**Exploring sleep intermittent tinnitus patients infradian tinnitus loudness periodicity**

***Supplementary Material:***

Supplementary material is organized in chapters addressing different topics. Chapter 1 brings complementary information on the prospective cohort. Chapter 2 focuses on the retrospective cohort of the TrackYourTinnitus database. Chapter 3 presents data from a third cohort of Sleep Intermittent Tinnitus (SIT) patients (N=10), composed of retrospective data from patients that did not wish to participate in the prospective cohort but had already compiled longitudinal tinnitus loudness diaries and accepted to share it (N=5) and from SIT patients that spontaneously collected tinnitus diaries and shared it with us since the end of the clinical trial (N=5). Chapter 4 presents a miscellaneous of complementary analyses on the available data.

***Chapter 1: Complementary information on the prospective cohort***

Detailed symptomatologic characterization of the prospective sample

Supplementary Tables 1 and 2 present more details on the etiological characteristics of the prospective sample.

Tinnitus intrusiveness rhythmicity analysis of the prospective sample

The rhythmicity analysis presented in the manuscript is based on the answers of the participants of the prospective cohort to the principal outcome of the present study: the Visual Numerical Scale (VNS) on tinnitus loudness. Yet, they also reported VNS scores on tinnitus intrusiveness each morning and each evening. In supplementary Table 3, we present the results of the rhythmicity analysis on the time series of the VNS on tinnitus intrusiveness. We followed the same statistical procedures as for VNS on tinnitus loudness. Over the whole prospective sample, after Holm-Bonferroni corrections, periodicity was found significant over the test frequency band (Corrected Stouffer combination p-value: p = 0.0019), while it was not significative over the control frequency bands (p=1.0).

Assessing correlation between subjective tinnitus loudness measurement and minimum masking level measurement

To assess whether our longitudinal measurements of tinnitus loudness through Visual Numerical Scales (VNS) on tinnitus loudness objectively reflects tinnitus loudness fluctuations, 7 of the 17 participants of the prospective cohort additionally received a MP4 device and were tasked to perform Minimum Masking Level (MML) measurements along with VNS-L measurements.

While remaining a subjective measurement as it requires the feedback of the patient, MML appears as a more objective measure of tinnitus loudness, using a calibrated physical sound to evaluate tinnitus loudness.

The procedure was as follows: MML was assessed with a MP4 device (Mobile Gear MP4 player, On.EARZ, Belgium) and intra-auricular JBL Wired Headset (Harman International Industries). The masking stimulation was a broadband white noise (20 Hz to 10 kHz). MML procedure started without any stimulation and then rising progressively the masking stimulation intensity up to the level tinnitus was masked. The exact instruction given to the participants was: “stop at the intensity where you cannot discriminate your tinnitus perception from the sound stimulus, without actively focusing to do so”. This procedure for MML assessment was performed and reported three consecutive times and then averaged in order to ensure stability of the measurement. MML assessments were measured using units of the MP4 device and were afterwards converted to dB measures using a conversion scale created from a previous calibration analysis using a combination of the MP4 and the intra-auricular headset on an artificial ear setup.

Supplementary Figure 1 shows the collection of the 7 plots of correlations between MML measurements and VNS-L measurements over the data collection period.

Spearman correlation tests were performed for each of the 7 patients to assess whether there was a significant correlation between MML and VNS-L. For each of the patients, we obtained p<0.001 for the Spearman correlation tests. Correlation coefficients for patients 0 to 6 (as displayed on the figure) were respectively: 0.80, 0.63, 0.93, 0.73, 0.83, 0.95 and 0.94. These overall strong correlation coefficients suggest that VNS-L is a robust proxy to monitor tinnitus loudness in our prospective and retrospective sample.

Moreover, it should be noted that we also performed the rhythmicity analysis on the test and control frequency bands for these 7 patients for their MML time series. The individual results of this rhythmicity analysis are reported in Supplementary table 2. After performing a Stouffer combination on individual p-values and Holm-Bonferroni corrections, we also found a specific rhythmicity in the test frequency band (p < 0.001) and not in the control frequency band 1 (p=1.0) and the control frequency band 2 (p=1.0). We used the same statistical methodology for this analysis as for VNS-L. It should be also noted that for 6 of the 7 subject who both performed MML and VNS-L measurements, the peak period test frequency bands were very similar (difference of less than 0.2 Hz), while for only 1 subject (subject #9), they were different.

Assessing correlation between sleep duration extracted from sleep diaries and from Circular Ring

In an attempt to verify sleep durations with objective measurements, 4 of the participants of the prospective cohorts were given the possibility to monitor their sleep with a smart ring during the duration of the data collection period (Circular Ring, Circular, Paris, France). Rings sizes were adjusted beforehand and were carried on the left ring finger, for one patient (patient 2) maximum ring size was too small and was thus carried on the left little finger. Automatic sleep scoring from Circular rings could be extracted only on a limited number of nights for each patient. From these extracts and from the sleep diaries, we calculated sleep durations (taking into account nocturnal awakenings detected by the rings and reported by the patients). Display of the obtained comparisons are shown in Supplementary Figure 2. Spearman correlation tests were performed to assess whether there was a significant correlation between these sleep durations. Correlation coefficients for patients 0 to 3 (as displayed on the figure) were respectively: 0.90 (p < 0.001), 0.42 (p = 0.059), 0.45 (p= 0.076), 0.92 (p < 0.001). While correlations were highly significative for patients 0 and 3, there was only a marginal association between objective and subjective sleep durations for patients 1 and 2. These poor associations could have several explanations: these 2 patients did not report all their nocturnal awakenings in the sleep diaries, automatic sleep scoring could be of limited quality and last in the case of patient 2, wearing the ring on the little finger could have limited the quality of the measurements.

Details of the morning and evening tinnitus and sleep assessments

Supplementary Figures 3 and 4 display the morning and evening tinnitus and sleep assessments used to collect data longitudinally in the prospective cohort.

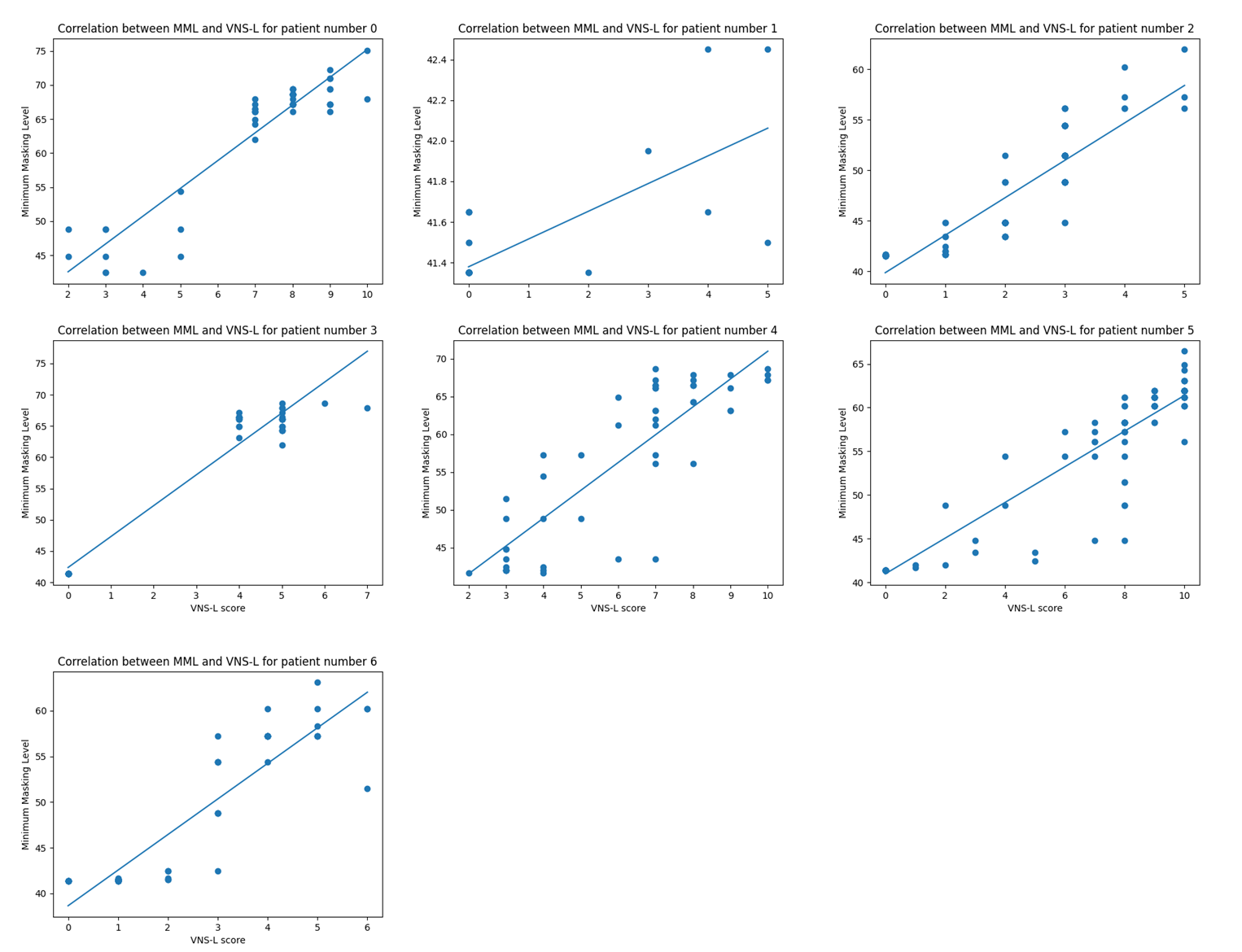
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| Supplementary table 1, Prospective sample characteristics for quantitative features (N =17) | | | | | |
|  | **Mean** | **Std** | **Min** | **Max** |
| Age (in years) | 61.71 | 13.76 | 39.0 | 79.0 |
| Tinnitus Handicap Inventory (THI) | 40.94 | 24.82 | 12.0 | 88.0 |
| Initial VNS scale Tinnitus loudness (0 to 10) | 6.35 | 2.55 | 2.0 | 10.0 |
| Initial VNS scale Tinnitus intrusiveness (0 to 10) | 6.24 | 2.77 | 2.0 | 10.0 |
| *Abbreviations : VNS : Visual Numeric Scale* | | | | | |

Supplementary Table 1 – Prospective sample characteristics for quantitative features, N=17, Abbreviations : VNS : Visual Analog Scale

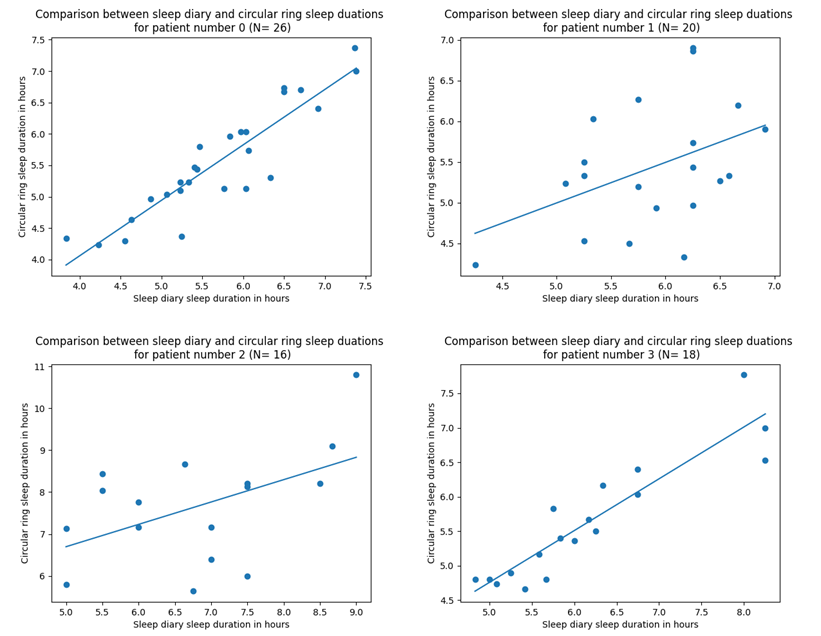
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| Supplementary table 2, Prospective sample symptomatologic characterisation (N = 17) | | | |
| **General tinnitus characteristics** | **Percentage** | **Tinnitus commorbidities** | **Percentage** |
| **Assumed cause of tinnitus\*** |  | **Tinnitus Duration** |  |
| *Exposure to loud sounds* | 17.65 % | *Between 6 months and 1 year* | 11.76 % |
| *Changes in hearing* | 5.88 % | *Between 1 and 2 years* | 11.76 % |
| *Exposure to a change in ambient pressure* | 5.88 % | *Between 2 and 5 years* | 23.53 % |
| *Flu, cold, or other infection* | 0.0 % | *Over 5 years* | 47.06 % |
| *Feeling of plugged ears* | 5.88 % | **Self-presumed hearing loss** |  |
| *Episode of stress* | 35.29 % | *No* | 23.53 % |
| *Head trauma* | 0.0 % | *Yes, a slight hearing loss* | 41.18 % |
| *Trauma to the neck (e.g., whiplash)* | 0.0 % | *Yes, a moderate hearing loss* | 17.65 % |
| *I don't know* | 11.76 % | *Yes, a significant hearing loss* | 5.88 % |
| *Other* | 47.05 % | *Don't know* | 11.76 % |
| **Description of tinnitus sound\*** |  | **Many everyday noises painful or bothersome** |  |
| *I perceive only one sound* | 23.53 % | *No* | 64.71 % |
| *I perceive several different sounds* | 17.65 % | *Yes* | 35.29 % |
| *The overall tone is high* | 64.71 % | **Cervical History\*** |  |
| *The overall tone is medium* | 11.76 % | *Cervical osteoarthritis* | 41.18 % |
| *The overall tone is low* | 11.76 % | *History of whiplash or cervical trauma* | 0.0 % |
| *One sound I hear resembles a pure tone* | 5.88 % | *Herniated disc* | 11.76 % |
| *One sound I hear resembles a whistling* | 52.94 % | *Cervical discopathy* | 5.88 % |
| *One sound I hear resembles a buzzing* | 17.65 % | *Scoliosis* | 5.88 % |
| *One sound I hear seems melodious* | 0.0 % | *Kyphosis / kyphotic posture* | 0.0 % |
| *One sound I hear resembles crickets* | 23.53 % | *Surgical intervention at the cervical level* | 11.76 % |
| *One sound I hear resembles a background noise* | 11.76 % | *Other* | 0.0 % |
| *One sound I hear resembles a hissing* | 29.41 % | *No history to declare* | 41.18 % |
| *Other* | 11.76 % | **Migraines or headaches** |  |
| **Tinnitus localisation (most of the time)** |  | *Almost never* | 58.82 % |
| *On both sides?* | 29.41 % | *Rarely* | 11.76 % |
| *On both sides but more to the left?* | 17.65 % | *Sometimes* | 23.53 % |
| *On both sides but more to the right?* | 17.65 % | *Often* | 0.00 % |
| *Exclusively to the right?* | 11.76 % | *Don't know* | 5.88 % |
| *Exclusively to the left?* | 11.76 % | **Feeling of ear fullness or plugged ears** |  |
| *In your head?* | 11.76 % | *Almost never* | 64.71 % |
| **Tinnitus onset** |  | *Rarely* | 11.76 % |
| *Sudden* | 52.94 % | *Sometimes* | 0.00 % |
| *Progressive* | 47.06 % | *Often* | 5.88 % |
|  |  | *Very often* | 17.65 % |
| *(\*) For these questions, responders could select multiple answers among the proposed choices* | | | |

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| Supplementary table 2, Prospective sample symptomatologic characterisation (N = 17), Continued | | | |
| **Tinnitus variation** | **Percentage** | **Sleep symptomatologic profile** | **Percentage** |
| **Variation of Tinnitus Over Time\*** |  | **Sleep parasomnia diagnoses\*** |  |
| *From second to second without any reason* | 23.53 % | *Sleep apnea* | 23.53 % |
| *Different intensities over different days* | 70.59 % | *Narcolepsy* | 0.0 % |
| *Frequently louder upon waking* | 23.53 % | *Sleepwalking, night terror* | 0.0 % |
| *Frequently louder in the evening* | 11.76 % | *Hypersomnia* | 0.0 % |
| *No tinnitus variation or negligible* | 0.0 % | *Behavioral disorder during REM sleep* | 0.0 % |
| *Other* | 0.0 % | *Restless legs syndrome* | 0.0 % |
| **Variation of Tinnitus with Movements\*** |  | *Bruxism (teeth grinding during sleep)* | 11.76 % |
| *When you clench your teeth* | 23.53 % | *No* | 58.82 % |
| *Mouth opening with resistance* | 35.29 % | *Other* | 0.0 % |
| *Jaw protrusion with resistance* | 23.53 % | **Effect of Sleeping Position on Tinnitus\*** |  |
| *Jaw diduction with resistance (left)* | 23.53 % | *Increase, when on my back* | 5.88 % |
| *Jaw diduction with resistance (right)* | 23.53 % | *Increase, when on the left side* | 0.0 % |
| *Head rotation (left or right)* | 11.76 % | *Increase, when on the right side* | 5.88 % |
| *Head rotation with resistance (left or right)* | 29.41 % | *Increase, when on my stomach* | 0.0 % |
| *Lowering the head* | 11.76 % | *Increase, when I sleep in a seated position* | 0.0 % |
| *Lower the head with resistance* | 29.41 % | *Decrease, when on my back* | 0.0 % |
| *Tilting the head backward* | 0.0 % | *Decrease, when on the left side* | 5.88 % |
| *Tilting the head backward with resistance* | 17.65 % | *Decrease, when on the right side* | 0.0 % |
| *None of the above* | 52.94 % | *Decrease, when on my stomach* | 0.0 % |
| **Loud sounds increase tinnitus** |  | *Decrease, when I sleep in a seated position* | 5.88 % |
| *No* | 47.06 % | *No influence of position on my tinnitus* | 88.24 % |
| *Yes* | 35.29 % | **Average hours of sleep per night** |  |
| *Don't know* | 17.65 % | *Less than 6 hours per night* | 11.76 % |
| **Other sources of tinnitus variation\*** |  | *Between 6 to 8 hours* | 88.24 % |
| *Driving or when in a car* | 23.53 % | *More than 8 hours per night* | 0.0 % |
| *Stress or anxiety* | 47.06 % | **Difficulty falling asleep or staying asleep** |  |
| *When tired or very tired* | 29.41 % | *No* | 70.95 % |
| *When I drink alcohol* | 29.41 % | *Yes, in staying asleep* | 17.65 % |
| *When I drink coffee* | 5.88 % | *Yes, in falling asleep* | 5.88 % |
| *When I take certain medications* | 0.0 % | *Yes, both* | 5.88 % |
| *When I use hearing aids* | 11.76 % | **Snoring** |  |
| *After exertion or sports* | 17.65 % | *Yes* | 64.71 % |
| *Pressing on the head, neck or near the ear* | 17.65 % | *No* | 23.53 % |
| *Other* | 5.88 % | *Don't know* | 11.76 % |
| *None of these situations* | 35.29 % |  |  |
| *(\*) For these questions, responders could select multiple answers among the proposed choices* | | | |

*Supplementary Table 2 – Prospective sample symptomatologic characterization N=17*



*Supplementary figure 1 – Comparison of tinnitus loudness as measured by Visual Numerical Scale on tinnitus Loudness (VNS-L, x-axis) and Minimum Masking Level (MML, measured in dB, y-axis) for the 7 patients that were equipped with a MP4 device to assess their MML during the data collection period of the protocol. All patients displayed a strong correlation between VNS-L and MML measurements.*



*Supplementary figure 2 – Comparison between sleep duration (in hours) extracted from sleep diaries (x-axis) and from Circular Ring sleep tracker (y-axis) for the 4 patients that were equipped with a Circular Ring device during the data collection period of the protocol. Patients 0 and 4 displayed a significant Spearman correlation between sleep duration sources, for patients 1 and 2, correlation was not significant (respectively, p = 0.059 and p = 0.075).*

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| Supplementary table 2, Prospective sample exhibits a specific significant 2.5-4.5 days rhythmicity for tinnitus intrusiveness (N=17) and minimum masking levels rhythmicity (N =7) | | | | | | | | | | | | |
| **Subject code** | **Sex** | Visual Numerical Scale on tinnitus intrusiveness | | | | | | Minimum Masking Level | | | | |
| **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** | **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** |
| #1 | M | 75 | 4.42 | 0.87 | 0.989 | 0.77 |  | |  |  |  |  |
| #2 | M | 27 | 2.58 | 0.898 | 0.996 | 0.837 |  | |  |  |  |  |
| #3 | F | 132 | 3.67 | p < 0.001 | 0.961 | 0.36 |  | |  |  |  |  |
| #4 | M | 113 | 2.75 | 0.036 | 0.914 | 0.992 | 113 | | 2.75 | 0.038 | 0.782 | 0.992 |
| #5 | F | 79 | 3.75 | 0.007 | 0.999 | 0.064 |  | |  |  |  |  |
| #6 | F | 83 | 4.33 | 0.41 | 0.944 | 0.684 | 83 | | 3.92 | 0.195 | 0.877 | 0.77 |
| #7 | M | 87 | 3.5 | 0.784 | 1.0 | 0.034 | 87 | | 3.33 | 0.872 | 1.0 | 0.073 |
| #8 | F | 114 | 4.17 | 0.004 | 0.996 | 0.135 |  | |  |  |  |  |
| #9 | M | 239 | 3.67 | 0.061 | 1.0 | 0.145 | 239 | | 2.92 | 0.072 | 1.0 | 0.147 |
| #10 | M | 169 | 2.83 | 0.422 | 1.0 | 0.01 | 169 | | 2.92 | 0.011 | 1.0 | 0.01 |
| #11 | M | 104 | 2.83 | p < 0.001 | 1.0 | 0.996 | 104 | | 2.83 | p < 0.001 | 1.0 | 0.938 |
| #12 | M | 91 | 3.08 | p < 0.001 | 0.977 | 0.476 | 91 | | 3.08 | p < 0.001 | 0.964 | 0.228 |
| #13 | F | 86 | 3.33 | 0.992 | 0.994 | 0.998 |  | |  |  |  |  |
| #14 | M | 79 | 3.33 | 0.97 | 0.255 | 0.688 |  | |  |  |  |  |
| #15 | M | 69 | 2.5 | 0.992 | 0.277 | 0.996 |  | |  |  |  |  |
| #16 | M | 112 | 2.75 | 0.473 | 0.312 | 0.328 |  | |  |  |  |  |
| #17 | M | 104 | 4.33 | 0.545 | 0.997 | 0.796 |  | |  |  |  |  |
| *Abbreviations : freq : frequency, std : Standard Deviation* | | | | | | | | | | | | |

*Supplementary Table 3 – Individual summary of the rhythmicity analysis for subjective tinnitus intrusiveness, measured through Visual Numeric Scale on tinnitus intrusiveness (VNS-I, N=17), and of Minimum masking level measured with mp4 devices (N=7) on the prospective sample. From left to right : Subject ID, gender, then for VNS-I and then MML: 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). Holm-corrected Stouffer p-value combination for the 3 frequency bands were respectively p = 0.0019, p=1.0 and p=1.0 for VNS-I and p < 0.001, p=1.0 and p=1.0 for MML.*

**Morning questionnaire**

Hello, in order to improve the quality of the results of the study, please fill in the questionnaire every morning during the period indicated by the coordinator.

What is your patient code (e.g. 5HW17, sent to you by e-mail)?

**Subjective measures of tinnitus:**

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

* 0 (I can't hear it)
* 1
* 2
* 3
* 4
* 5
* 6
* 7
* 8
* 9
* 10 (maximum imaginable loudness)

Currently, on a scale of 0 to 10, how bothersome is your tinnitus?

* 0 (They don't bother me at all)
* 1
* 2
* 3
* 4
* 5
* 6
* 7
* 8
* 9
* 10 (maximum discomfort imaginable)

**Sleep diary :**

What time did you go to bed last night? (HH:MM)

What time did you fall asleep last night? (HH:MM)

What time did you wake up this morning? (HH:MM)

What time did you get out of bed this morning? (HH:MM)

If you woke up in the middle of the night, please write for each wake-up: time of waking, intensity of tinnitus between 0 and 10 during this wake-up, time of going back to sleep.

How would you describe the quality of your sleep? [SHORT FREE TEXT]

How would you describe the quality of your awakening? [SHORT FREE TEXT]

How did you feel when you woke up this morning? [SHORT FREE TEXT]

OPTIONAL: Do you have any particular events or comments to report? [LONG FREE TEXT]

Thank you and have a nice day!  
*Supplementary Figure 3 – Morning daily tinnitus and sleep assessment.*

**Evening questionnaire**

To improve the quality of the results, we ask you to fill in the questionnaire every evening shortly before going to bed during the period indicated by the coordinator.

What is your patient code (e.g. 5HW17, sent to you by e-mail)?

**Subjective tinnitus measurements:**

* 0 (I can't hear it)
* 1
* 2
* 3
* 4
* 5
* 6
* 7
* 8
* 9
* 10 (maximum imaginable loudness)

Currently, on a scale of 0 to 10, how bothersome is your tinnitus?

* 0 (They don't bother me at all)
* 1
* 2
* 3
* 4
* 5
* 6
* 7
* 8
* 9
* 10 (maximum discomfort imaginable)

Did you nap or sleep briefly today? If so, please specify the time, duration and whether there was any change in intensity (score between 0 and 10 before and after).

Thank you and good night!

*Supplementary Figure 4 – Evening daily tinnitus and sleep assessment.*

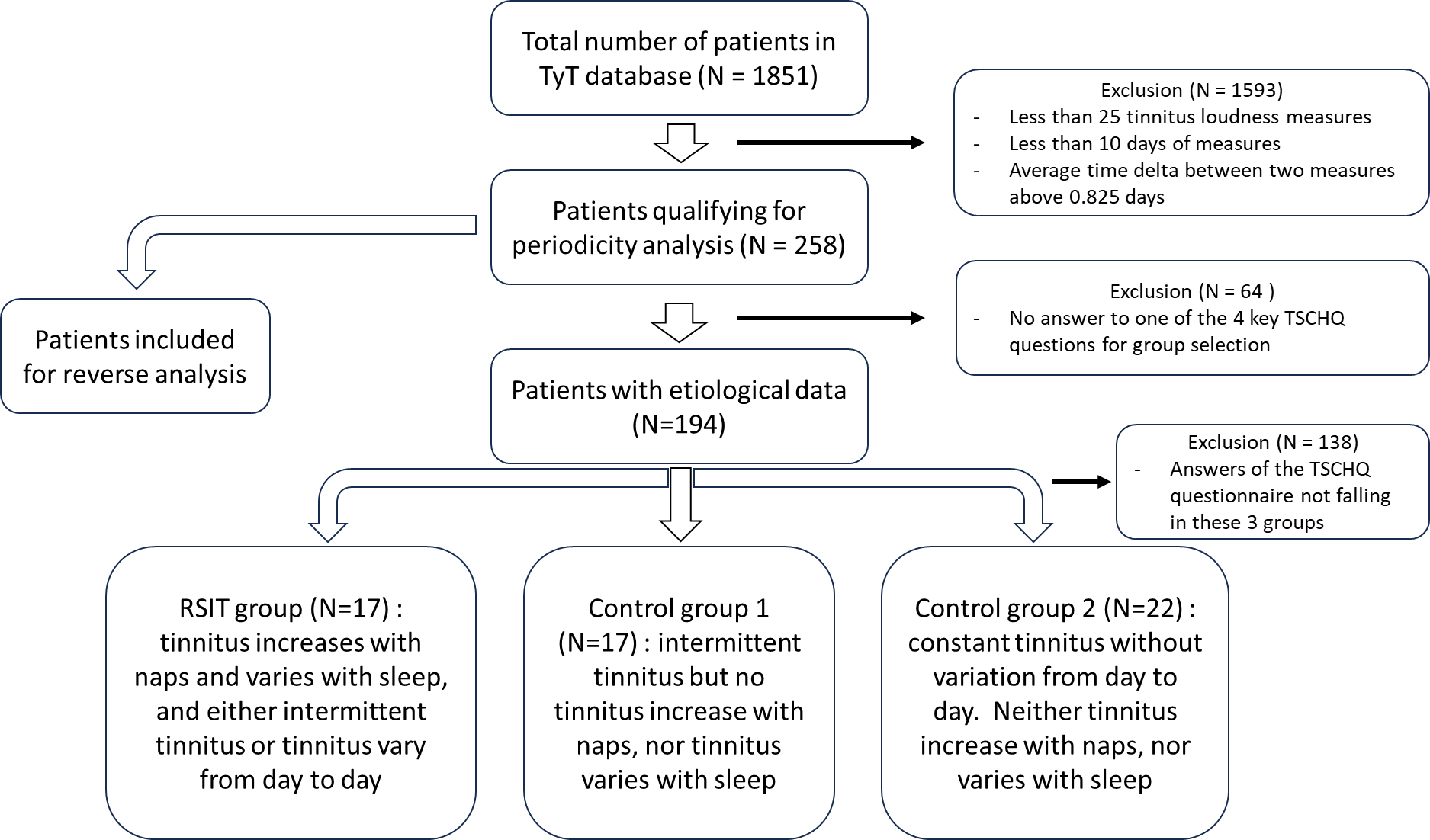
***Chapter 2: Complementary information on the retrospective cohort from TrackYourTinnitus Database:***

Retrospective sample group selection flowchart

Supplementary Figure 5 is a flowchart that summarizes the selection procedure for the attribution of patients to each group (RSIT, Control groups 1 & 2) as well as for the reverse symptomatologic analysis (detailed hereafter).

Detailed symptomatologic characterization of the retrospective samples

Supplementary Tables 4 and 5 presents the etiological characteristics of each group of the retrospective sample similarly to the prospective sample.



*Supplementary Figure 5 -- Retrospective sample group selection flowchart. Step by step filtering of the TrackYourTinnitus (Tyt) database to obtain the 3 groups for the rhythmicity analysis and the reverse analysis group.*

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| --- | --- | --- | --- | --- | --- |
| Supplementary table 4, Retrospective sample characteristics for quantitative features | | | | | |
| **Mean** | **Characteristic** | **Mean** | **Std** | **Min** | **Max** |
| RSIT (N=17) | Age (in years) | 54.98 | 7.93 | 41.39 | 65.5 |
| Tinnitus duration (in years) | 6.1 | 6.57 | 0.08 | 20.85 |
| Mini TQ score (0-24) | 14.35 | 4.12 | 8.0 | 23.0 |
| Initial Tinnitus loudness (0 to 1) | 0.57 | 0.28 | 0.11 | 1.0 |
| Initial Tinnitus stressfullness (0 to 1) | 0.54 | 0.3 | 0.0 | 1.0 |
| Control group 1 (N=17) | Age (in years) | 53.22 | 10.45 | 35.01 | 69.29 |
| Tinnitus duration (in years) | 8.86 | 9.25 | 0.09 | 30.78 |
| Mini TQ score (0-24) | 9.94 | 4.56 | 3.0 | 19.0 |
| Initial Tinnitus loudness (0 to 1) | 0.36 | 0.23 | 0.04 | 0.9 |
| Initial Tinnitus stressfullness (0 to 1) | 0.28 | 0.26 | 0.0 | 0.87 |
| Control group 2 (N=22) | Age (in years) | 56.68 | 13.87 | 26.42 | 77.98 |
| Tinnitus duration (in years) | 18.74 | 17.44 | 0.1 | 65.09 |
| Mini TQ score (0-24) | 9.95 | 7.26 | 0.0 | 24.0 |
| Initial Tinnitus loudness (0 to 1) | 0.53 | 0.25 | 0.2 | 1.0 |
| Initial Tinnitus stressfullness (0 to 1) | 0.38 | 0.29 | 0.0 | 1.0 |
| *Abbreviations : VNS : Visual Numeric Scale* | | | | | |

*Supplementary Table 4 – Retrospective sample symptomatologic characterization for quantitative features (RSIT N=17, Control group 1: N=17, Control group 2 : N=22). Abbreviations : VNS : Visual Analog Scale.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Supplementary table 5, Retrospective sample symptomatologic characterization | | | | | | | | |
| **Tinnitus characteristics** | **RSIT (N=17)** | **Control group 1 (N=17)** | **Control group 2 (N=22)** | **Tinnitus commorbidities** | **RSIT (N=17)** | **Control group 1 (N=17)** | **Control group 2 (N=22)** |
| **Assumed cause of tinnitus** |  |  |  | **Self-presumed hearing loss** |  |  |  |
| *Exposure to loud sounds* | 5.88 % | 5.88 % | 4.54 % | *No* | 52.94 % | 62.5 % | 50.0 % |
| *Changes in hearing* | 5.88 % | 5.88 % | 13.63 % | *Yes* | 41.17 % | 25.0 % | 50.0 % |
| *Episode of stress* | 47.05 % | 23.52 % | 18.18 % | *I don't know* | 5.9 % | 12.5 % | 0.0 % |
| *Head trauma* | 0.0 % | 0.0 % | 4.54 % | **Some noises are painful** |  |  |  |
| *Trauma to the neck (e.g., whiplash)* | 0.0 % | 0.0 % | 0.0 % | *No* | 41.18 % | 43.75 % | 72.73 % |
| *Other* | 41.17 % | 64.7 % | 59.09 % | *Yes* | 41.18 % | 37.50 % | 18.18 % |
| **Description of tinnitus sound** |  |  |  | *I don't know* | 17.64 % | 18.75 % | 9.09 % |
| *One sound I hear resembles a pure tone* | 64.71 % | 70.59 % | 59.09 % | **Cervical pain** |  |  |  |
| *One sound I hear resembles crickets* | 0.0 % | 11.76 % | 27.27 % | *No* | 58.82 % | 87.5 % | 77.27 % |
| *One sound I hear resembles a background noise* | 23.52 % | 11.76 % | 13.64 % | *Yes* | 41.18 % | 12.50 % | 22.73 % |
| *Other* | 11.76 % | 5.88 % | 0.0 % | **Migraines or headaches** |  |  |  |
| **Pitch of tinnitus sound** |  |  |  | *No* | 76.47 % | 93.75 % | 81.82 % |
| *The overall tone is very high* | 29.41 % | 41.18 % | 40.91 % | *Yes* | 23.53 % | 6.25 % | 18.18 % |
| *The overall tone is high* | 52.94 % | 52.94 % | 54.54 % | **Diziness or vertigo** |  |  |  |
| *The overall tone is medium* | 17.65 % | 0.0 % | 4.55 % | *No* | 88.24 % | 87.5 % | 95.45 % |
| *The overall tone is low* | 0.0 % | 5.88 % | 0.0 % | *Yes* | 11.76 % | 12.50 % | 4.54 % |
| **Tinnitus localisation (most of the time)** |  |  |  | **Temporomandibular disorder** |  |  |  |
| *On both sides?* | 5.88 % | 17.64 % | 22.72 % | *No* | 64.71 % | 81.5 % | 100.00 % |
| *On both sides but more to the left?* | 35.29 % | 11.76 % | 9.09 % | *Yes* | 35.29 % | 18.75 % | 0.0 % |
| *On both sides but more to the right?* | 17.64 % | 5.88 % | 13.64 % | **Stress influence on tinnitus** |  |  |  |
| *Exclusively to the right?* | 11.76 % | 23.52 % | 18.18 % | *No effect* | 23.53 % | 41.18 % | 50.0 % |
| *Exclusively to the left?* | 17.64 % | 23.52 % | 9.09 % | *Increases tinnitus* | 76.47 % | 58.82 % | 45.45 % |
| *In your head?* | 11.76 % | 17.64 % | 27.27 % | *Reduces tinnitus* | 0.0 % | 0.0 % | 4.54 % |
| **Tinnitus onset** |  |  |  | **Loud sounds increase tinnitus** |  |  |  |
| *Sudden* | 70.59 % | 58.82 % | 45.45 % | *No* | 29.41 % | 41.18 % | 45.45 % |
| *Progressive* | 29.41 % | 41.18 % | 54.54 % | *Yes* | 52.94 % | 17.65 % | 31.82 % |
| **Pulsatile tinnitus** |  |  |  | *Don't know* | 17.65 % | 41.18 % | 22.72 % |
| *No* | 94.12 % | 82.35 % | 90.91 % | **Tinnitus varies with neck / jaw movements** |  |  |  |
| *Yes, Different from heartbeat* | 5.88 % | 11.76 % | 9.09 % | *No* | 35.29 % | 70.59 % | 72.73 % |
| *Yes with heart beat* | 0.0 % | 5.88 % | 0.0 % | *Yes* | 65.71 % | 29.41 % | 27.27 % |

*Supplementary Table 5 – Retrospective sample symptomatologic characterization for all three groups (RSIT : N=17, Control group 1: N=17, Control group 2: N=22).*

***Chapter 3: Etiological presentation and rhythmicity analysis of a third SIT sample (retrospective data):***

With the objective to replicate the results we obtained in our prospective cohort, we gathered retrospective data from a third cohort of SIT patients. This third cohort is composed of retrospective data from patients that did not wish to participate in the prospective cohort but had already compiled longitudinal tinnitus loudness diaries and accepted to share it (N=5) and from SIT patients that spontaneously collected tinnitus diaries and shared it with us since the end of the clinical trial (N=6). All the patients of this cohort participated to a clinical interview with ENT A.L. and were assessed as SIT patients. All of them shared longitudinal time series of their tinnitus loudness. All these time series comprised more than 25 time points, over at least 10 days. Some of these patients only reported their tinnitus loudness once a day. As a consequence, for the rhythmicity analysis we conducted for this sample, we adapted the size of the control frequency band 1: instead of testing time periods that varied between 1.75 and 2.5 days (frequency band between 0.4 and 0.57 days-1), we tested time periods that varied between 2 and 2.5 days (frequency band between 0.4 and 0.5 days-1).

Detailed symptomatologic characterization of this third SIT sample

This third SIT sample comprised 9 men and 2 women (age: average: 69.3 +/- 12.33). Etiological characterization of 10 of the 11 patients of this cohort could be recovered (1 missing etiological characterization documentation). Supplementary Tables 6 and 7 present the etiological characteristics of the third retrospective sample.

Tinnitus loudness rhythmicity analysis of this third SIT sample

In supplementary Table 8, we present the results of the rhythmicity analysis on the time series of the VNS on tinnitus loudness of this third SIT cohort (N=11). We followed the same statistical procedures as for the prospective and the retrospective TrackYourTinnitus database samples, with the only exception of the reduction of the width of the first control frequency band (as described above). Over the whole third SIT cohort, 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).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Supplementary table 6, Third SIT sample characteristics for quantitative features (N =11) | | | | | |
|  | **Mean** | **Std** | **Min** | **Max** |
| Age (in years) | 69,3 | 12.33 | 46 | 85 |
| Tinnitus Handicap Inventory (THI) | 50.8 | 13.95 | 24 | 66 |
| Initial VNS scale Tinnitus loudness (0 to 10) | 7.4 | 1.17 | 5 | 9 |
| Initial VNS scale Tinnitus intrusiveness (0 to 10) | 6.4 | 2.27 | 4 | 9 |
| *Abbreviations : VNS : Visual Numeric Scale* | | | | | |

*Supplementary Table 6 – Third SIT sample symptomatologic characterization for quantitative features (N=10). Abbreviations : VNS : Visual Analog Scale. THI score and initial VNS scores could not be retrieved for 1 patient of this cohort.*

|  |  |  |  |
| --- | --- | --- | --- |
| Supplementary table 7, Third SIT sample symptomatologic characterization (N=10) | | | |
| **Tinnitus characteristics** | **RSIT2 (N=8)** | **Tinnitus commorbidities** | **RSIT2 (N=8)** |
| **Assumed cause of tinnitus** |  | **Self-presumed hearing loss** |  |
| *Exposure to loud sounds* | 10.0 % | *No* | 50.0 % |
| *Changes in hearing* | 10.0 % | *Yes* | 50.0 % |
| *Episode of stress* | 30.0 % | *I don't know* | 0.0 % |
| *Head trauma* | 0.0 % | **Some noises are painful** |  |
| *Trauma to the neck (e.g., whiplash)* | 0.0 % | *No* | 30.0 % |
| *Other* | 50.0 % | *Yes* | 70.0 % |
| **Pitch of tinnitus sound** |  | *I don't know* | 0.0 % |
| *The overall tone is high* | 90.0 % | **Cervical pain** |  |
| *The overall tone is medium* | 0.0 % | *No* | 50.0 % |
| *The overall tone is low* | 10.0 % | *Yes* | 50.0 % |
| **Tinnitus localisation (most of the time)** |  | **Migraines or headaches** |  |
| *On both sides?* | 20.0 % | *No* | 70.0 % |
| *On both sides but more to the left?* | 30.0 % | *Yes* | 30.0 % |
| *On both sides but more to the right?* | 20.0 % | **Temporomandibular disorder** |  |
| *Exclusively to the right?* | 0.0 % | *No* | 80.0 % |
| *Exclusively to the left?* | 10.0 % | *Yes* | 20.0 % |
| *In your head?* | 20.0 % | **Loud sounds increase tinnitus** |  |
| **Tinnitus onset** |  | *No* | 50.0 % |
| *Sudden* | 50.0 % | *Yes* | 40.0 % |
| *Progressive* | 50.0 % | *Don't know* | 10.0 % |
| **Pulsatile tinnitus** |  | **Tinnitus varies with neck/jaw movements** |  |
| *No* | 90.0 % | *No* | 80.0 % |
| *Yes, Different from heartbeat* | 0.0 % | *Yes* | 20.0 % |
| *Yes with heart beat* | 10.0 % |  |  |

*Supplementary Table 7 – Third SIT sample symptomatologic characterization (N=9, one missing data).*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Supplementary table 8, Third SIT sample exhibits a specific significant 2.5-4.5 days rhythmicity (N =11) | | | | | | |
| **Subject code** | **Sex** | **Number of time points** | **Peak period test freq band** | **P-value test freq band** | **P-value for ADJUSTED control freq band 1\*** | **P-value control freq band 2** |
| #3-1 | M | 55 | 3.0 | 0.002 | 0.98 | 0.957 |
| #3-2 | M | 38 | 2.83 | 0.001 | 0.987 | 0.881 |
| #3-3 | M | 75 | 3.0 | 0.81 | 0.93 | 0.757 |
| #3-4 | F | 181 | 4.08 | 0.133 | 1.0 | 0.974 |
| #3-5 | M | 174 | 3.33 | 0.296 | 1.0 | 1.0 |
| #3-6 | M | 39 | 2.5 | 0.94 | 0.0 | 0.949 |
| #3-7 | M | 107 | 3.5 | 0.021 | 1.0 | 0.055 |
| #3-8 | M | 73 | 2.67 | 0.033 | 1.0 | 0.913 |
| #3-9 | M | 160 | 3.0 | 0.003 | 0.999 | 0.9 |
| #3-10 | F | 122 | 2.75 | 0.13 | 0.999 | 0.994 |
| #3-11 | M | 92 | 3,67 | 0.368 | 0.999 | 0.97 |
| *Abbreviations : freq : frequency, std : Standard Deviation. \*ADJUSTED: periodicities between 2 and 2.5 days instead of between 1.75 to 2.5 days.* | | | | | | |

*Supplementary Table 8 – Individual summary of the rhythmicity analysis for subjective tinnitus loudness in the third SIT cample, measured through Visual Numeric Scale on tinnitus loudness (VNS-L). 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, Adjusted control frequency band 1 : for periods between 2 and 2.5 days, control frequency band 2 : for periods between 4.5 and 9 days). Holm-corrected Stouffer p-value combination for the 3 frequency bands were respectively p < 0.001, p=1.0 and p=1.0.*

***Chapter 4: Miscellaneous of complementary analyses:***

Tinnitus loudness levels depending on week days

As the rhythmicity analysis in the retrospective database highlighted significant rhythmicity in the control frequency band 2, accounting for periodicities between 4.5 and 9 days, one could question a potential influence of external zeitgebers which could be the alternations between working days and week-ends. To account for this potential confounding factor, for each patient we associated each of their tinnitus loudness measurement to the week day it was measured. We also calculated for each patient the overall average and standard deviation of all their tinnitus loudness measurements. Thanks to this we could calculate for each patient the distribution of Z-scores of their tinnitus intensities depending on each week days. As Z-scores enabled measurements to be standardized on the same scale for all the patient, we gathered the tinnitus intensities of all tinnitus patients depending on week days to study the whole samples together. For this purpose, we created Supplementary figures 6, 7, 8 and 9 as the display of tinnitus intensities depending on week days, for respectively the prospective cohort and the three groups of the retrospective database (RSIT, control groups 1 & 2). As for the prospective cohort we had 2 measurements per day identified specifically for the mornings and the evenings, we brought more granularity for Supplementary figure 6 with two measurements per day. We additionally performed Mann-Whitney tests to test if tinnitus loudness was different on average between classical working week days (Monday to Friday) and week-ends (Saturday and Sunday).

For the prospective cohort we did not identify a significative difference between working days and week-ends.

For the RSIT group of the retrospective database, we identified that tinnitus intensities during the weekend was significantly lower than during the working days (p < 0.001, Cohen d: 0.21).

For the control group 1 of the retrospective database (intermittent tinnitus without sleep-induced modulations), we identified that tinnitus intensities during the weekend was significantly lower than during the working days (p < 0.01, Cohen d: 0.09).

For the control group 2 of the retrospective database (constant tinnitus without day to day variations and without sleep-induced modulations), we did not identify a significative difference between working days and week-ends.

The fact that a weekly rhythmicity was present in the RSIT group of the retrospective database and not in the prospective cohort could be attributed to the difference between the average age of these two samples (Prospective sample : 61.71 +/- 13.76, RSIT : 54.98 +/- 7.93). There are probably more retired people in the prospective cohort than the RSIT group, which are hence probably more influenced by the rhythmicity between working days and weekends. It can also contribute to explain why we observed a significative rhythmicity in the control frequency band 2 (periodicities between 4.5 and 9 days) in the RSIT group and not in the prospective cohort.

Markov chain tinnitus loudness simulation

In order to demonstrate that our results may not be necessarily elicited by an internal infradian biological clock, we designed a simple simulation using Markov chains. The goal of this simulation was to illustrate that a stochastic process with memory can give the same observable results that we observed in our prospective and retrospective analyses.

To generate the simulated tinnitus loudness time series, we used Markov chains of order 2 (also called Markov chains with memory of order 2) with two states (0: “Tinnitus absent” and 1: “Tinnitus present”) to simulate an intermittent tinnitus. In such Markov chains, the future state observation depends on the past values of the last 2 observed states. In mathematical terms, we can write :

Where is the random variable following the Markov property at the state , to are all the past random variables associated with the past states to 1, and to respectively the state values these variables have taken.

To parametrize such Markov chains of order 2 with 2 states, a transition matrix A = of size 2 x 2 can be built and then the random variable follows the law:

Given a set of fixed parameters for the transition matrix A, we simulated 20 tinnitus intensities time series of 60 points (corresponding of 2 months of data reporting with 1 value per day) with initial states set as (0, 0). Supplementary Figure 10 illustrates an example of a simulated intermittent tinnitus time series with the transition matrix set to :

With these 20 simulated time series, we then went through the same statistical procedure as for the prospective and retrospective database to test the rhythmicity on the test and control frequency bands. We could then calculate a combined p-value out the individual p-values of each test. We could identify several combinations of coefficients for matrix A (including the one given in example) that enabled to obtain specific significative periodicity in the test frequency band and not in the control frequency bands.

Sleep pressure simulation from sleep diaries and correlation with tinnitus loudness

Our Markov chains simulations suggested that physiological processes with memory over several days could potentially induce periodic oscillations as observed in our results. Moreover, we observed a relation between sleep and tinnitus variations in SIT patients (more tinnitus variations during night sleep and nap sleep than during day periods without sleep). These led us to interrogate whether homeostatic sleep pressure and/or sleep debt could play a role in the observed tinnitus loudness variations. Indeed, not enough sleep for several successive days accumulates a sleep debt which translates in increased sleep pressure during wake. This increase in sleep pressure then leads to deeper sleep often designated as recovery sleep on the next sleep occurrence as a rebound effect. Such variations in sleep pressure and sleep depth depending on days could follow a rhythmic pattern as the one observed for tinnitus. Moreover, previous studies postulated that tinnitus could be mitigated by higher sleep pressure and/or higher sleep depth [1,2].

It should be noted that there are actually two types of sleep debt: the lack of deep sleep (the one commonly refered 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 processes [3–5].

In the current study, we did not perform polysomnographic measurements of our participants, we only could use sleep diaries measures. As a consequence, we could only model deep sleep homeostatic pressure and test if it could be correlated with tinnitus loudness levels.

*First model : two process model adapted from Borbely and Achermann (1999):*

To perform this analysis, we first derived from the sleep diaries of each participant of the prospective cohort a time series with 0.1 day time step indicating if the participant was awake or asleep (0 or 1). This simulation included the declarations of sleep onset and morning awakenings of the participant as well as the initiation and the end of each nocturnal awakenings. Naps during the day could not be included in the analysis as their report often missed associated durations or hours of initiations. From this awake/asleep time series were derived individual simulations of sleep pressure through time, using the model and associated parameters proposed in [6]. Each sleep pressure signal was initialized at the value 0.1 at the first declared morning awakening by each individual.

Data collection periods for sleep diaries sometimes included missing data. When the information of the sleep onset and the awakening of one day were not known, the sleep pressure simulation was interrupted and reset at the value 0.1 at the next occurrence of a declared morning awakening.

With these individual simulations of sleep pressure with 0.1 day time step precision we could associate each tinnitus loudness measurement with an associated sleep pressure simulated value. This enabled to perform individual correlation analyses between sleep pressure and tinnitus loudness. An example of such simulated sleep pressure time series and associated tinnitus loudness levels is displayed as Supplementary Figure 10.

We performed 2 analyses: we tested individual signed Spearman correlations between tinnitus loudness level and sleep pressure at awakenings (nocturnal and morning awakenings) time points and at sleep onset time points. We then concluded at the level of the whole sample by applying a Fisher p-value combination method.

We observed a significative negative correlation between sleep pressure at nocturnal and morning awakenings and associated tinnitus loudness levels (p < 0.001). This correlation was not observed at sleep onset.

The fact that the observed correlation is negative means that overall participants of the prospective cohort reported that their tinnitus was lower when they woke with a high sleep pressure. Although this result can first appear counter-intuitive, it aligns with the report of tinnitus patients that they more often observe absence of tinnitus during nocturnal awakenings than during morning awakenings [7]. Moreover, it aligns with the hypothesis proposed in past studies that slow waves during sleep could potentially interfere with tinnitus and mitigate it. Indeed, waking up with a high sleep pressure means higher chance of waking up from a sleep containing slow wave sleep. In such cases, slow waves can still be present in the brain activity despite the subject being awake, this phenomenon, which translates in dizziness and confusion, is often referred as sleep inertia [8,9] and is common during nocturnal awakenings and awakening from long naps.

We could also argue that the correlation between sleep pressure and tinnitus loudness was not found significative at the time of sleep onset as sleep pressure probably accounts for a part of the causes that can modulate tinnitus for these patients, in addition to additional factors such as sound exposition, somatosensory modulation, stress modulation [10] that they may or may not have experienced during their day before sleep onset. On the contrary, the advantage with awakening measurements of tinnitus is that we know patients were not engaged in any other activity than sleep before the tinnitus loudness level measurement.

These analyses could not be conducted in the retrospective database sample as this database did not include longitudinal sleep diaries.

*Limits of the Two-Process model:*

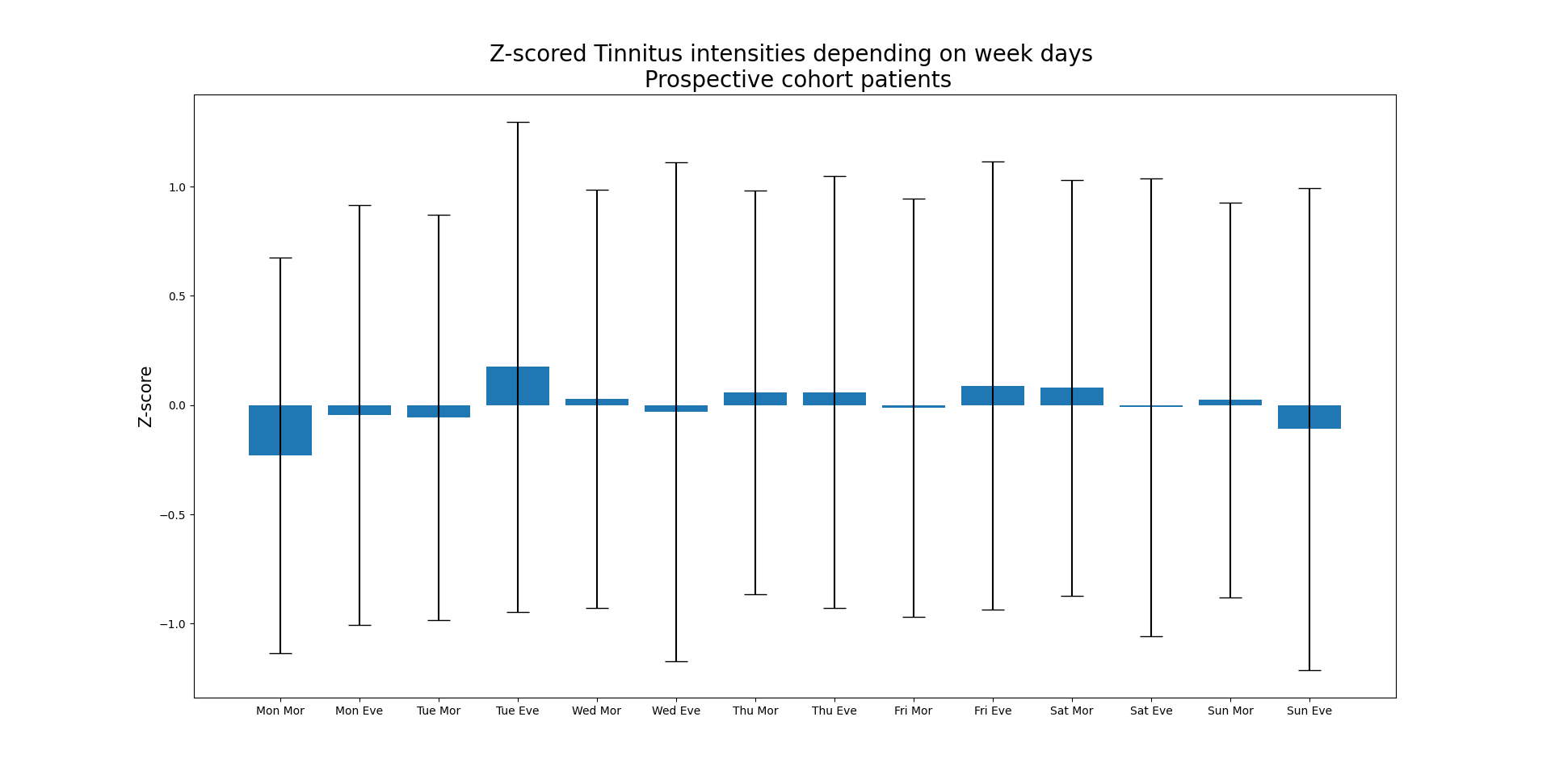
An important limit of the Two-Process model regarding our objective is that it does not accurately account for the accumulation of chronic sleep debt over several days. Indeed, the sleep homeostat tends to come back to the same values each morning and each night. This model has been shown to be efficient when it comes to model acute sleep deprivation but it has shown limits when it comes to model chronic sleep restriction. This is why more recent models were put in place to account for this discrepancy. It motivated us to continue our work to create a second model for chronic sleep debt, the Unified model [11].

*Second model: Unified Model (Rajdev, 2013):*

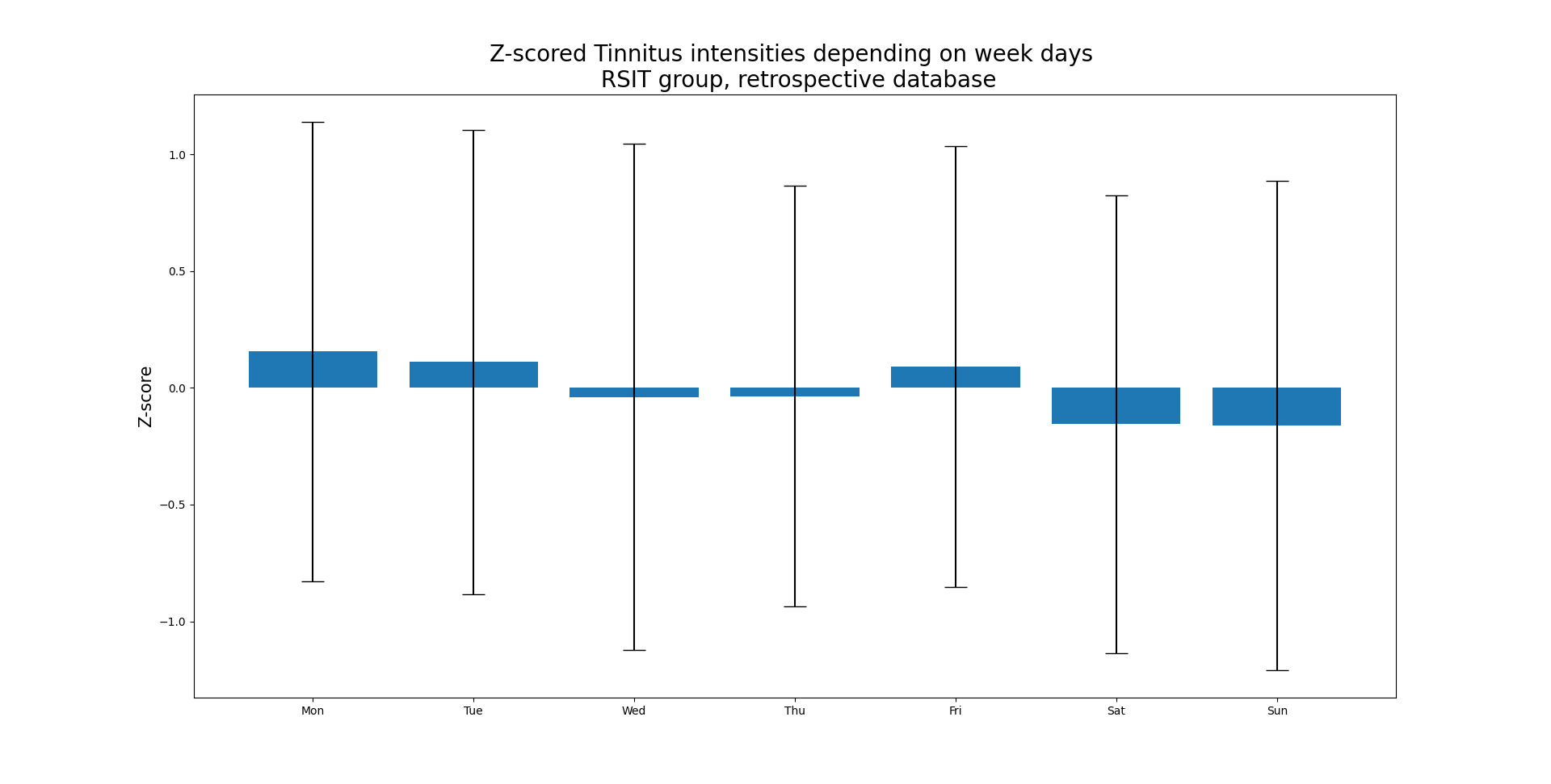
In this model, two variables are created out of sleep diary inputs: a sleep homeostat (in the same sense as for the two-process model) and sleep debt signal, that is supposed to be representative of the accumulation of sleep debt over multiple days. This model requires to introduce more parameters, which we set according to the recommendations presented in their study [11], as well as for the initialization values. In their study, they made the hypothesis that the sleep need of each individual was systematically of 8h, although it can be different from one individual to another. For this reason, as we had the estimated sleep duration for all participants for multiple nights, we defined sleep need as the average sleep duration over all the night we recorded.

We performed individual simulations of sleep pressure through this model with 0.1 day time step precision and associated each tinnitus loudness measurement with an associated sleep pressure and chronic sleep debt simulated value. This enabled to perform individual correlation analyses between sleep pressure, sleep debt and tinnitus loudness. An example of such simulated sleep pressure time series and associated tinnitus loudness levels is displayed as Supplementary Figure 8.

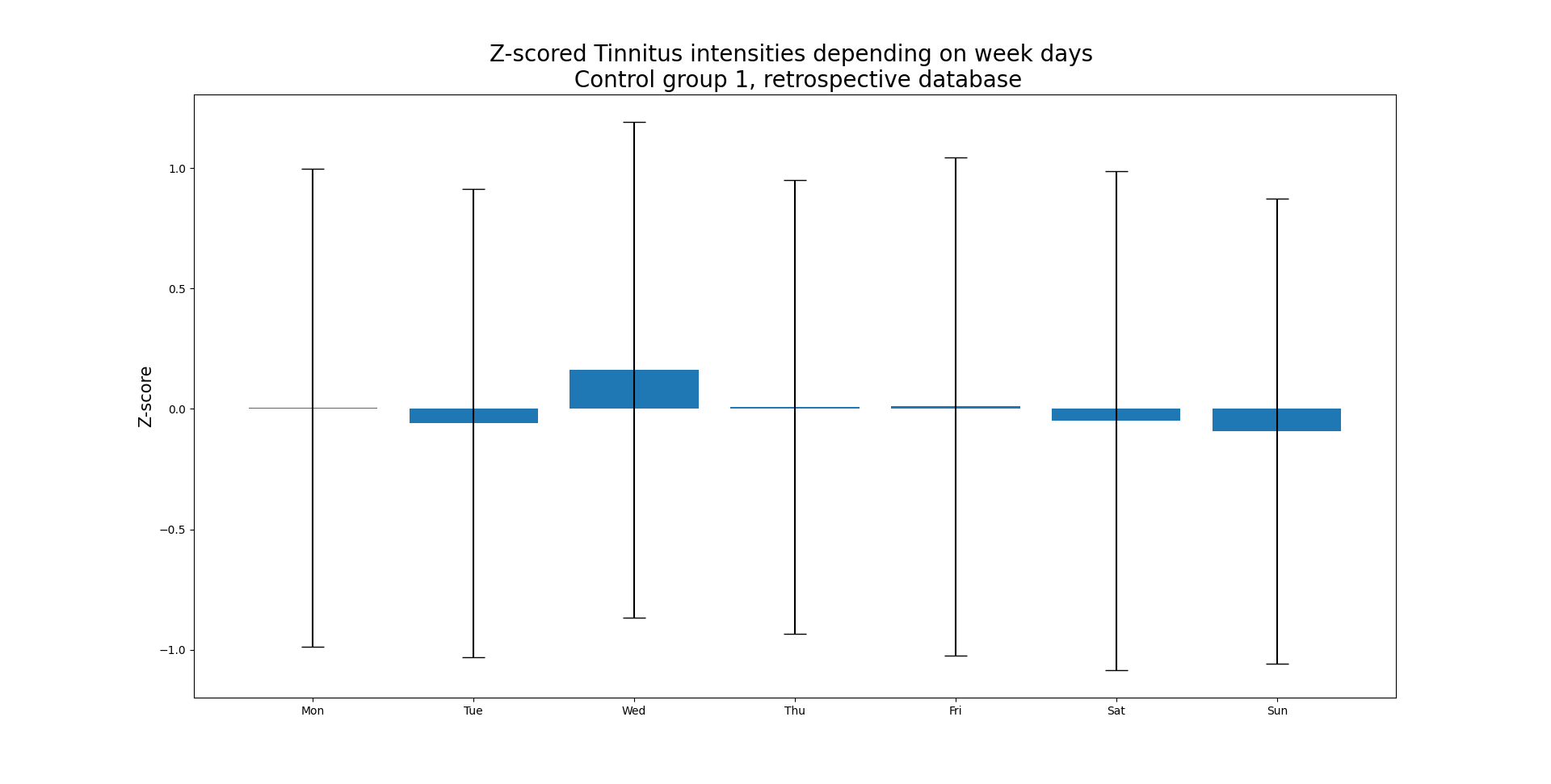
We then performed individual signed Spearman correlations between tinnitus loudness level and sleep pressure and sleep debt at awakenings (nocturnal and morning awakenings) time points and at sleep onset time points, as we did for the first model (two-process model). We then concluded at the level of the whole sample by applying a Fisher p-value combination method. At group level, none of the tests we conducted was found significant.



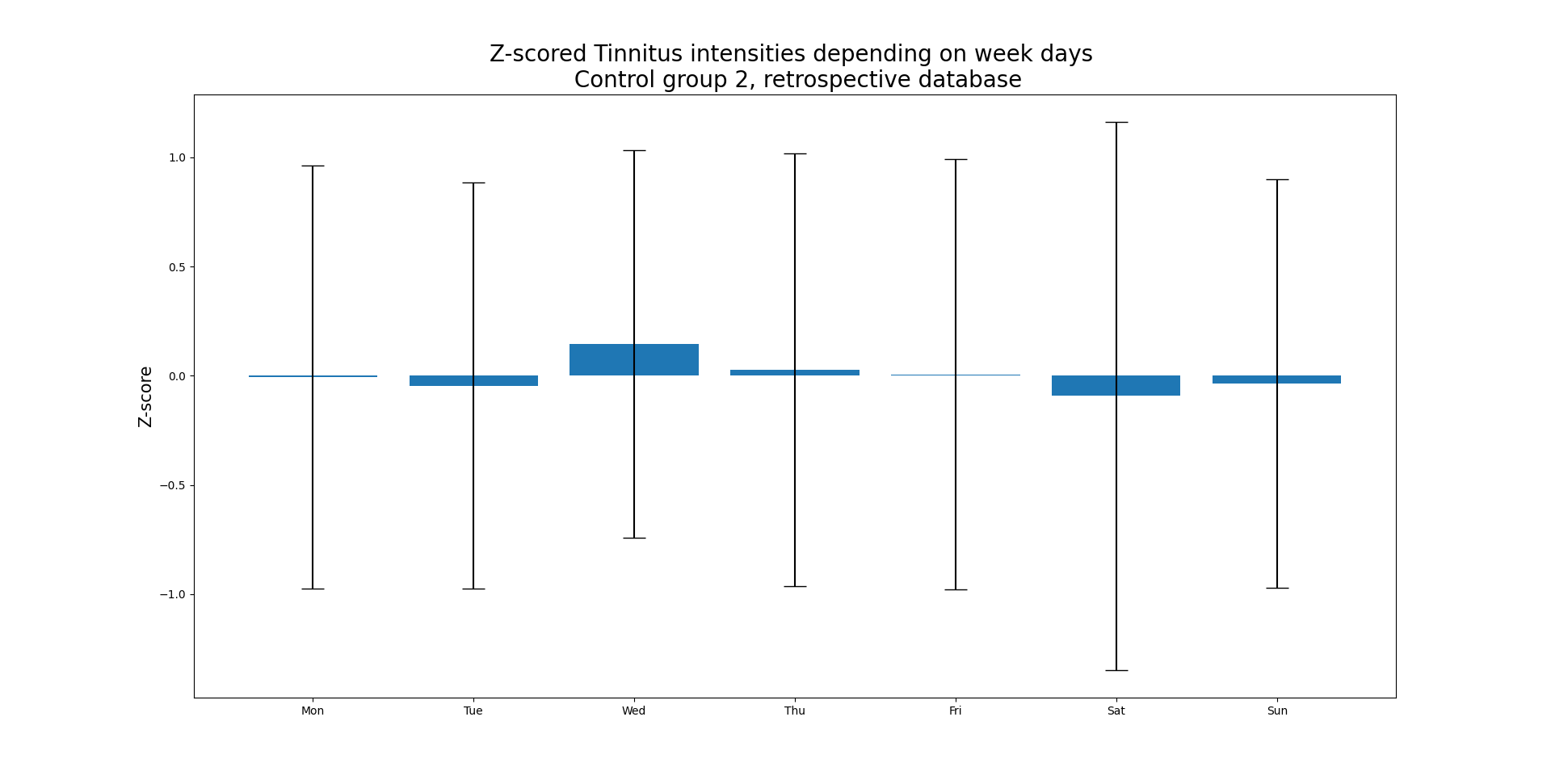
*Supplementary figure 6 – Z-scored tinnitus loudness levels depending on week days for the prospective sample. As participants measured tinnitus each morning and each evening, week days loudness was reported twice for each day, once the morning and once the evening.*



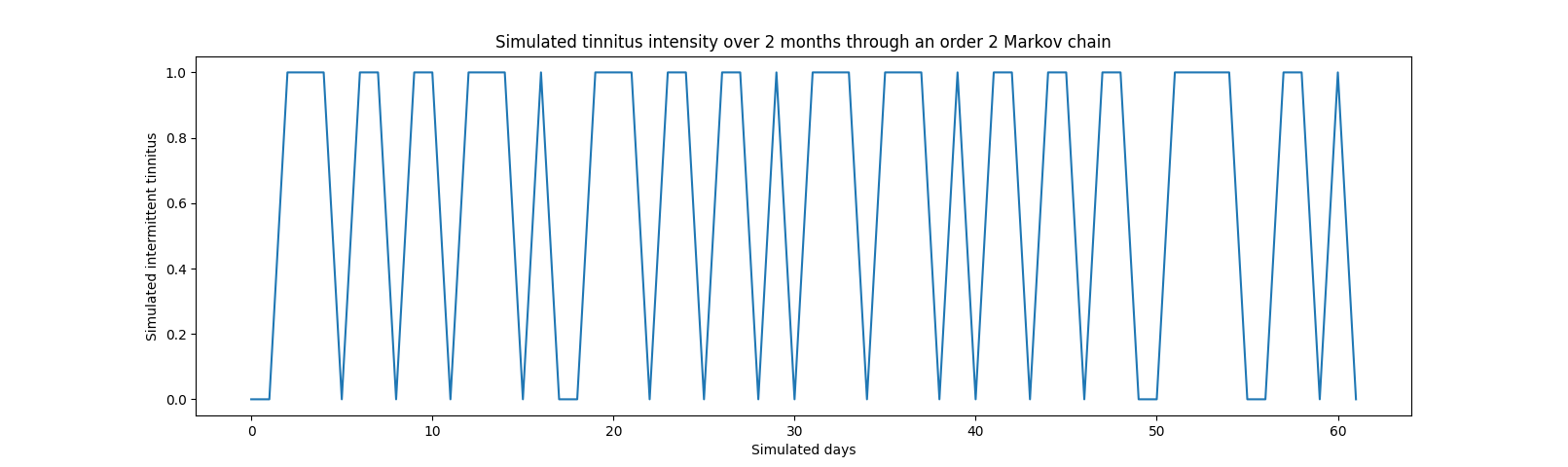
*Supplementary figure 7 – Z-scored tinnitus loudness levels depending on week days for the RSIT group of the retrospective sample.*



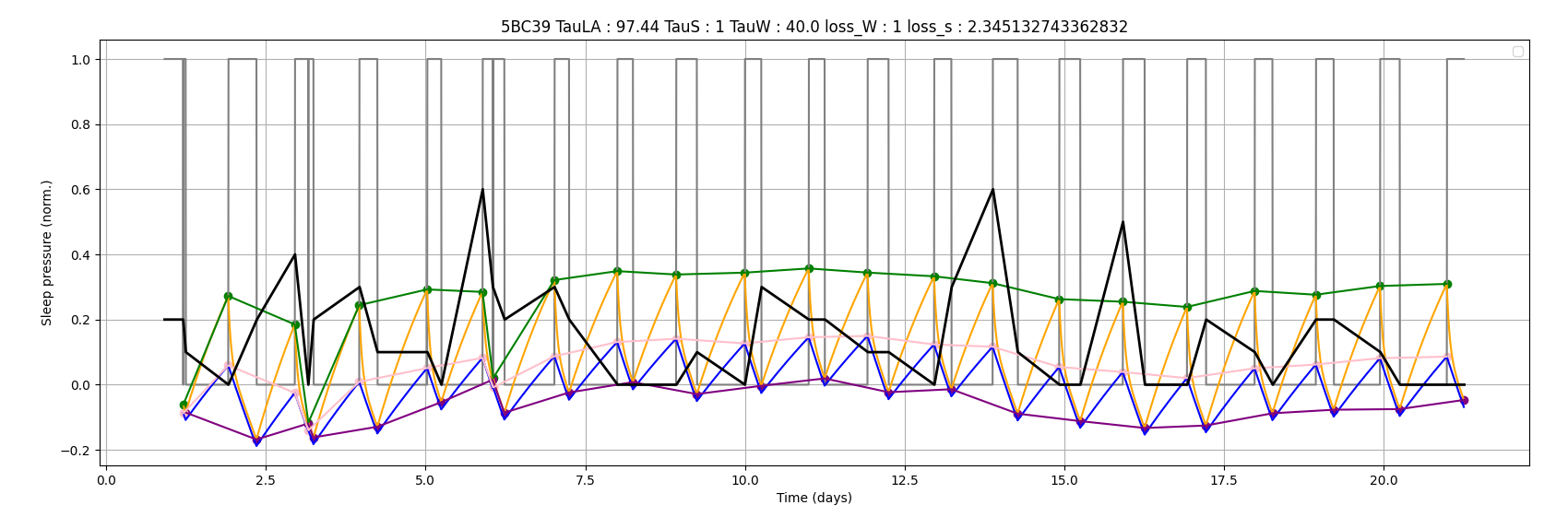
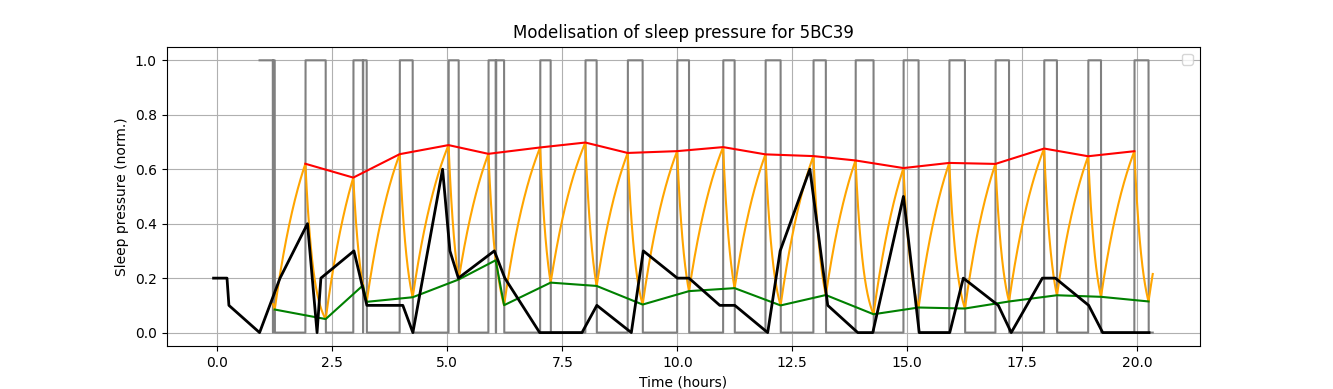
*Supplementary figure 8 – Z-scored tinnitus loudness levels depending on week days for the control group 1 of the retrospective sample (group with intermittent tinnitus without sleep-induced modulations).*



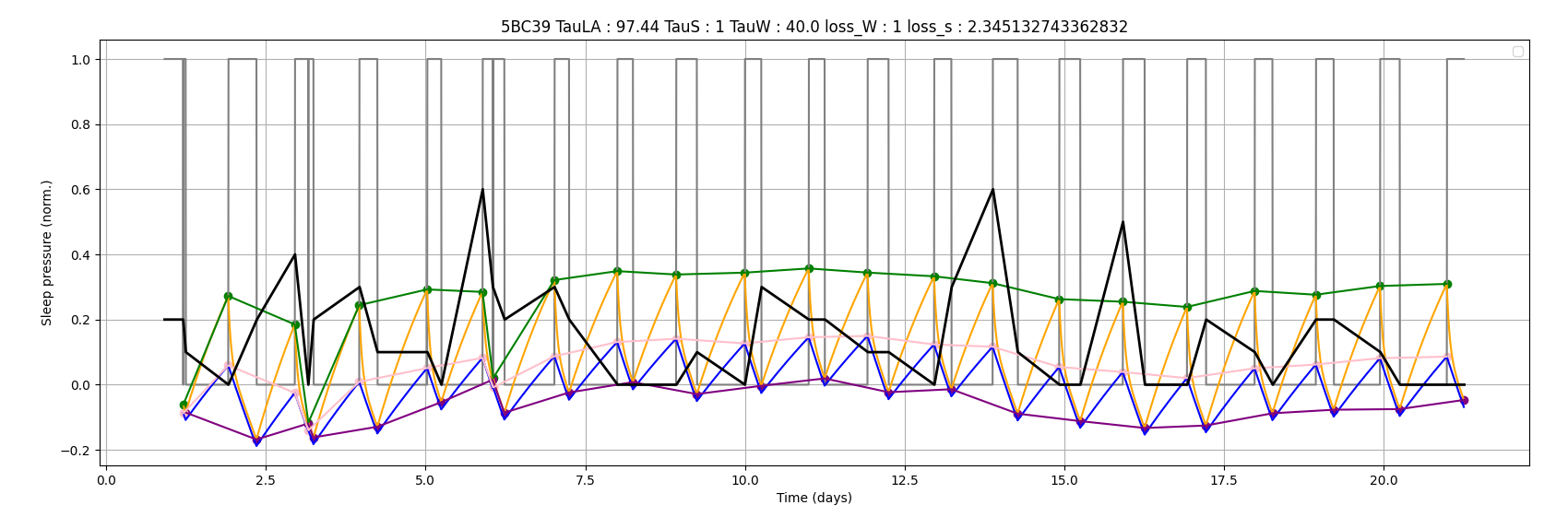
*Supplementary figure 9 – Z-scored tinnitus loudness levels depending on week days for the control group 2 of the retrospective sample (group with constant tinnitus without sleep-induced modulations).*



*Supplementary figure 10 – Example of a simulated intermittent tinnitus time series through an order 2 Markov chain process with the transition matrix set to*



*Supplementary figure 11 – Two-process model simulation for a given patient. The x-axis represents time in days. In grey, the sleep/wake signal, 0 meaning awake, 1 meaning asleep. In orange, the sleep pressure signal obtained through the application of the Two-process model* [6]*. In green and red, the envelope of the signal, corresponding to the awakening and sleep onset times. In black, tinnitus loudness, represented as the series of VNS values scaled down by a factor 10 to match a range between 0 and 1.*



*Supplementary figure 12 – Unified model simulation for the same patient as Supplementary figure 11. The x-axis still represents time in days. In grey, the sleep/wake signal, 0 meaning awake, 1 meaning asleep. In orange, the sleep pressure signal and in blue the chronic sleep debt signal, obtained through the application of the Unified model* [11]*. In green and purple, the envelope of the sleep pressure signal, corresponding to the awakening and sleep onset times. In pink the maxima envelope of the chronic sleep debt signal. The minima envelope is the same for both signals. In black, tinnitus loudness, represented as the series of VNS values scaled down by a factor 10 to match a range between 0 and 1.*

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