of the University Medical Center Groningen (UMCG). Since 2007, this clinic has been specialized for tinnitus patients through a multidisciplinary care group. After earlier consulting an audiologist and/or an otorhinolaryngologist, patients with bothersome and persistent tinnitus are referred to this tertiary care group for further consultation and psychological help. In the clinic, patients are evaluated by an audiologist, an ENT doctor, a medical social worker and a psychologist.

Data from 366 patients who visited the tinnitus clinic at the UMCG throughout a period of 3 years were collected. The dataset contains multiple variables like demographic information, audiometric diagnostics, results from quality of life and tinnitus questionnaires, psychoacoustical data and therapies followed by the patients.

2.2 Audiometry and MML

Hearing thresholds were obtained by means of pure tone audiometry for all patients, measuring octave frequencies from 0.25 to 8 kHz, as well as 3 and 6 kHz, using TDH39 headphones with an Interacoustics Affinity or Equinox audiometer. The MMLs were obtained using the same equipment. A narrowband noise (1/3-octave), with the same center frequencies as the tone audiometry, was used as a stimulus. A monolateral up procedure in each ear was followed, presenting maskers for each frequency at an initial level of 15dB below the hearing thresholds. The sound level was increased in steps of 5dB until the patient could no longer perceive his/her tinnitus. The level at which the tinnitus was no longer audible, was recorded as MML. When a level of 90dB HL was reached, the process was stopped regardless of whether the tinnitus was still audible or not.

Tinnitus pitch and loudness were obtained by means of the regular clinical protocol in which pure tones, narrowband noise or wideband noise are presented monaurally to the contralateral ear (in case of lateralized tinnitus), or to the better hearing ear (in case of bilateral tinnitus). The patient provides feedback to the clinician, who adapts the frequency and loudness of the stimulus until it matches the tinnitus percept best. Patients reporting similar tinnitus loudness in both ears or localizing their tinnitus "in the head", were considered as bilateral cases in this study. Those who described their tinnitus as partially or totally predominant in one ear were considered as lateralized cases.

2.3 PCA and cluster analysis

In order to reduce the dimensionality of the data, a principal component analysis (PCA) was carried out. Each subject contributed 8 audiometric thresholds and 8 MMLs, for each ear. Thus 2 ears * (8 thresholds + 8 MMLs) = 32 values entered the PCA. The components obtained from the PCA that described most of the data's covariance were included in the subsequent cluster analysis.

Since only continuous variables were included in the analysis, the selected clustering method was *k*-means. As this method requires fixing the number of clusters in advance, the choice was made by the elbow criterion algorithm to minimize bias. A silhouette coefficient was obtained as a measure of cohesion and separation between clusters.

3 Results

3.1 Hearing thresholds and MML

Masking was not possible in 37 patients. The tinnitus of a patient was considered non-maskable (NM) when the MML values obtained were 90dB for a minimum of six frequencies in each ear out of the eight tested (from 250 to 8kHz), and this was true for both ears. Table 1 shows the comparison between the NM and the M group, this latter group consisting of 329 subjects.

Boxplots of the hearing thresholds and MMLs of both the NM and the M group are shown in Fig. 1. The mean hearing threshold per subject was calculated as the pure tone average in both ears (PTA) of frequencies 2, 4 and 8kHz, and they did not significantly differ between the two groups (see Table 1). Most of the patients presented no hearing loss larger than 25dB for frequencies up to 2kHz. For higher

Table 1 Characteristics of masking (M) and non-masking (NM) groups: median values with standard deviations.

	M	NM	*p*-Value
Group size (n)	329	37	
Average hearing threshold (dB HL)	35.8±17.0	42.5±18.3	0.159
MML (dB HL)	64.6±19.5	–	
Tinnitus loudness (dB SL)	1.5±12.2	5.1±12.2	0.118
Tinnitus pitch (kHz)	4.0±2.5	4.8±2.9	0.141
		One-way ANOVA	

Values of tinnitus loudness and pitch represent the matching stimulus. The average of hearing thresholds was obtained by pure tone average (PTA) of frequencies 2, 4 and 8kHz, for both ears. MML values are averaged across all frequencies in both ears.

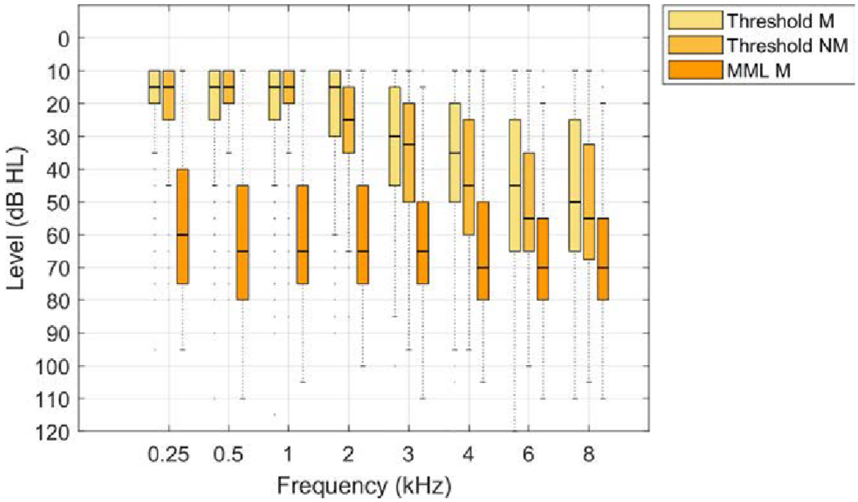

FIG. 1

Hearing thresholds and MML across frequencies for the M group ($n=329$) and the NM group ($n=37$). For each subject, data from both ears were averaged. Median values are represented with lines crossing the boxplots.

frequencies, this gradually shifted toward mild and moderate hearing loss. MML values were, on average, constant across frequencies (for the M group), reaching values closer to the hearing thresholds as frequency increases. No significant differences between the two groups in tinnitus loudness nor pitch were found.

Lateralized cases had a prevalence of 65% in our database, and their characteristics are shown in Table 2. These subjects presented higher thresholds in the ipsilateral ear for both M and NM groups. MML means did not differ significantly between the ipsilateral and contralateral ear within the M group, although the hearing was significantly worse in the ipsilateral ear.

Table 2 Characteristics of patients with lateralized tinnitus for both the masking (M) and non-masking (NM) groups: median values with standard deviations.

	NM (n = 21)		***p*-Value**	**M (n = 216)**		***p*-Value**
	Ipsilateral	Contralateral		Ipsilateral	Contralateral	
Hearing threshold (dB HL)	41.6 ± 23.8	28.3 ± 17.8	**0.049**	40 ± 20.7	26.6 ± 16.8	**<0.001**
MML (dB HL)	–	–		63.4 ± 18.8	66.8 ± 21.2	0.573
					One-way ANOVA	

The average of hearing thresholds was obtained by pure tone average (PTA) of frequencies 2, 4 and 8 kHz. MML values are averaged across all frequencies in both ears. Bold p*-values indicate a significance level <0.05.*

3.2 PCA and cluster analysis

Using the hearing thresholds and MMLs of the 329 subjects in the M group, a principal component analysis was conducted to obtain the main vectors, the so-called higher eigenvalues that describe most of the variance of the data. In order to assess the feasibility of the PCA, a Kaiser-Meyer-Olkin test and a Barlett's test were performed. The first one resulted in a sampling adequacy of 0.912, and the second test rejected the sphericity assumption ($p < 0.001$). Both results suggested that a component analysis might be appropriate (Bartlett, 1937; Kaiser, 1974). From all the eigenvalues obtained, the first four components were chosen based on the criteria of eigenvalues >1, which are considered stable (Girden and Kabacoff, 2010). These four components explained the 83.8% of the variance of the entire dataset.

Based on the four components obtained, the elbow criterion was used to determine the optimal number of clusters (Syakur et al., 2018), which suggested a solution of five clusters. The chosen clustering method was k-means, and the average silhouette coefficient (SC) obtained was 0.458, interpreted by the literature as "weak structure and could be artificial" ($0.26 \leq SC \leq 0.50$) (Kaufman and Rousseeuw, 2009).

Boxplots of the hearing thresholds and the MMLs of the five clusters are shown in Fig. 2. Clusters were also compared according to variables that were not included in the PCA. Table 3 shows characteristics of the clusters based on significant differences between these variables.

Cluster 1 (Fig. 2A) includes a majority of middle-aged female patients with values of tinnitus pitch lower than the median. Patients in this cluster present a mild hearing loss and lower MML values indicating an easily maskable tinnitus.

Cluster 2 (Fig. 2B) is a large group of middle-aged patients with a mild hearing loss. MML values are approximately 70 dB across all frequencies, much higher than the median tinnitus loudness.

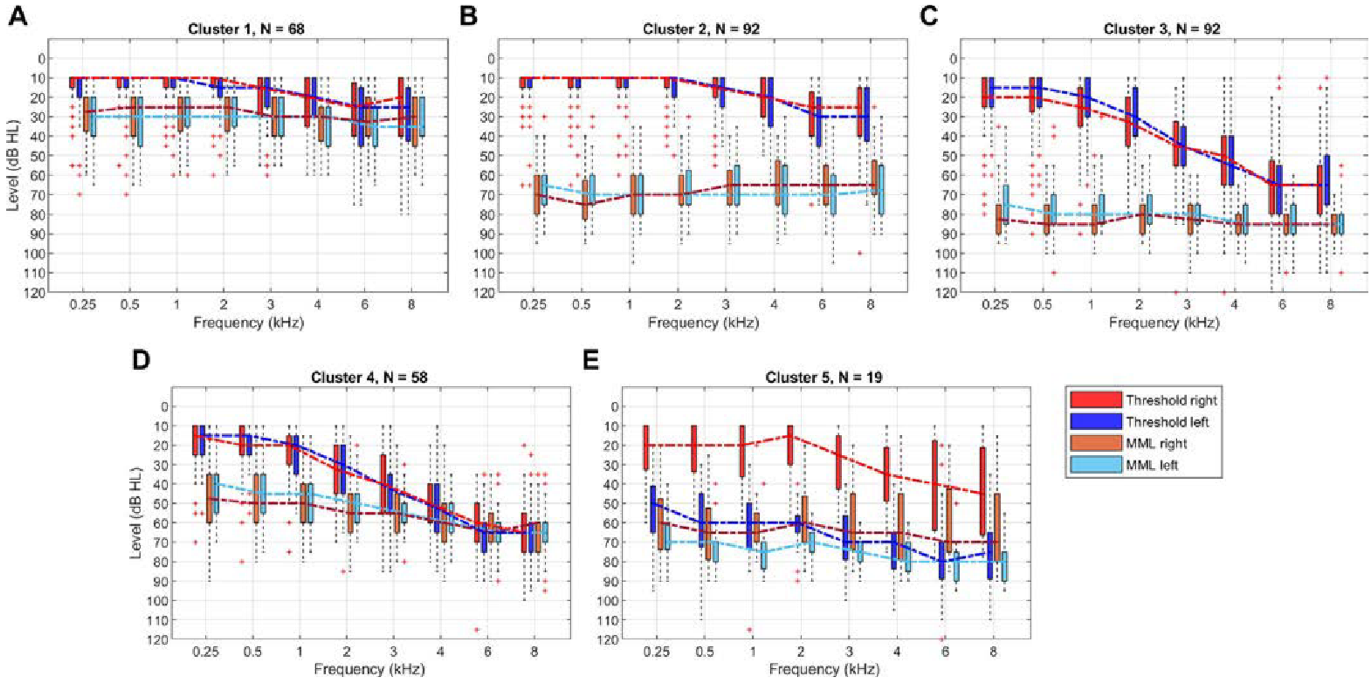

FIG. 2

Boxplots of hearing thresholds and MMLs for all the clusters found. (A, B) Clusters 1 and 2 represent subjects with relative good hearing thresholds. However, cluster 1 includes patients for whom tinnitus is easily maskable across frequencies, while patients in cluster 2 present higher MMLs. (C, D) Both clusters 3 and 4 include patients with moderate hearing loss, but differ in MMLs. Cluster 3 presents higher MMLs while cluster 4 represents the classical convergency type (Feldmann, 1971). (E) Cluster 5 represents patients with asymmetrical HL and high MMLs.

Table 3 Characteristics of the five clusters obtained: median values with standard deviations.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	*p*-Value
Cluster size (*n*)	68	92	92	58	19	
Silhouette coefficient	0.55	0.54	0.39	0.37	0.26	
Age	56.0 ± 13.2	55.5 ± 14.1	64.5 ± 9.5	66.0 ± 9.2	63.0 ± 11.8	**<0.001**
Gender (% M/F)	43/57	63/37	73/27	67/33	68/32	**0.002**
Tinnitus pitch (kHz)	3.2 ± 2.6	4.1 ± 2.5	4.7 ± 2.3	3.2 ± 2.3	0.9 ± 2.1	**<0.001**
Tinnitus loudness (dB SL)	11.2 ± 13.6	8.8 ± 10.1	6.3 ± 12.8	6.3 ± 15.1	6.7 ± 10.3	0.315
Tinnitus lateralized (% yes/no)	65/35	63/37	59/41	70/30	89/11	**<0.001**
Hearing threshold (dB HL)	20.8 ± 11.2	23.3 ± 8	47.0 ± 11.9	48.7 ± 10.2	52.5 ± 20.4	**<0.001**
MML (dB HL)	30.9 ± 9.4	65.6 ± 10.1	80.9 ± 5.9	54.6 ± 8.7	68.1 ± 9.6	**<0.001**
Asymmetry of HL (dB HL)	3.3 ± 6.5	5.0 ± 8.4	6.6 ± 15.9	6.6 ± 10.2	31.6 ± 18.7	**<0.001**
				One-way ANOVA for continuous variables, chi-squared for categorical variables		

Clusters are sorted by descending silhouette value. Differences between groups were calculated by using one-way ANOVA. The average hearing threshold was obtained by pure tone average (PTA) of frequencies 2, 4 and 8 kHz, for both ears. Asymmetry of HL was obtained by the absolute difference between the PTA of the same frequencies in both ears. Bold p-values *indicate a significance level <0.05.*

Cluster 3 (Fig. 2C) is another large group which includes a majority of older male patients with moderate hearing loss. Tinnitus pitch presents high values, and MML values are in the limit of the non-maskable condition.

Cluster 4 (Fig. 2D) represents another group of older patients with moderate hearing loss and MML median values in the range from 40 to 65 dB, close to the hearing thresholds.

Cluster 5 (Fig. 2E) mainly consists of patients with a large asymmetry in their hearing loss. This is the smallest cluster which also has the lowest silhouette value. Tinnitus presents relatively low frequency values.

All clusters presented similar tinnitus loudness values when these are expressed in dB SL, in line with previous studies reporting that most patients experience tinnitus at a level of within 5–10 dB SL of their thresholds (Goodwin and Johnson, 1980).

4 Discussion

To our knowledge, there are only a few studies relating MML contours and tinnitus (Feldmann, 1971; Mitchell, 1983; Tyler and Conrad-Armes, 1984; Zagólski and Stręk, 2014). The aim of this study was to identify specific subtypes of tinnitus through the analysis of MML contours and hearing thresholds. First, our patients' database was divided into a masking and a non-masking group, resulting in a proportion of 90/10 with no significant differences in hearing thresholds, tinnitus loudness or pitch between both groups. The majority of subjects in both groups presented lateralized tinnitus with poorer hearing thresholds in the ipsilateral ear. The diversity in findings between subjects motivated a cluster analysis for subtyping. The analysis resulted in five clusters underlining differences between the groups, but the separation and cohesion of the clusters was weak.

Minimum masking levels may seem counterintuitive in the psychoacoustical context. In principle, it can be expected that louder tinnitus would require higher levels of masking to relieve patients from its perception. The neurophysiological model of tinnitus (Jastreboff et al., 1994) suggests that the tinnitus percept might be originated in the auditory system at a subcortical level. According to this model, the level of intrusiveness can decrease as a result of habituation, therefore the neuronal networks are detuned from recognizing the "tinnitus signal" and lower levels of masking should be required to suppress it. In line with this model, it can be derived that MML can provide very useful clinical information when measured at different times, since it could be an indicator of changes in the auditory system during the course of a treatment. A decrease in MML would suggest that the tinnitus percept is more difficult to detect than before (Jastreboff, 1990).

In our study, the non-masking group represented 10.1% of the population, which is consistent with the reports from the literature (Feldmann, 1971). Interestingly, these subjects presented similar thresholds, tinnitus loudness and pitch to those in the masking group. Previous studies reported no correlation between neither the loudness nor the pitch of the tinnitus percept and its maskability (Mitchell, 1983;

Mitchell et al., 1993). A recent study reported lower intensity levels of maskers for frequencies close to the tinnitus pitch, but only for normal hearing subjects (Fournier et al., 2018). In our data, no clear relation between pitch, loudness and maskability was found. Moreover, masking contours showed a large variability for all degrees of hearing loss. Considering maskability as the attainability of covering the tinnitus sensation, our study suggests that it does not rely on hearing loss or on tinnitus loudness. However, in the cases in which tinnitus is maskable, the MML contours were relatively flat and the thresholds present different slopes, resulting in a decrease of masking levels relative to the thresholds with increasing frequency.

Previous studies using MML to discriminate between groups showed different masking patterns determined by the relation of hearing thresholds and MML contours (Feldmann, 1971; Mitchell, 1983). Despite the fact that similar patterns could be found in our database, we considered that this classification method is not systematic and is open to interpretation. Thus, we opted for an unsupervised method, such as clustering, whereby more flat frequency patterns were obtained. It seems that the key distinction between our clusters lies in the difference between hearing thresholds and MML, resulting in two types of masking pattern: easy and difficult to mask; and two types of hearing loss profile: mild and moderate hearing loss. These findings are consistent with the study from Tyler and Conrad-Armes (1984), which suggested a lack of relation between the frequency contours of maskers and hearing thresholds.

One of the clusters found, was distinctively represented by female patients (cluster 1). This group was mainly characterized by mild hearing loss and low masking levels. Unlike Seydel et al. (2013), we did not find significantly lower tinnitus loudness among female subjects, but rather a good acceptance of masking. In addition to gender differences in tinnitus patients, one study also reported lower tinnitus pitch among female subjects (Oakes et al., 2013). This gender difference in tinnitus pitch was only partially consistent with our results, where cluster 1 described a pitch lower than the median of the entire dataset but similar to another cluster with higher male representation. The gender differences found, could reaffirm the predominance of mild hearing loss and among female patients (Nicolas-Puel et al., 2002; Seydel et al., 2013).

In our study, while most clusters were characterized by symmetric hearing loss, cluster 5 presented a considerable asymmetry. Despite being the smallest group and having the lowest silhouette value, it is to be noted that the vast majority of subjects in this cluster had unilateral tinnitus. Particularly worth mentioning is the concordance between the worst ear and the lateralization of tinnitus, both on the left side. Sixteen subjects out of 17 with left-side tinnitus in this group had higher hearing loss in the left ear. In our cluster 5, the high asymmetry of hearing thresholds is remarkable ($\approx$30 dB), whereas the same is not true for MML. A recent latent class analysis from Langguth et al. (2017) found the same link between tinnitus laterality and the side of unilateral hearing loss. To our knowledge, the largest study providing evidence of the relation between tinnitus laterality and hearing asymmetry is the one from Nuttall et al. (2004), which is based on the grand average audiometric thresholds of 1033 subjects. The study found averaged threshold differences between 5 and

20 dB higher in the poorer ear in case of unilateral tinnitus. Results of another study pointed to 15 dB as the minimum average threshold difference in order to predict tinnitus laterality (Tsai et al., 2012). Another study from Vielsmeier et al. (2015) restricted the difference in thresholds to the high frequency (HF) audiometry (>8 kHz), highlighting that the mean HF threshold difference was higher for left-side tinnitus compared to right-side or bilateral cases. In our study, it is worth stressing that the silhouette value of this cluster highlighted its instability, indicating that this deviation could be the residual outcome of the cluster analysis instead of an accurate representation of the data.

It is to be noted that the chosen clustering method may play a role in the separation and cohesion of the resulting clusters, since the performance of the algorithm is constrained by the number of clusters which are previously established (Pelleg and Moore, 2000). However, whereas this constraint may exert some influence in the result, the choice was made by an unsupervised method (the elbow criterion) to avoid bias. Also, the available audiometric data included in the analysis might have been decisive in the resulting groups, but this limitation is characteristic of every cluster analysis. For instance, hearing thresholds and MMLs were included in the PCA up to 8 kHz, while values above in frequency were not taken into consideration. In a study of Roberts et al. (2006) it was shown that 25% of the participants presented normal hearing up to 8 kHz (thresholds $\leq$25 dB HL), but they revealed hearing loss for higher frequencies. However, this large proportion might be due to their method of patient selection. In our study, 48 subjects (13.1%) had normal hearing up to 8 kHz, following the same criteria. In a study from Shim et al. (2009), 9.6% of subjects did not show a decrease in hearing ability in this frequency range, but when using an extended high frequency audiogram, the prevalence of hearing loss in this specific group was 67%. Although in our dataset hearing thresholds at 10, 12.5 and 16 kHz were available for most participants, this was not the case for MML. Therefore, these frequencies were excluded from the analysis in order to adhere to the corresponding frequencies between thresholds and MML. Another example of the limitation that the audiometric data entails is when it is treated as a continuous metric of hearing loss instead of ranges of threshold levels such as mild, moderate or severe hearing loss, which can better describe different possible pathological mechanisms (Langguth et al., 2017; Shekhawat et al., 2014). In our study, this problem was handled by the PCA, reducing the dimensionality of both MML and hearing threshold, which in turn can elude pre established ranges.

Here we explored a cluster analysis based on audiometric data. This did reveal a diverse pattern of patient characteristics. Although our analysis showed five clusters, these are not very sharply divided from each other (as expressed in a low silhouette value). Our findings do not preclude the existence of tinnitus subtypes, but the use of audiometric data alone does not provide clear clusters. Future research could sharpen these clusters, if the analysis is combined with the outcome of treatments, such as hearing aid fitting or psychological interventions. On the other hand, there might not be different etiologies of tinnitus and clustering might be drawing our attention away from a common origin. Tinnitus percept and its associated distress could be an individual-dependent manifestation of a general source. Whatever the cause, tinnitus could unbalance the regular neuronal activity resulting in a rather arbitrary new state which might explain the different phenotypes.

5 Conclusion

To summarize, our findings suggest that the main groups found in this analysis are characterized by either easy or difficult maskability, and by better or worse hearing, which is expressed by the relation between frequency contours of MML and hearing thresholds. Although the analysis highlighted the diversity across tinnitus patients, there seems to be a continuum of patients' characteristics rather than discrete subgroups.

Acknowledgments and funding

This paper is part of the ESIT project (Schlee et al., 2018) that has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant agreement number 722046.

References

Andersson, G., 2003. Tinnitus loudness matchings in relation to annoyance and grading of severity. Auris Nasus Larynx 30, 129–133.

Baguley, D., McFerran, D., Hall, D., 2013. Tinnitus. Lancet 382, 1600–1607.

Bartlett, M.S., 1937. Properties of sufficiency and statistical tests. Proc. R. Soc. London. Ser. A Math. Phys. Sci. 160, 268–282.

Cederroth, C.R., Gallus, S., Hall, D., Kleinjung, T., Langguth, B., Maruotti, A., Meyer, M., Norena, A., Probst, T., Pryss, R., Searchfield, G., Shekhawat, G., Spiliopoulou, M., Vanneste, S., Schlee, W., 2019. Editorial: towards an understanding of tinnitus heterogeneity. Front. Aging Neurosci. 11, p. 53.

Feldmann, H., 1971. Homolateral and contralateral masking of tinnitus by noise bands and pure tone. Audiology 10 (3), 138–144.

Fournier, P., Cuvillier, A., Gallego, S., Paolino, F., Quemar, A., Londero, A., Norena, A., 2018. A new method for assessing masking and residual inhibition of tinnitus. In: 11th Tinnitus Res. Initiat. Conference 22, p. 80.

Girden, E.R., Kabacoff, R., 2010. Evaluating Research Articles from Start to Finish. Sage.

Goodwin, P.E., Johnson, R.M., 1980. The loudness of tinnitus. Acta Otolaryngol. 90, 353–359.

Hazell, J.W.P., 1981. Tinnitus masking—a significant contribution to tinnitus management. Br. J. Audiol. 15, 223–230.

Hobson, J., Chisholm, E., El Refaie, A., 2012. Sound therapy (masking) in the management of tinnitus in adults. Cochrane Database Syst. Rev. (11).

Jastreboff, P.J., 1990. Phantom auditory perception (tinnitus): mechanisms of generation and perception. Neurosci. Res. 8, 221–254.

Jastreboff, P.J., Hazell, J.W.P., Graham, R.L., 1994. Neurophysiological model of tinnitus: dependence of the minimal masking level on treatment outcome. Hear. Res. 80, 216–232.

Kaiser, M.O., 1974. Kaiser-Meyer-Olkin measure for identity correlation matrix. J. R. Stat. Soc. 52, 296–298.

Kaufman, L., Rousseeuw, P.J., 2009. Finding Groups in Data: An Introduction to Cluster Analysis. John Wiley & Sons.

Landgrebe, M., Zeman, F., Koller, M., Eberl, Y., Mohr, M., Reiter, J., Staudinger, S., Hajak, G., Langguth, B., 2010. The tinnitus research initiative (TRI) database: a new approach for delineation of tinnitus subtypes and generation of predictors for treatment outcome. BMC Med. Inform. Decis. Mak. 10 (1), 1–7.

Langguth, B., Landgrebe, M., Schlee, W., Schecklmann, M., Vielsmeier, V., Steffens, T., Staudinger, S., Frick, H., Frick, U., 2017. Different patterns of hearing loss among tinnitus patients: a latent class analysis of a large sample. Front. Neurol. 8, 46.

Mitchell, C., 1983. The masking of tinnitus. Audiology 22, 73–87.

Mitchell, C.R., Vernon, J.A., Creedon, T.A., 1993. Measuring tinnitus parameters: loudness, pitch, and maskability. J. Am. Acad. Audiol. 4, 139–151.

Newman, C.W., Jacobson, G.P., Spitzer, J.B., 1996. Development of the tinnitus handicap inventory. Arch. Otolaryngol. Head Neck Surg. 122, 143–148.

Nicolas-Puel, C., Faulconbridge, R.L., Guitton, M., Puel, J.L., Mondain, M., Uziel, A., 2002. Characteristics of tinnitus and etiology of associated hearing loss: a study of 123 patients. Int. Tinnitus J. 8, 37–44.

Nuttall, A.L., Meikle, M.B., Trune, D.R., 2004. Peripheral processes involved in tinnitus. In: Snow, J.B. (ed.), Tinnitus: Theory and Management, pp. 52–68.

Oakes, M.P., Anwar, M.N., Panchev, C., 2013. Data mining for gender differences in tinnitus. In: Int. Conf. Data Min. Knowl. Eng. III, pp. 1504–1509.

Pelleg, D., Moore, A., 2000. X-means: extending K-means with efficient estimation of the number of clusters. In: ICML '00 Proc. Seventeenth Int. Conf. Mach. Learn, pp. 727–734.

Roberts, L.E., Moffat, G., Bosnyak, D.J., 2006. Residual inhibition functions in relation to tinnitus spectra and auditory threshold shift. Acta Otolaryngol. 126, 27–33.

Savage, J., Waddell, A., 2013. Tinnitus. BMJ Clinical Evidence, pp. 1–32.

Schlee, W., Hall, D., Canlon, B., Cima, R.F.F., de Kleine, E., Hauck, F., Huber, A., Gallus, S., Kleinjung, T., Kypraios, T., Langguth, B., Lopez-Escamez, J.A., Lugo, A., Meyer, M., Mielczarek, M., Norena, A., Pfiffner, F., Pryss, R.C., Reichert, M., Requena, T., Schecklmann, M., van Dijk, P., van de Heyning, P., Weisz, N., Cederroth, C.R., 2018. Innovations in doctoral training and research on tinnitus: the European School on Interdisciplinary Tinnitus Research (ESIT) perspective. Front. Aging Neurosci. 9, 1–7.

Seydel, C., Haupt, H., Olze, H., Szczepek, A.J., Mazurek, B., 2013. Gender and chronic tinnitus: differences in tinnitus-related distress depend on age and duration of tinnitus. Ear Hear. 34, 661–672.

Shekhawat, G.S., Searchfield, G.D., Stinear, C.M., 2014. The relationship between tinnitus pitch and hearing sensitivity. Eur. Arch. Otorhinolaryngol. 271 (1), 41–48.

Shim, H.J., Kim, S.K., Park, C.H., Lee, S.H., Yoon, S.W., Ki, A.R., Chung, D.H., Yeo, S.G., 2009. Hearing abilities at ultra-high frequency in patients with tinnitus. Clin. Exp. Otorhinolaryngol. 2, 169–174.

Syakur, M.A., Khotimah, B.K., Rochman, E.M.S., Satoto, B.D., 2018. Integration K-means clustering method and elbow method for identification of the best customer profile cluster. IOP Conf. Ser. Mater. Sci. Eng. 336 (1), 012017.

Tsai, B.S., Sweetow, R.W., Cheung, S.W., 2012. Audiometric asymmetry and tinnitus laterality. Laryngoscope 122, 1148–1153.

Tyler, R., Conrad-Armes, D., 1984. Masking of tinnitus compared to masking of pure tones. J. Speech Lang. Hear. Res. 27, 106–111.

Tyler, R., Coelho, C., Tao, P., Ji, H., Noble, W., Gehringer, A., Gogel, S., 2008. Identifying tinnitus subgroups with cluster analysis. Am. J. Audiol. 17, 176–185.

van den Berge, M.J., Free, R.H., Arnold, R., de Kleine, E., Hofman, R., van Dijk, J.M.C., van Dijk, P., 2017. Cluster analysis to identify possible subgroups in tinnitus patients. Front. Neurol. 8, 115.

Vernon, J., 1977. Attempts to relieve tinnitus. J. Am. Audiol. Soc. 2, 124–131.

Vernon, J., Griest, S., Press, L., 1990. Attributes of tinnitus and the acceptance of masking. Am. J. Otolaryngol. 11, 44–50.

Vielsmeier, V., Lehner, A., Strutz, J., Steffens, T., Kreuzer, P.M., Schecklmann, M., Landgrebe, M., Langguth, B., Kleinjung, T., 2015. The relevance of the high frequency audiometry in tinnitus patients with normal hearing in conventional pure-tone audiometry. BioMed Res. Int. 2015, 302515. https://doi.org/10.1155/2015/302515.

Ward, J., Vella, C., Hoare, D.J., Hall, D., 2015. Subtyping somatic tinnitus: a cross-sectional UK cohort study of demographic, clinical and audiological characteristics. PLoS One 10, 1–11.

Zagólski, O., Stręk, P., 2014. Tinnitus pitch and minimum masking levels in different etiologies. Int. J. Audiol. 53, 482–489.