

Application to the Research Prize Tinnitus & Hearing of the German Tinnitus and Hearing Foundation Charité

Dear members of the Foundation committee,

I am applying to the Research Prize Tinnitus & Hearing as a postdoctoral researcher of IHU reconnect (Institut Pasteur) in Paris, France, currently in transition to start a new postdoctoral position at the Mignot Lab within Stanford University. I wish to submit to your evaluation for this prize the research manuscript “Exploring sleep intermittent tinnitus patients infradian tinnitus loudness periodicity” currently submitted to Nature Communications Medicine, for which we recently provided a rebuttal letter to our reviewers.

Research Context of the Manuscript:

At Institut IHU reConnect (associated with Institut Pasteur, Paris, France), and in close collaboration with Dr. Alain Londero, we are investigating the physiological bases of tinnitus. Over the past 18 months, our team has been investigating the complex relationship between sleep dynamics and tinnitus perception. Indeed, a specific subgroup of tinnitus patients exhibit an intriguing symptomatologic pattern. These patients report a link between the occurrence of sleep and the intermittence of their tinnitus. 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 a high tinnitus loudness immediately after waking, which can persist 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.

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 pathophysiology (Langguth et al, 2024). To date, and to our knowledge, no study has attempted to investigate objectively whether such tinnitus loudness variations are purely random or periodical. In our study, the principal objective was to test in SIT patients if a 3-4 days periodicity was present in the time course of tinnitus loudness fluctuations and/or intermittence in a prospective sample and to confirm this finding in two retrospective samples. The secondary objective was to study the relation between tinnitus loudness variations and reported sleep parameters.

Samples and methodology:

Our prospective sample comprised longitudinal data from 20 tinnitus patients over two months, 17 of which were exploitable for analysis. This dataset includes self-reported tinnitus intensity (morning and evening), detailed sleep diaries with report of nocturnal awakenings. A confirmatory analysis was performed on 2 retrospective datasets. The first dataset was composed of the retrospective records that had been already collected by 1851 tinnitus patients with the TrackYourTinnitus (TyT) app (Schlee et al, 2016) from which a SIT group was selected (N=17) as well as 2 control groups: intermittent tinnitus without sleep influence on tinnitus loudness (CInt, N=17) and constant tinnitus without sleep influence (CConst, N=22). The last dataset was composed of 11 SIT patients that did not directly participate in the prospective clinical trial but that provided longitudinal tinnitus measures enabling us to conduct the same analysis.

To analyze periodicity in collected tinnitus loudness time series, Baluev False Alarm Probability test was used on the Lomb-Scargle periodogram of the loudness time series of each participant. The test periodicity band was set between 2.5 and 4.5 days, surrounded by two control periodicity bands between 1.75 and 2.5 days and 4.5 to 9 days (equivalent in frequency band sizes). Tests were then combined using Fisher p-value combination and controlled by Holm-Bonferroni for multiple statistical testing.

Results:

We observed that in our 3 SIT cohorts, independently, a significative periodicity of duration between 2.5 and 4.5 days was present ($p < 0.001$). In the TyT SIT cohort, we also observed a significant periodicity in the 4.5 to 9 days periodicity band ($p=0.02$). These 2 periodicity bands were also significant for the Cint sample ($p<0.001$). All other tests were not significant.

There was no significant correlation between overnight tinnitus variations and sleep duration in the prospective cohort (nor with chronic deep sleep debt, see suppl material). Moreover, we observed that nights of sleep and days with naps elicited significantly more tinnitus variations than (awake) days without naps.

We sought to investigate the etiological characteristics of the patients with a specific significant 2.5 to 4.5 days tinnitus periodicity. We conducted a reverse analysis where we separated these patients in the TyT dataset ($N=32$) from patients without such specific periodicity ($N=226$). We observed that specific 2.5 to 4.5 days periodicity was significantly associated with symptoms of the SIT population: worsening of tinnitus following naps (Mann-Whitney, $p=0.011$), sleep ($p=0.033$) and stress ($p=0.019$) modulations, variations of tinnitus from day to day ($p=0.035$).

Significance:

Our study shows that **tinnitus loudness longitudinal dynamics do not appear random in SIT patients**, it appears to follow a periodicity between 2.5 to 4.5 days. Such periodicity appears **specific** to this subgroup of tinnitus patients, as our reverse analysis showed **the association etiology and periodicity appears bidirectional**.

Moreover, we report that sleep (through naps or nights) induced more tinnitus variations in these patients than days without sleep. The absence of correlation between overnight tinnitus variations and sleep duration (and with chronic deep sleep debt), illustrates that the relation between tinnitus loudness variations and sleep is not trivial, we are exploring such relations in subsequent research.

Associated research and perspectives:

In an earlier study (Guillard et al 2023), we reported that overnight tinnitus variations were negatively correlated with Rapid Eye Movement (REM) sleep duration in SIT patients. Earlier research had already shown that REM sleep appeared specifically damaged in tinnitus patients (Attanasio et al 2013, Teixeira et al 2018). Our current hypothesis is that **specific REM sleep debt could be associated with SIT patients' tinnitus loudness variations**. Indeed, short naps are known to be devoid of REM sleep and Non-REM sleep during naps could increase REM sleep debt (Benington & Heller 1994). Moreover, a study has shown that REM sleep duration appears to have an infradian 4-day periodicity (Hecht et al 2005). To test this hypothesis, we made a new analysis of the data of our former 2023 polysomnography study and we made a model of REM sleep debt along the night using a REM sleep homeostasis model (Diniz Behn et al 2013). We found that overnight tinnitus loudness variations in our sample were significantly correlated with levels of REM sleep debt (Spearman, $r=0.62$, $p = 0.0011$).

These results tend to support that REM sleep debt could be associated with tinnitus loudness variations in SIT patients. It opens new avenues for clinical interventions for this subgroup, notably pharmacological ones using molecules as the Dual Orexin Antagonists (DORAs: Daridorexant, Lemborexant, Suvorexant) which are known to specifically increase REM sleep. Pregabalin and Lamotrigine could also have the same effect and for these drugs, we have pilot data demonstrating beneficial effects in SIT patients.

Thank you very much for considering my application.

Sincerely,
Robin Guillard