Title Page

Exploring sleep intermittent tinnitus patients infradian tinnitus loudness periodicity  
*A case-control study*

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Article

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**Abstract:**

Background : A subpopulation of tinnitus patients experiences complete intermittence of their tinnitus in relation to sleep. On some days, they report perceiving higher tinnitus loudness immediately after waking, which persists throughout the day. On other days, they wake up without tinnitus and may remain tinnitus-free until the next sleep episode, unless they take a nap. To date, and to our knowledge, no study has attempted to determine whether such alternations are purely random or periodical.

Methods: 17 tinnitus patients exhibiting this symptomatology were prospectively recruited and reported daily tinnitus loudness and sleep diary for two months. Lomb-Scargle periodogram was used to determine whether periodic oscillations in their tinnitus were present. A confirmatory analysis was conducted on a retrospective database of 1851 patients, from which were extracted a test group (N=17) and two control groups (N=17 and N=22). Additionally, tinnitus intensities in relation to sleep durations were analyzed.

Results: A periodicity between 2.5 and 4.5 days was significantly present in the prospective sample and in the test group of the retrospective sample (p < 0.001). Tinnitus loudness absolute variations were more important during the night than the day without naps (p < 0.001).

Conclusions: The alternation between the presence and absence of tinnitus in this subpopulation does not appear to be random. While it is evident that sleep plays a precipitating role in the loudness transitions of tinnitus reported by this subpopulation, the observed infradian rhythmicity suggests an underlying endogenous physiological phenomenon such as sleep pressure or sleep debt.

**Keywords:** Tinnitus, sleep, intermittence, periodicity   
 **Clinical trial details** : Evaluation of Potential Causes of Nap Modulated Tinnitus (TinniNap), number: NCT05467059, <https://clinicaltrials.gov/study/NCT05467059?cond=tinnitus&term=nap&rank=1>   
Protocol reviewed and approved by French ethical committee Paris Ile-De-France 3, under approbation code 2022-A00197-36

Highlights:

* A subgroup of tinnitus patients exhibiting the same sleep-related intermittence of tinnitus symptomatology was explored longitudinally.
* Their records confirm tinnitus varies more during night sleep than during days without sleep.
* They exhibit a specific rhythmicity of duration between 2.5 and 4.5 days.

List of abbreviations

CRF : Case Report Form  
ET : Eustachian Tube  
MML : Minimum Masking Level  
NITM : Nap-Induced Tinnitus Modulation  
SIT : Sleep-Intermittent Tinnitus  
THI : Tinnitus Handicap Inventory  
TIAN : Tinnitus Increases After Naps  
TMA : Tinnitus Momentary Assessment  
VNS-L : Visual Numeric Scale of tinnitus Loudness  
VNS-I : Visual Numeric Scale of tinnitus Intrusiveness

1. Introduction

Tinnitus is defined as “the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source”1. This chronic symptom is widely prevalent, affecting approximately 14% of the world population, 2% of which in a severe form2.

Tinnitus is known to be heterogeneous in its manifestations3,4 and studies suggest that there may not be a one size fits all solution to cure tinnitus5,6. In this context, progress in finding a cure may rely on studying specific homogeneous subphenotypes in depth. Among the variety of tinnitus manifestations, not all tinnitus patients experience tinnitus continuously. Some patients report hearing it intermittently7,8. Some tinnitus models have made propositions on why tinnitus could present itself in an intermittent form. For example, the fronto-striatal gating model proposed by Rauschecker and colleagues proposed that intermittent tinnitus patients could have fluctuating levels of central serotonin, causing an intermittent limbic-driven gating of the tinnitus signal at the level of the thalamus9.

While for some of these patients the intermittence of tinnitus appears erratic or triggered by occupational and private stress7, some of them report a link between the occurrence of sleep and the intermittence of their tinnitus10,11. For these patients, each nap or night of sleep can act as an on-off switch. Such patients, referred to as Sleep Intermittent Tinnitus (SIT) patients, report that on some days they experience higher tinnitus loudness immediately after waking, which persists throughout the day. On other days, they wake up without tinnitus and may remain tinnitus-free until the next sleep episode, unless they take a nap. In a previous study11, we identified that these SIT patients present a lighter sleep than controls and that the lesser the duration of Rapid-Eye Movement (REM) sleep during their night, the more intense they experience tinnitus next morning.

Patients of this subgroup often report that their tinnitus comes and goes on a period of 3 to 4 days. This clinical insight has been reported in a recent review on tinnitus pathophysiology12. Such 3 to 4 days periodic physiological rhythms have been reported in past studies in humans13–15 and animal (mammal and bird) subjects16,17 and have sometimes been referred to a circasemiseptan (periodical with periods of around *half* a week) rhythm18. Likewise, periodicities of around a full week are referred as circaseptan.

To date, and to our knowledge, no study has attempted to investigate objectively whether such tinnitus loudness variations are purely random or periodical. In the present study, the principal objective was to test in SIT patients if a circasemiseptan periodicity was present in the time course of tinnitus fluctuations and/or intermittence in a prospective sample and to confirm this finding in a retrospective sample. The secondary objective was to study the relation between tinnitus variations and reported sleep parameters.

2. Materials and Methods:

2.1. Prospective sample:

2.1.1 Participants :

37 tinnitus patients presenting signs of being SIT patients were contacted to participate to the present study. Most of them were among patients who consulted ENT M.D. (A. L.), whereas some enrolled spontaneously with a communication help of a French patient tinnitus association (France-Acouphènes) and the mutual help digital community Siopi19.

Following contact, 8 patients didn’t reply, 7 patients declined or didn’t match inclusion criteria, 5 shared a tinnitus diary they compiled on their own and did not want to participate in the prospective cohort (a rhythmicity analysis on their diaries and more recent records is presented in supplementary material, chapter 3). This resulted in the recruitment a prospective cohort of 20 SIT patients. Time series of patients were included for further analysis only if they reported at least 25 times their tinnitus loudness and over at least 10 days, at least 1.2 times a day on average to properly estimate the periodogram values of all frequency bands covered. 3 patients did not report enough data for them to be included in the time series analysis. This resulted in a final cohort of 17 SIT patients included for analyses (age: 61.75 *±* 13.8, 12 men, 5 women).

Inclusion criteria, beyond drastic modulations of tinnitus following naps and sleep, with potential complete intermittence (SIT patient profile), are reported in a previous study20.

2.1.2. Ethics :

All the prospective cohort patients gave their informed consent to participate to the present study, which was part of a larger clinical trial that received approval from the local ethical committee (CPP Idf3 2022-A00197-36). Before submission to the ethical committee, this protocol has also been validated by the patients’ association board committee of France-Acouphènes. It was approved to take participants’ best interests into consideration.

2.1.3. Clinical assessment :

2.1.3.1. Anamnesis case report form:

The participants completed a comprehensive Case Report Form (CRF), including questions on tinnitus characterization and sleep disorders. It included the Tinnitus Handicap Inventory (THI)21 and Visual Numerical Scales on tinnitus Loudness and Intrusiveness (VNS-L and VNS-I), following the methodological advice of the Comit’Id consensus22. VNS-L and VNS-I were formulated as follows (literal translation from French):

“Currently, on a scale of 0 to 10, how loud do you hear your tinnitus?”

“Currently, on a scale of 0 to 10, how much does your tinnitus bother you?”

2.1.3.2. Daily tinnitus and sleep assessment:

Each morning, participants filled VNS-L and VNS-I as well as short questionnaire included a sleep agenda set of questions. They were asked to estimate the time at which they fell asleep and woke up, as well as to indicate whether there were any nocturnal awakenings or other notable events during the night. Each evening, participants also filled VNS-L and VNS-I and were asked if they did any nap during the day. The detail of these assessments are presented in Supplementary Material, chapter 1.

2.2. *Retrospective sample*:

2.2.1 Participants :

A confirmatory analysis was performed on a retrospective database. This database was composed of the retrospective records that had been already collected by 1851 tinnitus patients with the TrackYourTinnitus app23. This app enables to systematically investigate the variation of one’s tinnitus over time and find out how it may be associated with one’s daily routine and activities.

2.2.2. Ethics :

The TrackYourTinnitus users were informed that the data would be used for scientific purposes as indicated on the TrackYourTinnitus website, and the analysis of anonymized data from this smartphone app has been approved by the Ethics Committee of the University Clinic of Regensburg23,24.

2.2.3. Clinical assessment :

2.2.3.1. Anamnesis case report form:

Patients that registered to this app completed the Tinnitus Sample Case History questionnaire (TSCHQ)25. These items enable to screen potential SIT patients. Patients who responded that naps induced in them an increase of their tinnitus, who declared sleep modulates their tinnitus and who either declared their tinnitus was intermittent, or that their tinnitus loudness varied from day to day were selected as the retrospective SIT (RSIT) group. Two control groups were selected from this database: in both these groups, neither naps nor sleep were declared by the patients as modulating tinnitus, while in the first control group tinnitus was declared as intermittent (control group 1) and in the second tinnitus was declared as constant without any variation from day to day (control group 2). Patients time series were only included if their tinnitus loudness time series met the criteria defined in section 2.1.1. This resulted in the selection of 17 patients for the RSIT group, 17 patients for control group 1 and 22 patients for control group 2. A flowchart displayed in supplementary material chapter 2 summarizes the process of constitution of these 3 groups in further detail.

2.2.3.2. Daily tinnitus assessment:

TrackYourTinnitus users would be notified at several -potentially random- time points during the day to fill out a short questionnaire, which contained a question about whether they perceive or not their tinnitus at this moment (answer with yes or no) and a question about the loudness of the tinnitus (visual analog scale implemented as a slider without pre-set values to avoid anchoring affects26). The latter question on loudness was used to conduct similar analyses as for the prospective sample.

2.2.4. Reverse symptomatologic analysis:

Additionally, a reverse analysis was conducted to identify the symptomatologic characteristics of the subgroup of patients presenting a significative circasemiseptan rhythmicity in the retrospective database. To achieve this purpose, all patients in the TrackYourTinnitus database that matched the following selection rules (used for the other analyses): more than 25 tinnitus loudness records, over at least 10 days, with an average distance between 2 point of 0.875 days or below, as chosen in the rest of the study. This procedure resulted in the selection of a total of 258 patients.

This group of patients were either attributed to a test group (patients that displayed a significative circasemiseptan rhythmicity, but not a circaseptan rhythmicity, N=33), or a control group (patients who did not display a significative circasemiseptan rhymicity or had a concomitant circaseptan rhythmicity, N= 225) and were then compared in terms of symptomatologic characteristics.

2.3. *Statistical analyses:*

Data were exported on a common anonymized CSV (Comma Separated Value) file and analyzed using Python, pandas library27 and Scipy library28.

To compare sample characteristics between the prospective and the three groups of the retrospective sample, ANOVA test was used for continuous variables (F statistics) and Chi² test was used for categorical variables.

To analyze periodicity in collected tinnitus loudness time series, Lomb-Scargle periodogram was used29. This method is comparable to a Fourier spectrogram, as it enables to estimate a frequency power spectrum with the advantage that it can be applied to time series with missing values and unevenly spaced time points, which was the case for the time series of the present study. For this reason, it has been often used in astronomy and genomics 30,31. To assess if a power peak on a specific frequency band in Lomb-Scargle periodogram was significant, Baluev’s False Alarm Probability (FAP) statistical test was used32. To perform this analysis in Python, the Astropy library was used 33. To specifically test our hypothesis, FAP test was applied on three frequency bands, the test band for which time periods varied between 2.5 and 4.5 days (frequency band between 0.22 and 0.4 days-1), a first control frequency band, in which time periods varied between 1.75 and 2.5 days (frequency band between 0.4 and 0.57 days-1) and a second control frequency band in which time periods varied between 4.5 and 9 days (frequency band between 0.11 and 0.22 days-1) . Lomb-Scargle periodogram was sampled on these frequency bands with the same number of 25 points. The selection of the second control frequency band of lower frequencies also enabled to control if the results in the test frequency band were the result of harmonics of lower frequencies (and a potential circaseptan/weekly rhythm). Time series of patients were included for this analysis only if they reported at least 25 times their tinnitus loudness and over at least 10 days, with at least 1.2 measures per day to properly estimate the periodogram values of all frequency bands covered. This selection procedure resulted in the exclusion of three subject for the prospective sample. To make a conclusion over the whole group of patients for the test and control frequency bands, Stouffer p-value combination was used from the individual FAP scores.

To test the relation between tinnitus variations and sleep parameters, we performed 3 analyses.

First, we tested if there was a direct correlation between overnight tinnitus variation and night sleep duration. Calculation of sleep duration per night was performed by subtracting hour of sleep onset to the hour of awakening while also subtracting the accumulated nocturnal awakening duration when reported. One-sided Spearman correlation tests in both directions were individually performed between sleep durations and overnight tinnitus loudness variation (VNS-L from the morning minus VNS-L of the evening). To make a conclusion over the whole group of patients for these correlation tests, Fisher p-value combination was used over the one-sided correlation p-values, resulting in 2 combined p-values.

SIT patients declare that nights can either switch on or switch off their tinnitus while naps always ignite their tinnitus. To verify these clinical observations, two additional tests were performed. To test if night sleep occurrences resulted in more important overall tinnitus loudness variation, absolute night variations of tinnitus loudness (measured as absolute delta of VNS-L scores between the morning and the preceding evening) were compared to absolute day variations of tinnitus loudness (absolute delta of VNS-L scores between the evening and the preceding morning). For this test days which contained a nap (as declared by patients) were removed from analysis. Then, delta VNS-L on days containing a nap were compared to delta VNS-L on days without a nap. Individual signed Mann-Whitney tests were conducted for each patient that had at least 5 measurements in both categories tested. Fisher p-value combination was used to conclude for the whole sample.

Holm-Bonferroni method34 was applied to control for multiple statistical testing on all group statistical tests conducted.

For the reverse analysis, False Alarm probability tests were used on the test frequency band (corresponding to 2.5 to 4.5 days periodicity) and control frequency band 2 (corresponding to 4.5 to 9 days periodicity) of the Lomb-Scargle periodograms of the tinnitus loudness time series of each patient. According to the result of this test, patients were either attributed to the test group or the control group. Then, we used a Mann-Whitney test to compare the symptomatologic characteristics of this subgroup with the group of patients that did not display a significant circasemiseptan rhythmicity. This analysis was conducted on each of the symptomatologic characteristic associated with each patient in the TrackYourTinnitus database. Hedges’ g effect size was also calculated for each Mann-Whitney test35.

3. Results :

3.1. Demographics :

The clinical characteristics for both samples are presented in Tables 1 and in more specific details in supplementary material chapter 1 and 2. The comparison of the characteristics between each group did not show any significative differences. The audiometric characteristics of the prospective sample are illustrated in Figure 1.

3.2. Tinnitus periodicity :

Over the whole prospective sample, after corrections, periodicity was found significant over the test frequency band (Corrected Stouffer combination p-value: p < 0.001), while it was not significative over the control frequency bands (p=1.0). Details of individual periodicity analyses are illustrated in Table 2. Figure 2 illustrates the tinnitus loudness dynamics of an emblematic SIT patient of the prospective sample.

For the retrospective sample, after corrections, combined p-value for the test frequency band was found significative for the RSIT group and control group 1 (p < 0.001) but not for control group 2. For the control frequency bands, the RSIT group exhibited a significative rhythmicity for control frequency band 2 (p=0.020), as well as control group 1 (intermittent tinnitus not modulated by sleep, p<0.001). Details of individual periodicity analyses are illustrated in Table 3.

3.3. Reverse symptomatologic analysis

A reverse analysis was conducted in the retrospective sample to compare the symptomatologic characteristics of the subgroup of patients presenting a specific significative periodicity only in the test frequency band to other patients of the TyT sample. Patients displaying a specific rhythmicity in the test frequency bands declared significantly more often increases of tinnitus loudness after naps (p=0.011) and variability of tinnitus (p=0.035). The control group reported more often no modulation by sleep (p=0.033). A summary of the results is presented in Table 4.

3.4. Tinnitus loudness and sleep characteristics analysis :

the corrected combined p-values for both directions of the one-sided Spearman correlation tests between reported night sleep duration and overnight variation of tinnitus for the prospective sample were not significative.

However, we observed a significative corrected combined p-value for Mann-Whitney tests p-values for the differences between tinnitus loudness absolute variations upon nights and upon days without naps (p<0.001). We also observed that days with naps lead significantly more often to tinnitus increase than days without naps (p<0.001), although these latter tests could be performed only if 5 measures were done in each category, resulting in some missing values.

Details of individual correlation tests are displayed in Table 2.

4. Discussion

This study demonstrates that at least a subgroup of tinnitus patients, the SIT subgroup, exhibit non-random tinnitus loudness oscillations through time, with a period ranging between 2.5 and 4.5 days. For this subgroup, sleep seems to play an important role in such oscillations as tinnitus variations were more important when it occurs and we exhibited a correlation between sleep pressure and tinnitus loudness level at awakening.

While conducting our confirmatory analysis, it appeared that the RSIT subgroup also displayed a circasemiseptan rhythmicity, as well as a less significative circaseptan rhythmicity. Tinnitus patients declaring tinnitus intermittence in the absence of modulation by sleep (control group 1) presented both a significative circasemiseptan and circaseptan periodicity. This led us to question whether alternation of working days and week-ends could play a role in the observed patterns of rhythmicity. This analysis, presented in Supplementary Material chapter 4, concludes this alternation seems to be present in the RSIT group and the Control group 1 of the retrospective cohort, but not in the prospective cohort. This could account for the observation of a circaseptan rhythm in the RSIT group and not in the prospective cohort and could be explained by the probable presence of more retired people in the prospective cohort than the RSIT group (age averages, Prospective sample : 61.71 +/- 13.76, RSIT : 54.98 +/- 7.93). In all cases, in both SIT patient samples, it appears circasemiseptan rhythmicity was the dominant mode of rhythmicity.

4.1.Physiological parameters exhibiting similar infradian periodicity:

Circasemiseptan periodicity has been detected in diverse human biological activities such as mitosis cycles notably in case of cancer36 and epileptic seizures occurrences37. Several studies suggest that vascular and cardiac functions comprise circasemiseptan periodicity : cardiovascular risks and endothelin peptides (vasoconstrictors)38, as well as blood pressure and heart rate, which have been documented in Minnesota39, the Czech Republic40, India41, and Japan42. It is interesting to note that tinnitus has been identified to be linked with hypertension43 but not with cardiovascular disease44.

Stress hormones such as (urinary) cortisol, norepinephrine, epinephrine were also reported to display a 4-day rhythm37. It is worth noting in regards to our SIT patients that such observations were made in a study analyzing the effect of nocturnal sound pollution. Another study observed a 4-day rhythm in a human subject testosterone, cortisol, and interleukin-1 receptor antagonist15. Yet, it should be noted that other studies from another team did not reproduce such results45–47. Stress and stress hormones have been shown to be related to tinnitus modulation48,49. It should be mentioned that interestingly, corticosterone (animal equivalent of cortisol) was also found to display a 4-day rhythm, which was found to be associated to hypoxic resistance16. The latter could be put in perspective with the association between snoring, sleep apnea and nap-induced tinnitus modulations we identified in a recent study20 and in a previous polysomnography case-report exploration of an SIT patient11.

4.2. Sleep and infradian periodicity :

Circasemiseptan rhythms have also been identified in link with sleep, which appears important considering our SIT population. In a study on 33 healthy subjects, 3.5-days rhythms were found in lying down time, sleep duration and sleep efficiency14, in a second study from the same team with a mobile polysomnographic device, a 4-day rhythmicity was observed in REM sleep duration50.

In the prospective sample, no direct correlation was found between the duration of sleep and the overnight tinnitus variation. Yet, variations of tinnitus in this sample appeared to be strongly related to sleep as nights and naps elicited more variations than days without sleep. Moreover, looking at the important variability of the individual peak periods in the present prospective sample, it appears unlikely that an external *zeitgeber* affected tinnitus loudness in prospective sample.

Additionally, as shown through simulations in supplementary material chapter 4, stochastic processes with memory, such as Markov chains of order superior or equal to two, can generate time series that display a specific rhythmicity as observed in the present study.

Taken together, this suggests that a sleep regulation physiological endogenous process with some form of memory over several days may be at play.

Sleep pressure, or sleep debt, which can be cumulated or dissipated over several days appears as a suitable candidate51. It should be noted that there are actually two kinds of sleep debts: the lack of deep sleep (the one we commonly refer as sleep debt) and REM sleep debt, which corresponds to the specific lack of REM sleep. Indeed, several studies highlight that these two stages of sleep have two independent homeostatic regulation processes52–54.

Deep sleep pressure conditions the regulation of sleep depth, which has been suggested to potentially interfere with tinnitus neural correlates55, with some recent evidence of this theory shown in animal models56. Such interference could be prolongated to waking period upon awakening from deep sleep, through a phenomenon referred to as sleep inertia57.

Put together, we could hypothesize that on the course of days, SIT patient could have variable amount of sleep debt, resulting in having higher sleep pressure upon sleep onset on some days.

As described in Supplementary material Chapter 4, we modeled deep sleep pressure and deep sleep debt using the sleep diaries data of the prospective sample through two models58,59. Our results show limited evidence that deep sleep debt and tinnitus loudness would be associated.

Due to the absence of polysomnographic measurements, we could not model REM sleep debt in the present study. Yet it remains important to test it as in our previous polysomnography study on SIT patients11, we observed a correlation between REM sleep duration and overnight tinnitus modulation.

4.3. Limitations and suggestions for future research :

A first limitation to the present study lies in the small sample size of the samples : SIT patients are a rather rare subgroup of tinnitus patients making them difficult to recruit. It should be noted the additional limit that not all recruited SIT patients displayed a circasemiseptan rhythm, which questions the homogeneity of the sample.

Moreover, the participation to such an observational study requires a lot of personal motivation, which resulted in three patients not reporting enough data for analysis, and often missing data occurrences for the rest of the participants.

Last, another limitation lies in the subjective nature of measures of loudness reported by the patients. Currently there are no consensual objective biomarkers of tinnitus but if such biomarker is identified in the future, it would be important to validate these results with this biomarker.

Future studies should also aim to reproduce the present results by recruiting prospectively SIT samples with an additional constant tinnitus control group, properly matched to the SIT group. Ideally, future research should also aim to unravelling the physiological mechanisms behind such circasemiseptan periodicity, notably by investigating the role of REM homeostatic sleep pressure and sleep depth biomarkers. This could be achieved by making longitudinal polysomnographic measurements of SIT patients.

**Supplementary Materials:** A supplementary material, comprising 4 chapters is attached to the present manuscript.

**Author Contributions:** Conceptualization, R.G., K.R. and A.L.; methodology, R.G., and A.L.; software, R.G. and A.C.; validation, R.G. and A.L.; formal analysis, R.G. A.C.; investigation, R.G., A.C and A.L.; data curation, R.G., A.C., W.S.; writing—original draft preparation, R.G.; writing—review and editing, R.G., A.C, W.S, M.C., K.R. and A.L; supervision, R.G., M.C., W.S. and A.L.; project administration, R.G.; funding acquisition, R.G. All authors have read and agreed to the published version of the manuscript.

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The other authors did not declare financial interests.

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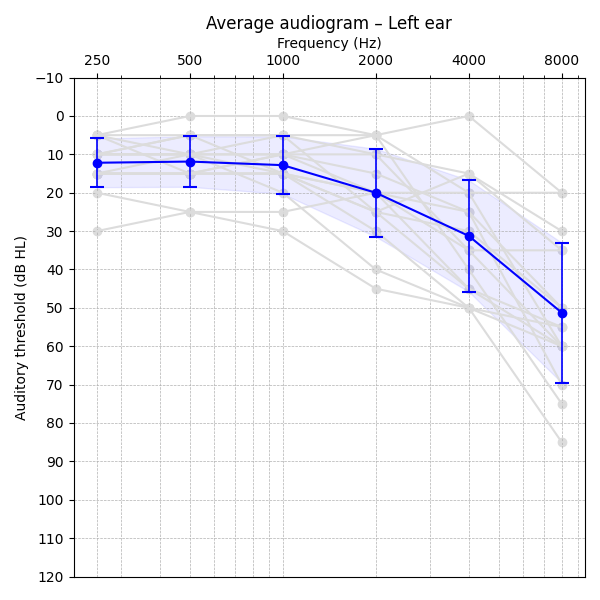
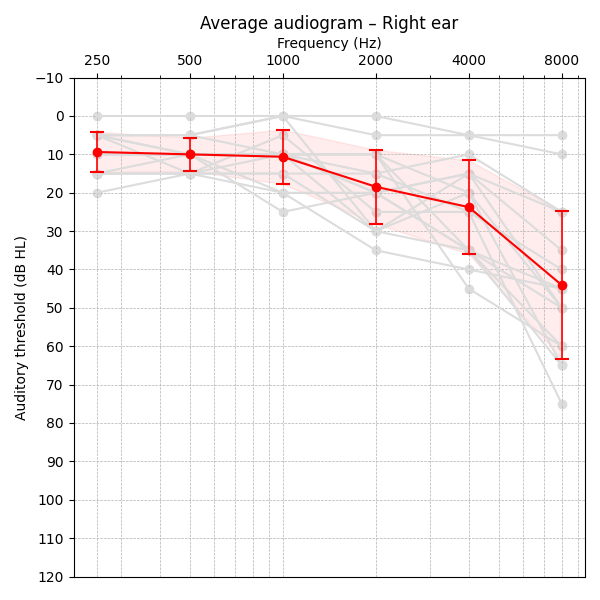
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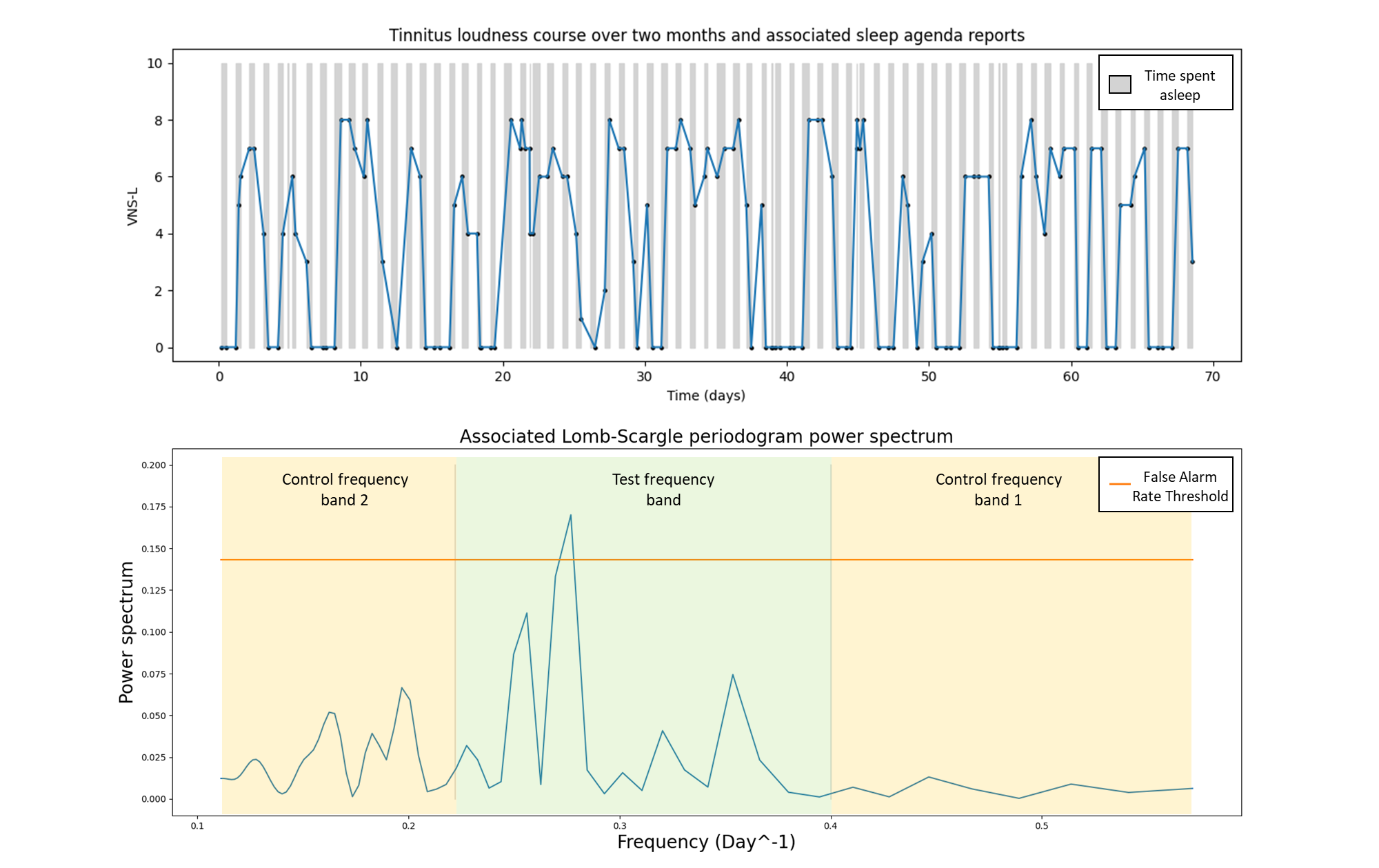
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*Figure 1: Average audiogram characteristics of the prospective sample for the right ear (red, left) and the left ear (right, blue), N=16, one missing data. Individual audiograms are displayed in dim grey. Wilcoxon test comparison of the average hearing loss between the left and right ear (average of frequencies from 500 to 4000 Hz) on the whole sample highlighted a hearing loss significantly more pronounced on the left ear compared to the right (p < 0.02). The difference was above all concentrated on the 4000Hz.*



*Figure 2: Illustration of the circasemiseptan periodicity of one of the SIT patients of the prospective sample. Above, the complete time series of the patient tinnitus loudness levels, grey rectangles represent when the patient declared he/she was asleep. Below, the associated Lomb-Scargle periodogram on the test and control frequency bands. Orange horizontal line presents the FAP level threshold for a significative peak. In the case of the present patient, one significative frequency peak appears, corresponding to a period of 3.67 days (frequency 0.27 days -1).*

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|  | Table 1, No significant differences in sample characteristics comparison | | | | | | | |  | |
|  |  | **Prospective sample (N=17)** | **RSIT sample (N=17)** | **Control group 1 (N=17)** | **Control group 2 (N=22)** | **F or Chi²** | **P- value** |  | |
|  | Age, mean ± SD, y\* | 61.7 ± 13.8 | 55.0 ± 7.9 | 53.2 ± 10.5 | 56.6 ± 13.9 | F=1.46 | 0.23 |  | |
|  | Female sex, % | 29% | 24% | 24% | 9% | Chi²=2.77 | 0.42 |  | |
|  | Average VNS Tinnitus loudness (0 to 10), mean ± SD (missing) | 3.92 ± 1.7 | 3.2 ± 1.7 | 3.2 ± 1.4 | 4.0 ± 2.1 | F=0.93 | 0.43 |  | |
|  | Average VNS Tinnitus Intrusiveness / stress associated with tinnitus (0 to 10), mean ± SD | 3.72 ± 1.67 | 3.49 ± 2.12 | 2.39 ± 1.54 | 2.94 ± 1.14 | F=1.97 | 0.13 |  | |
|  | **Tinnitus Duration\*** |  |  |  |  | Chi²=7.08 | 0.85 |  | |
|  | *Less than 6 months* | 0.0 % | 6.7 % | 11.8 % | 4.8 % |  |  |  | |
|  | *Between 6 months and 1 year* | 11.76 % | 26.7 % | 11.8 % | 4.8 % |  |  |  | |
|  | *Between 1 and 2 years* | 11.76 % | 6.7 % | 5.9 % | 4.8 % |  |  |  | |
|  | *Between 2 and 5 years* | 23.53 % | 20.0 % | 17.6 % | 14.3 % |  |  |  | |
|  | *Over 5 years* | 47.06 % | 40.0 % | 52.9 % | 71.4 % |  |  |  | |
|  | **Assumed causes of tinnitus\*\*** |  |  |  |  | Chi²=12.27 | 0.65 |  | |
|  | *Exposure to loud sounds* | 17.65 % | 5.88 % | 5.88 % | 4.54 % |  |  |  | |
|  | *Changes in hearing* | 5.88 % | 5.88 % | 5.88 % | 13.63 % |  |  |  | |
|  | *Episode of stress* | 35.29 % | 47.05 % | 23.52 % | 18.18 % |  |  |  | |
|  | *Head trauma* | 0.0 % | 0.0 % | 0.0 % | 4.54 % |  |  |  | |
|  | *Trauma to the neck (e.g., whiplash)* | 0.0 % | 0.0 % | 0.0 % | 0.0 % |  |  |  | |
|  | *Other* | 47.05 % | 41.17 % | 64.7 % | 59.09 % |  |  |  | |
|  | **Self-presumed hearing loss** |  |  |  |  | Chi²=9.31 | 0.16 |  | |
|  | *No* | 23.53 % | 52.94 % | 62.5 % | 50.0 % |  |  |  | |
|  | *Yes* | 64.7 % | 41.17 % | 25.0 % | 50.0 % |  |  |  | |
|  | *Don't know* | 11.76 % | 5.9 % | 12.5 % | 0.0 % |  |  |  | |
|  | *(\*) For these 2 questions, 2 values were missing in the RSIT group and one in the Control group 1*  *(\*\*) For this question, for the prospective sample, responders could select multiple answers among the proposed choices.*  *Abbreviations : VNS : Visual Numeric Scale, SD: Standard Deviation, TyT: TrackYourTinnitus, RSIT: Retrospective Sleep-induced tinnitus (group)* | | | | | | | |  | |
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*Table 1 : Sample characteristics of the prospective sample and each group of the retrospective samples. Statistical comparisons were performed with ANOVA test for continuous variables (F statistics) and with Chi² test for categorical variables. No significant differences emerge from groups comparison. It should be noted that in the TyT database, the formulation of the question for VNS-I was slightly different, translating from German as: “How stressful is the tinnitus right now?”. This difference can contribute to explain why the average in the prospective cohort may appear as higher than the others (without reaching significance in the ANOVA test).*

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| Table 2, Prospective sample exhibits a specific significant 2.5-4.5 days rhythmicity and their tinnitus loudness variations depends on whether they are asleep or not (N =17) | | | | | | | | | | | |
| **Subject code** | **Sex** | **Number of time points** | **Peak period test freq band** | **P-value test freq band** | **P-value control freq band 1** | **P-value control freq band 2** | **Mean +/- std sleep duration** | **Sleep / tinnitus Spearman correlation coefficient** | **Overnight VS days without naps p-value** | **Days with VS without naps p-value** |
| #1 | M | 75 | 4.42 | 0.707 | 0.381 | 0.631 | 7.66 +/- 1.49 | 0.088 | 0.199 |  |
| #2 | M | 27 | 3.75 | 0.38 | 1.0 | 0.97 | 8.33 +/- 0.68 | -0.039 |  |  |
| #3 | F | 132 | 3.67 | p < 0.001 | 0.965 | 0.314 | 8.22 +/- 1.42 | 0.234 | p < 0.001 | 0.091 |
| #4 | M | 113 | 2.75 | 0.073 | 0.761 | 0.995 | 8.39 +/- 0.59 | -0.039 | p < 0.001 | 0.102 |
| #5 | F | 79 | 3.67 | 0.027 | 0.972 | 0.01 | 7.52 +/- 0.59 | 0.011 | 0.003 | 0.072 |
| #6 | F | 83 | 4.0 | 0.324 | 0.873 | 0.727 | 7.14 +/- 1.41 | 0.053 | 1 |  |
| #7 | M | 87 | 3.5 | 0.784 | 1.0 | 0.034 | 7.48 +/- 1.14 | -0.088 | 0.004 |  |
| #8 | F | 114 | 4.25 | p < 0.001 | 1.0 | 0.135 | 7.52 +/- 0.86 | 0.104 | 0.039 | 0.013 |
| #9 | M | 239 | 3.67 | 0.102 | 0.998 | 0.148 | 6.13 +/- 1.2 | -0.026 | 0.07 | 0.046 |
| #10 | M | 169 | 2.92 | 0.015 | 0.999 | 0.004 | 5.7 +/- 0.84 | 0.126 | 0.059 |  |
| #11 | M | 103 | 2.83 | p < 0.001 | 1.0 | 0.998 | 6.45 +/- 1.5 | -0.268 | 0.069 |  |
| #12 | M | 91 | 3.08 | p < 0.001 | 0.932 | 0.418 | 5.82 +/- 0.85 | 0.153 | 0.166 |  |
| #13 | F | 86 | 3.33 | 0.987 | 0.995 | 0.997 | 6.6 +/- 2.7 | -0.042 | 0.087 | 0.242 |
| #14 | M | 79 | 2.5 | 0.286 | 0.226 | 0.665 | 8.08 +/- 1.33 | 0.117 | p < 0.001 |  |
| #15 | M | 69 | 2.5 | 0.272 | 0.027 | 0.994 | 7.77 +/- 0.55 | -0.217 | 0.006 |  |
| #16 | M | 112 | 2.75 | 0.637 | 0.252 | 0.372 | 6.89 +/- 1.07 | -0.387 | 0.178 | 0.057 |
| #17 | M | 104 | 4.42 | 0.372 | 0.99 | 0.406 | 7.65 +/- 1.43 | -0.129 | 0.153 | 0.020 |
| *Abbreviations : freq : frequency, std : Standard Deviation* | | | | | | | | | | | |

*Table 2 : Individual summary of the results of the tests conducted on the prospective sample. From left to right : Subject ID, gender, number of collected time points, period length (in days) associated with the maximum Lomb-Scargle periodogram power value in the test frequency band, individual p-values associated with the FAP tests on the test and control frequency bands (test frequency band : for periods between 2.5 and 4.5 days, control frequency band 1 : for periods between 1.75 and 2.5 days, control frequency band 2 : for periods between 4.5 and 9 days), average and standard deviation of the sleep duration over the collected period (sleep durations were adjusted to take in account the declared nocturnal awakenings), Individual Spearman correlation coefficients between sleep duration and overnight variation of tinnitus loudness, Individual p-values of the Mann-Whitney test between the absolute variation of tinnitus loudness during the nights and during the days without naps (left blank if less than 5 measures in one of the two conditions), Individual p-values of the Mann-Whitney test between the variation of tinnitus loudness during the days with and without naps (left blank if less than 5 measures in one of the two conditions)*

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| Table 3, RSIT group and Control group 1 in the retrospective sample exhibit significant 2.5-4.5 days and 4.5-9 days rhythmicity | | | | | | | |
| **Group** | **Subject code** | **Sex** | **Number of time points** | **Peak period test freq band** | **P-value test freq band** | **P-value control freq band 1** | **P-value control freq band 2** |
| RSIT | 1909 | M | 259 | 3.25 | 0.062 | 0.248 | p < 0.001 |
| 2396 | M | 28 | 2.75 | 0.473 | 0.999 | 0.246 |
| 2557 | F | 214 | 4.0 | 0.262 | 0.999 | 0.047 |
| 2888 | M | 818 | 3.25 | p < 0.001 | 1.0 | 1.0 |
| 3092 | F | 30 | 2.83 | 0.003 | 0.997 | 0.68 |
| 3989 | M | 28 | 3.08 | 0.258 | 0.489 | 0.613 |
| 3993 | M | 128 | 2.92 | 0.453 | 0.059 | 0.927 |
| 4173 | M | 55 | 4.08 | 0.001 | 0.135 | 0.053 |
| 4215 | M | 201 | 2.5 | 0.673 | 0.311 | 0.083 |
| 4279 | M | 140 | 3.58 | 0.008 | 0.266 | 0.142 |
| 4360 | M | 427 | 3.5 | p < 0.001 | 0.998 | 0.073 |
| 4445 | M | 78 | 3.33 | 0.032 | 0.323 | 0.901 |
| 4841 | M | 602 | 3.33 | p < 0.001 | 0.582 | 0.284 |
| 5093 | F | 59 | 2.5 | p < 0.001 | p < 0.001 | 0.041 |
| 5570 | M | 116 | 4.5 | 0.727 | 0.986 | p < 0.001 |
| 5871 | M | 41 | 3.75 | 0.921 | 0.341 | 0.91 |
| 5845 | F | 50 | 3.0 | p < 0.001 | 0.166 | 0.094 |
| Control group 1 | 1837 | F | 26 | 2.75 | 0.095 | 0.506 | 0.489 |
| 1871 | M | 876 | 4.17 | p < 0.001 | 0.875 | 0.273 |
| 1861 | M | 501 | 3.58 | p < 0.001 | 0.986 | 0.001 |
| 1863 | M | 39 | 4.25 | 0.943 | 0.99 | 0.761 |
| 2122 | F | 49 | 3.58 | 0.11 | 0.935 | 0.225 |
| 2592 | M | 140 | 3.25 | p < 0.001 | 0.507 | 0.023 |
| 2578 | M | 348 | 3.67 | p < 0.001 | 0.002 | 0.01 |
| 2838 | M | 192 | 2.83 | 0.935 | 0.942 | 0.054 |
| 3076 | M | 48 | 3.08 | 0.452 | 0.836 | 0.629 |
| 3169 | F | 314 | 3.33 | 0.778 | 1.0 | 0.126 |
| 3469 | M | 93 | 3.92 | 0.661 | 0.877 | 0.368 |
| 3487 | F | 56 | 2.75 | 0.867 | 0.922 | 0.855 |
| 3791 | M | 512 | 4.0 | 1.0 | 1.0 | 0.833 |
| 3996 | M | 38 | 3.75 | 0.044 | 0.51 | 0.001 |
| 4010 | M | 194 | 4.33 | 0.013 | 0.059 | 0.002 |
| 4916 | M | 296 | 3.5 | 0.9 | 0.994 | 0.041 |
| 5188 | M | 79 | 4.17 | 0.032 | 0.866 | 0.031 |
| Control group 2 | 1632 | M | 80 | 2.5 | 0.226 | 0.305 | 0.859 |
| 1659 | M | 46 | 2.58 | 0.979 | 0.785 | 0.684 |
| 1814 | M | 48 | 2.83 | 0.611 | 0.997 | 0.099 |
| 1886 | M | 35 | 3.5 | 0.155 | 0.993 | 0.126 |
| 2040 | M | 66 | 2.58 | 0.107 | 0.376 | 0.893 |
| 2127 | M | 76 | 2.5 | 0.946 | 0.981 | 0.024 |
| 2675 | M | 122 | 3.0 | 0.813 | 0.946 | 0.787 |
| 3486 | F | 56 | 4.0 | 0.635 | 0.336 | 0.811 |
| 3570 | M | 56 | 3.67 | 0.88 | 0.948 | 0.291 |
| 3659 | M | 55 | 4.08 | 0.574 | 0.975 | 0.83 |
| 3716 | M | 39 | 3.0 | 0.375 | 0.787 | 0.381 |
| 3739 | M | 49 | 2.67 | 0.249 | 0.515 | 0.906 |
| 3741 | M | 52 | 2.83 | 0.801 | 0.977 | 0.092 |
| 3864 | M | 273 | 4.33 | 0.155 | 0.883 | 0.467 |
| 4163 | M | 137 | 2.67 | 0.987 | 0.989 | 0.829 |
| 4454 | M | 31 | 3.42 | 0.967 | 0.951 | 0.811 |
| 4779 | M | 51 | 2.75 | 0.992 | 0.693 | 0.77 |
| 5134 | M | 33 | 2.92 | 0.239 | 0.665 | 0.641 |
| 5141 | M | 226 | 3.83 | 0.999 | 0.987 | 0.99 |
| 6229 | M | 43 | 3.83 | 0.436 | 0.979 | 0.444 |
| 6305 | M | 35 | 2.75 | 0.002 | 0.786 | 0.227 |
| 5927 | F | 170 | 2.75 | 0.002 | 0.004 | p < 0.001 |
| *Abbreviations : freq : frequency, std : Standard Deviation* | | | | | | | |

*Table 3: Individual summary of the confirmatory periodicity analysis on the retrospective database. From left to right : group name, subject ID, gender, number of time points per individual time series, , period length (in days) associated with the maximum Lomb-Scargle periodogram power value in the test frequency band, individual p-values associated with the FAP tests on the test and control frequency bands (test frequency band : for periods between 2.5 and 4.5 days, control frequency band 1 : for periods between 1.75 and 2.5 days, control frequency band 2 : for periods between 4.5 and 9 days).*

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| Table 4, Symptomatologic characteristics of tinnitus patients displaying significative 2.5-4.5 days rhythmicity | | | | |
| **Symptomatologic characteristic** | **P-value** | **Hedge's g** | **Sample size patients with specific rhythmicity** | **Sample size control group** |
| Naps worsens tinnitus | 0,011 | 0.51 | 24 | 171 |
| Headaches : No | 0.013 | 0.49 | 24 | 170 |
| Tinnitus location : inside the head | 0.014 | 0.42 | 32 | 226 |
| Tinnitus varies from day to day | 0.035 | 0.35 | 32 | 225 |
| Tinnitus sound level | 0.02 | -0.21 | 32 | 226 |
| Tinnitus duration | 0.046 | -0.26 | 31 | 220 |
| Family history of tinnitus : Yes | 0.048 | -0.32 | 32 | 226 |
| Relation between sleep at night and tinnitus during the day : No | 0.033 | -0.40 | 24 | 171 |
| Naps have no effect on tinnitus | 0.029 | -0.42 | 24 | 171 |
| Stress influences tinnitus : No effect | 0.019 | -0.45 | 24 | 171 |
| Family history of tinnitus : Parents | 0.03 | -0.85 | 6 | 57 |
| *A negative Hedges' g score means that the effect is more present in the control group than in the group of patients exhibiting a specific rhythmicity in the test frequency band.* | | | | |

*Table 4 – Reverse analysis symptomatologic characterization of tinnitus patients displaying specific significant rhythmicity in the test frequency band and not in the control frequency bands. A positive Hedge G score is a characteristic specific to the group presenting such specific rhythmicity (N=32), while a negative Hedge G characterizes the symptomatologic profile of patients without such specific significant rhythmicity (N=226). Sample sizes varied from questions to questions due to missing values in the TyT database.*