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# Epidemiological and physiological explorations of patients with sleep-induced tinnitus modulations

Robin Guillard

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THÈSE

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**Explorations épidémiologiques et physiologiques de patients  
présentant des modulations de leurs acouphènes par le sommeil**

**Epidemiological and physiological explorations of patients with  
sleep-induced tinnitus modulations**

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# Epidemiological and physiological explorations of patients with sleep-induced tinnitus modulations

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A thesis submitted for the degree of

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*A ma grand-mère et à J-C Ameisen pour m'avoir donné goût aux neurosciences  
Aux 2 Alain qui m'ont toujours soutenus et guidés sur ma voie*

# Abstract

Tinnitus can be defined as the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source. This debilitating chronic symptom is widely prevalent, affecting approximately 14% of the world population, 2% of which in a severe form. The intrinsic heterogeneous nature of tinnitus poses challenges in conducting research to understand its pathophysiological mechanisms and develop effective treatments. To address this issue, some studies propose adopting a divide and conquer strategy. This approach involves dividing the heterogeneous population of tinnitus patients into homogeneous subgroups and then investigating the underlying pathophysiology in each subgroup to develop targeted treatments. In this particular thesis, we contribute to this effort by providing a validated French translation of a standardized screening questionnaire (ESIT-SQ). Additionally, we propose a segmentation of the tinnitus population into homogeneous subgroups. Then, we focused our efforts on analyzing the specific characteristics of two tinnitus subgroups with the objective of identifying physiological correlates of tinnitus. Both subgroups share the characteristic of experiencing sleep-induced modulations of tinnitus. The first subgroup, known as the Tinnitus Increases After Naps (TIAN) group, reports changes in the psychoacoustic characteristics of their tinnitus following naps, particularly an increase in tinnitus loudness. The second, rarer subgroup, referred to as the Sleep Intermittent Tinnitus (SIT) group, experiences intermittent perception of tinnitus after awakening from sleep. In their case, any sleep occurrence acts as a random switch. Patients in this subgroup report that on certain days, they can wake up after a night's sleep and go through the entire day without experiencing any tinnitus, even when wearing a noise cancelling headset. This absence of tinnitus persists until the next nap or night sleep episode. By identifying and studying these distinct subgroups within the tinnitus population, we aim to contribute to the understanding of tinnitus pathophysiology and potentially develop more targeted treatments for this condition.

A cross-sectional database analysis was conducted on 9742 patients to evaluate the prevalence and symptom pattern of the TIAN population, highlighting that 1 out of 5 tinnitus patients belonged to this group. The tinnitus percept of TIAN patients appeared to be more likely influenced by sleep, sounds, stress, physical activity, and somatosensory maneuvers compared to the rest of tinnitus patients, indicating a heightened sensitivity profile. This heightened sensitivity profile was associated with a greater reported tinnitus burden.

To gain a deeper understanding of the pathophysiology of TIAN and SIT patients, two polysomnographic investigations were carried out. A one-night polysomnographic study comparing SIT patients with tinnitus controls showed that SIT patients had lower levels of deep sleep (N3) and rapid-eye movement (REM) sleep. Furthermore, a negative correlation was found between the duration of REM sleep and the modulation of tinnitus loudness overnight. In a longitudinal study involving 37 TIAN patients, several audiologic and kinesiologic assessments were conducted before and after each nap attempt. The results

indicated that nap-induced tinnitus modulations were correlated with the duration of naps, cumulative snoring duration, average sound intensity, as well as the number of sleep apnea and hypopnea events. Thanks to these observations, we then present several hypotheses that could explain what underlying pathophysiological mechanisms could result in such sleep-induced tinnitus modulations.

## Résumé

Les acouphènes peuvent être définis comme la conscience d'un bruit tonal ou composite pour lequel il n'existe pas de source acoustique externe identifiable. Ce symptôme chronique débilitant est largement répandu, affectant environ 14 % de la population mondiale, dont 2 % sous une forme sévère. La recherche de mécanismes physiopathologiques et de traitements efficaces pour les acouphènes est entravée par leur nature intrinsèquement hétérogène. Plusieurs études préconisent de s'attaquer à ce problème en adoptant une stratégie "diviser pour régner" dans laquelle nous devrions d'abord diviser la population hétérogène de patients acouphéniques en sous-groupes homogènes et ensuite travailler à identifier la pathophysiologie sous-jacente dans chaque cas afin de développer des traitements ciblés. Dans la présente thèse, nous contribuons à cet effort en fournissant une traduction française validée d'un questionnaire de dépistage standardisé (ESIT-SQ) ainsi qu'une proposition de segmentation de la population acouphénique en sous-groupes homogènes. Ensuite, nos efforts se sont concentrés sur l'analyse des caractéristiques spécifiques de deux sous-groupes de patients acouphéniques dans lesquels notre objectif a été d'identifier les corrélats physiologiques de l'acouphène. Les patients des deux sous-groupes sélectionnés présentent la caractéristique de subir des modulations de leurs acouphènes induites par le sommeil. Le premier sous-groupe rapporte des modifications des caractéristiques psychoacoustiques de leurs acouphènes suite à des siestes et en particulier des augmentations de la sonie de leurs acouphènes. Nous appelons ce sous-groupe le groupe des acouphènes augmentant suite aux siestes (TIAN). Le deuxième sous-groupe, plus rare, rapporte une intermittence de la perception des acouphènes après le réveil. Dans leur cas, tout épisode de sommeil agit comme un interrupteur aléatoire. Les patients de ce dernier sous-groupe rapportent que certains jours, ils peuvent se réveiller après une nuit de sommeil et passer une journée entière sans ressentir d'acouphènes, même en portant un casque anti-bruit, et ce jusqu'à la prochaine sieste ou au prochain épisode de sommeil nocturne. Nous appelons ce sous-groupe le groupe des acouphènes intermittents du sommeil (SIT).

Grâce à une analyse transversale de deux bases de données portant sur un total de 9742 patients, nous avons évalué la prévalence et le profil des symptômes de la population TIAN et estimé qu'elle concernait 1 patient sur 5 souffrant d'acouphènes. Il apparaît que la perception de l'acouphène chez les patients TIAN peut être significativement plus fréquemment modulée par le sommeil, les sons, le stress, l'activité physique et les manœuvres somatosensorielles par rapport au reste de la population acouphénique. Cela semble indiquer un profil d'hypersensibilité de la perception des acouphènes dans la population TIAN qui se combine avec une plus grande détresse associée.

Afin de mieux comprendre la physiopathologie des patients TIAN et SIT, nous avons mené deux études polysomnographiques. Dans une première exploration polysomnographique nocturne, nous avons comparé un échantillon de patients SIT et un échantillon apparié de témoins acouphéniques. Nous avons identifié que les patients SIT

avaient des proportions moindres de sommeil profond (N3) et de sommeil paradoxal (REM) par rapport aux témoins. En outre, nous avons identifié une corrélation négative entre la durée du sommeil paradoxal et la modulation de l'intensité sonore de l'acouphène pendant la nuit. Dans le cadre d'une étude longitudinale portant sur six siestes consécutives, nous avons procédé sur une cohorte de 37 patients atteints de TIAN à plusieurs évaluations audiologiques et kinésiologiques avant et après chaque tentative de sieste. Nous avons constaté que certaines de nos mesures des modulations de l'acouphène induites par la sieste étaient corrélées à la durée des siestes, à la durée cumulée et à l'intensité sonore moyenne des ronflements ainsi qu'au nombre d'apnées et d'hypopnées du sommeil. Grâce à ces observations, nous présentons plusieurs hypothèses qui pourraient expliquer quels mécanismes physiopathologiques sous-jacents pourraient entraîner de telles modulations de l'acouphène induites par le sommeil.

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# Chapter 1

## State of the art

*Anatomy of the human auditory system, tinnitus, sleep  
and auditory functioning during sleep*

# State of the art

## 1.1 Anatomy of the human auditory system

Auditory perception is the sensory mechanism through which living organisms detect and interpret mechanical vibrations in the air surrounding them. Vertebrates utilize a specialized organ known as the cochlea to sense these vibrations. The sense of hearing in vertebrates emerged relatively late in evolutionary history, approximately 380 million years ago (Maudoux et al., 2022). It initially appeared in amphibians as a primitive structure called the basilar papilla, which was derived from the vestibular system responsible for balance. Over time, this basilar papilla gradually transformed into the spiral-shaped cochlea found in mammals today, a process that occurred around 120 million years ago, just prior to the divergence of marsupial and placental mammals from their common therian ancestor (Köppl and Manley, 2019).

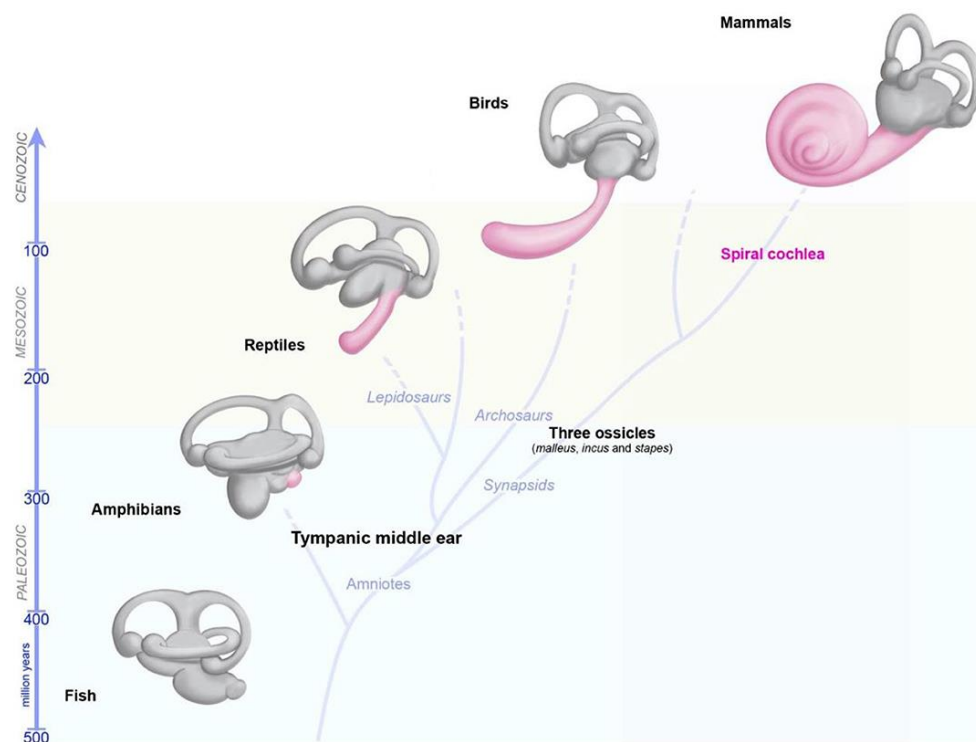


Figure 1.1.1 : Evolution of the inner ear in vertebrates. The cochlea stems from the vestibuli.

Reproduced from (Maudoux et al., 2022) under CCBY license

Different lineages independently developed surrounding structures that enhanced the efficiency of this sensory organ. These structures include a bony transmission organ known as

the middle ear and an external cartilaginous structure called the pinna. Convergent evolution led to the emergence of multiple solutions in response to similar selective pressures. Mammals evolved a three-ossicle middle ear, while nonmammals developed a single ossicle middle ear (Manley, 2010).

The emergence of this organ led to a transformation in both the sub-cortical and cortical regions of the brain, influencing the processing of transmitted information. Moving forward, we will delve into the evolution of the human auditory system, examining each component from the most external part, the outer ear, to the auditory cortex.

### 1.1.1 The peripheral organ

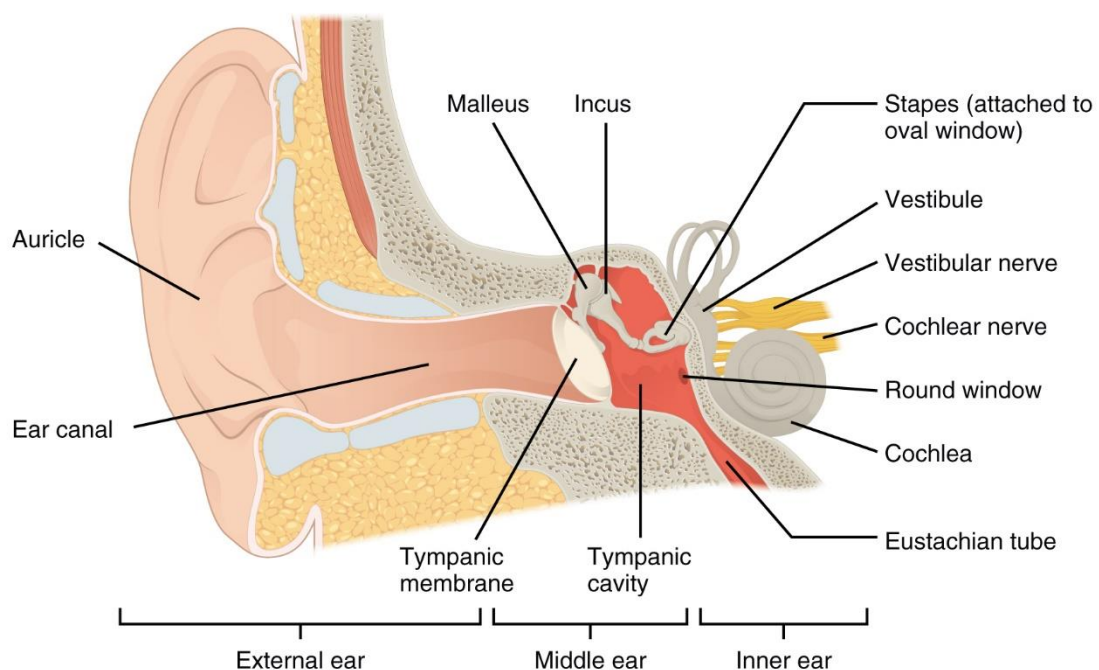


Fig 1.1.2 : View of the ear, comprising outer, middle and inner ear. From University of Wisconsin

(<https://wisc.pb.unizin.org>) free for access and sharing.

#### 1.1.1.1 The outer ear

The outer ear consists of three main components: the auricle, the external ear canal, and the external surface of the eardrum. The auricle, also known as the pinna, is the visible part of the outer ear and has a unique shape for each individual due to its cartilaginous structure. It is held in place by tendons, muscles, and fibrous tissue. The auricle is primarily innervated by the greater auricular nerve and the auriculotemporal nerve. Additionally, it receives autonomous innervation from the vagus nerve in two specific locations: the tragus, which is the cartilaginous projection opposite the auricle above the ear canal opening, and the ear canal itself. Functionally, the auricle plays the role of funneling omnidirectional sound waves into a

guided one-dimensional wave through the acoustic meatus and directing them towards the eardrum. The pinna also has the ability to filter sound in the frequency range of human speech. Interestingly, most mammals have the capability to orient their auricle in the direction of incoming sound. However, humans have lost this ability, and the movement of the auricle is limited to reflex slight vertical and lateral translations.

The external ear canal, or auditory meatus, extends from the pinna to the eardrum. In adults, this meatus measures approximately 2.5 cm in length and 0.7 cm in diameter, with an oval-shaped cross-section. It is comprised of an elastic cartilaginous section (approximately 8-9 mm) and a bony section (approximately 16-17 mm). The cartilaginous part of the auditory meatus contains small hairs and specialized sweat glands known as apocrine glands, which secrete cerumen (ear wax).

The eardrum serves as the physical barrier between the outer ear and the middle ear. It is a translucent membrane with a diameter of 9 to 10 mm and a thickness of around 0.1 mm. The eardrum consists of two distinct regions: the pars tensa, a rigid structure that covers most of the surface, and a more flexible part called the pars flaccida. The primary function of the pars tensa is sound conduction, while the pars flaccida is thought to have baroreceptive properties (Didyk et al., 2007) and is suggested to monitor pressure changes in the middle ear. The eardrum receives, amplifies, and transmits the mechanical vibrations of air. It is innervated by three cranial nerves, with the auriculotemporal nerve of the mandibular branch of the trigeminal nerve supplying the anterior portion of the lateral surface, the vagus nerve innervating the posterior part, and the glossopharyngeal nerve innervating the medial surface.

### 1.1.1.2 The middle ear

The middle ear functions as a bony cavity that facilitates the transmission and amplification of sound between the eardrum and the oval window of the cochlea within the inner ear. Comprising three ossicles - the malleus, incus, and stapes - the human (and more broadly, mammalian) middle ear is enclosed by the tympanic part of the temporal bone. Tendons and two muscles, the tensor tympani muscle and the stapedius, work together to maintain the position of the ossicles. The tensor tympani muscle is innervated by the mandibular branch of the trigeminal nerve, while the stapedius is innervated by the facial nerve.

Ventilation of the middle ear is facilitated by the auditory tube, also known as the Eustachian tube, which connects to the nasal cavity (nasopharynx). This conduct enables pressure equalization between the middle ear and the throat. Normally closed, the auditory tube opens through the contraction of the tensor veli palatini muscle, which forms a functional unit with the tensor tympani (Ramirez Aristeguieta et al., 2010). This muscle is innervated as well by the mandibular branch of the trigeminal nerve and can be considered also part of the middle ear as such.

The middle ear serves a crucial role in amplifying sound waves that travel from the eardrum to the inner ear. This amplification is achieved through two interconnected factors: the size ratio between the tympanic membrane and the oval window, and the lever effect resulting

from the configuration of the ossicles. The resulting amplification is not constant across all frequencies, but rather varies depending on the frequency of the sound wave. Research conducted by Merchan (1997) indicates that the average gain of the middle ear system is approximately 20 dB between 250 and 500 Hz. The gain then reaches its peak at around 26.6 dB at 1 KHz, before gradually decreasing at a rate of approximately 8.6 dB per octave as the frequency increases. At frequencies of 7 KHz and above, the gain diminishes to nearly zero. On average, the sound pressure gain amounts to 23 dB.

### 1.1.1.3 The inner ear

The human inner ear is composed of two sensory organs : the vestibule which is the sensory organ of balance and motion, and the cochlea which is the organ of hearing.

#### A. The vestibule

The vestibule, although not the focal point of the current thesis, will be briefly discussed as it is of significant interest.

Each vestibule contains two sets of sensors: three semicircular canals (superior, lateral, and posterior) that detect rotational acceleration in three spatial directions, and two maculae (the utricle and the saccule) that detect translational acceleration. Hair cells in both the semicircular canals ampullae and maculae transduce their hair movements into action potentials, which are then relayed to the brain via the vestibular nerve.

#### B. The cochlea

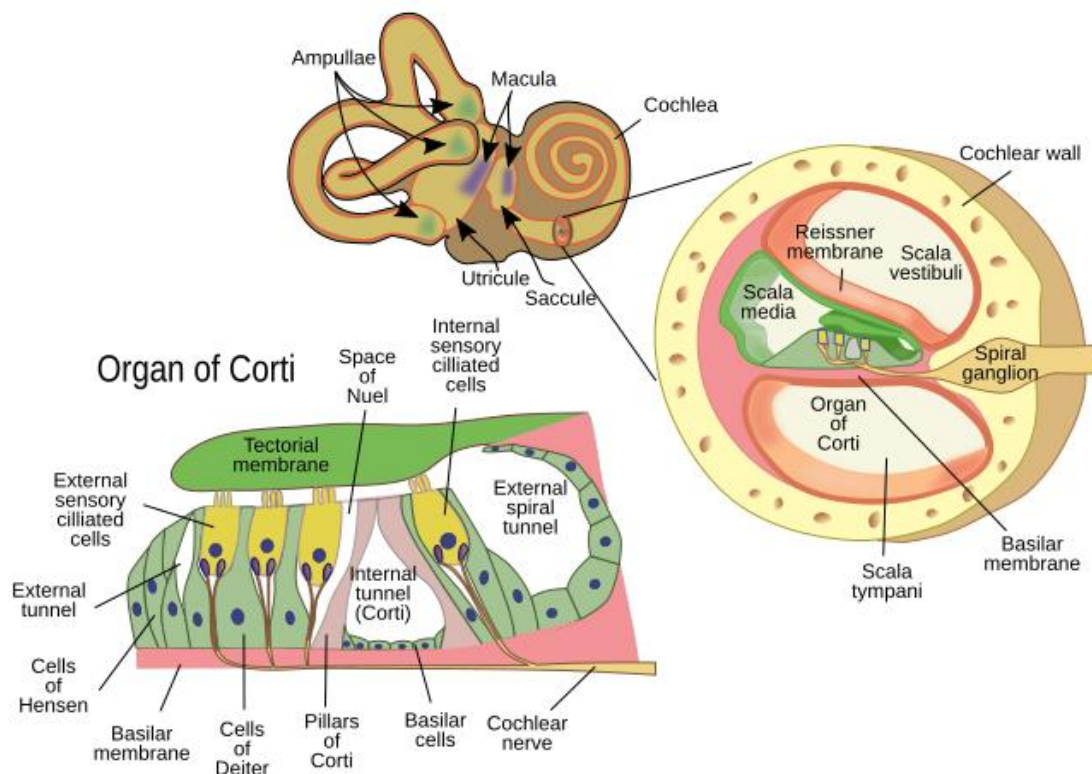


Fig 1.1.3 : The inner ear (top), slice view of the three scalae (right) and zoom on one organ of Corti along the cochlea, supported by the basilar membrane (free for access from [mmegias.webs.uvigo.es](http://mmegias.webs.uvigo.es))

The cochlea is the true organ for hearing. It receives mechanical sound vibrations from the stapes in the middle ear through the oval window. These vibrations are then converted into electrical impulses, which are transmitted as action potentials through the auditory nerve, also known as the cochlear nerve.

The cochlea is spiral shaped, spanning a length of 31-35 mm. It starts at the base near the middle ear and culminates at its apex at the top or center of the spiral. It is divided into two separate compartments that are completely filled with two distinct ionic solutions. The scala media is filled with endolymph, while the scala vestibuli and the scala tympani are filled with perilymph. These two compartments are connected by the helicotrema located at the apex.

Within the cochlea, there are two membranes that separate the scala vestibuli and the scala media, as well as the scala media and the scala tympani. Reissner's membrane separates the scala vestibuli and the scala media, while the basilar membrane separates the scala media and the scala tympani. Figure 1.1.3 illustrates this arrangement.

Attached to the basilar membrane and replicated in approximately 3500 copies along the spiral is a collection of cells known as the organ of Corti. This intricate structure plays a crucial role in the process of hearing.

### *B.1 The basilar membrane*

The basilar membrane has the astonishing mechanical property to perform a spectral Fourier transform of the sound wave passing through it. In fact, due to its physical proportions (narrow and thick at the base, wide and thin at the apex), low frequencies propagating through it resonate best at the apex, while high frequencies resonate best at the base. Consequently, the sound waves that are conducted through it will have a peak of maximum resonance at a different distance from the base along the spiral axis of the cochlea, depending on their frequencies. For instance, high frequencies (8000 Hz and above) will resonate most at the base, while low frequencies will resonate closer to the apex. This continuous spatial distribution of frequencies is known as tonotopy, and this tonotopical arrangement of sound representation remains a consistent property throughout the various stages of auditory processing along the primary auditory pathway up until the core of the auditory cortex (A1).

### *B.2 The organ of Corti*

The organ of Corti is the heart of sound mechano-transduction. It comprises 3500 functional units of generally three outer hair cells, one inner hair cell and several Deiter's supporting cells, which are all attached to the basilar membrane and follow it along the axis of the cochlea. Consequently, each individual organ of Corti is specifically attuned to resonate at a particular frequency.



The ability to discriminate between different resonance frequencies is further enhanced by the row of three outer hair cells (sometimes four at the apex). These outer hair cells possess the unique property of electromotility, meaning they contract rhythmically to actively compress incoming sound waves into the optimal range for sensory transduction by the inner hair cell. In doing so, they amplify low sound intensities and reduce the intensity of very loud sounds. In same time, they tune each functional unit of the organ of Corti to respond only to a very sharp frequency range (increasing the system sensibility).

The inner hair cells are responsible for converting mechanical sound waves into electrical action potentials. When the hair bundle of these cells is deflected to a sufficient degree, tip links attached to the top of the two shortest rows of hairs open up. This opening allows calcium and potassium ions to enter the cell, leading to its depolarization. Through intra-cell mechanisms, an action potential is generated at the level of the glutamatergic synapses that bind inner hair cells with the auditory nerve fibers that are attached to it at their bottom. The auditory fibers from various hair cells converge in the spiral ganglion, where the somas of the first-order auditory neurons are located.

## 1.1.2 The primary auditory pathway

### 1.1.2.1 The auditory nerve

The auditory nerve transmits the information generated by the inner hair cells to the first nuclei of the central auditory pathway: the cochlear nuclei. It is composed of 30 000 nerve fibers. As each fiber connects with a specific inner hair cell, each fiber is sensitive to a specific sound frequency. A review of auditory nerve sound encoding properties is provided by Huet and colleagues (2019). At low frequencies, spikes in the auditory nerve fibers are able to phase lock to the sound wave, while at higher frequencies, temporal coding is replaced by rate coding due to the limitation of the refractory period of action potentials.

Liberman showed in 1978 that sound intensity is encoded by auditory nerve fibers by three different classes of fibers in cats: the high-spontaneous rate (SR) fibers ( $SR > 18$  spikes/s) encoding for low sound intensities, the medium- ( $0.5 < SR < 18$  spikes/s) encoding for moderate sound intensities and low-SR fibers ( $SR < 0.5$  spike/s) encoding for high sound intensities (Liberman, 1978).

Unfortunately, the low-SR fibers, which are crucial in processing loud sound environments, are the most vulnerable. The gradual loss of these fibers in aging or noise-exposed cochleae, known as synaptopathy, has been documented by (Kujawa and Liberman, 2015). Loss of these fibers, even without significant loss of inner hair cells, can lead to difficulties in hearing in noisy situations, despite normal or sub-normal audiograms. This phenomenon, termed hidden hearing loss, raises questions about the accuracy of using audiograms as the gold standard for assessing hearing abilities.

### 1.1.2.2 The cochlear nuclei

The cochlear nuclei are the first stage of subcortical sound processing. Each cochlear nucleus comprises two parts. Firstly, it comprises the ventral cochlear nucleus (VCN) composed of bushy and T-Stellate neuron cells, which receives afferences from all types of auditory nerve fibers and projects to the olivary complex. Secondly, the dorsal cochlear nucleus (DCN) is primarily composed of fusiform and inhibitory tuberoventral neuron cells. It exclusively receives inputs from low and medium SR auditory nerve fibers and then directly projects to the inferior colliculus (Eggermont, 2021; Shore et al., 2016). Interestingly, the DCN also contains unipolar brush cells, a unique neuron type found in specific regions of the cerebellar cortex, leading some researchers to draw comparisons between its structure and that of the cerebellum (Saldaña, 2015).

The separation between efferences from the VCN and the DCN is interpreted by several authors as the bifurcation point between the primary auditory pathways (from ventral cochlear nucleus to the olivary complex, taking into account both ipsilateral and contralateral projections) and the non-primary auditory pathways, as presented by (Eggermont, 2021; Moller et al., 1992; Zhang et al., 2018).

It is worth mentioning with regard to current interest in cochlear nuclei for the tinnitus field that the caudal part of the spinal ganglion of the trigeminal complex (Sp5) projects with glutamatergic excitatory synapses on granule cells of the DCN (Wu et al., 2015). Additionally, cochlear nuclei receive afferences from the dorsal column nuclei and in particular the second cervical dorsal root ganglion (Itoh et al., 1987; Zhan et al., 2006). Retro propagation information from the auditory cortices seems also to be received by the cochlear nuclei, as shown in rats and guinea pigs models (Schofield et al., 2006; Weedman and Ryugo, 1996). Last, activity of the cochlear nuclei is modulated by excitatory serotonergic afferences from the raphe nuclei (Felix et al., 2017; Thompson and Thompson, 2001).

### 1.1.2.3 The Superior Olivary complex

The superior olivary complex (SOC) is a collection of brainstem nuclei. Fibers originating from the anterior part of the VCN project to the contralateral medial superior olivary nuclei. These fibers play a crucial role in assessing the timing of stimuli from each ear, which helps in determining the localization of the incoming sound source. Furthermore, the anterior part of the VCN also projects ipsilaterally to the lateral superior olive, but this time to compare the intensity of the input stimuli.

The output fibers from the medial superior olive combine with the output fibers from the contralateral lateral superior olive and ascend towards the inferior colliculus as a bundle known as the lateral lemniscus. SOC hence provide an additional attribute to central auditory representation : localization, which emerges as a combination of relative timing and intensity of the stimuli in each ear.

#### 1.1.2.4 The inferior colliculus

The inferior colliculus (IC) is a critical hub of the central auditory system. It integrates auditory information coming from the SOC and the DCN. Additionally, it processes this auditory input alongside a vast array of information derived from different sensory modalities. In fact, as Gruters and Groh (2012) describe, IC receives refined somatosensory information, notably information relative to eye position, and as well visual information from different stages of the central visual pathway. Last, it receives behavioral context information, notably via the amygdala.

The IC can be further divided into three distinct subregions. The central nucleus of the IC (ICC) serves as the main relay of the primary auditory pathway, while two satellite regions, the dorsal cortex of the IC and the external cortex of the IC are mainly implicated in the non-primary auditory pathway and the efferent corticofugal pathway according to Liu and colleagues (2022). This comprehensive review also mentions that the IC receives neuromodulation from various neuromodulators: serotonin, dopamine, acetylcholine, norepinephrine.

#### 1.1.2.5 The medial geniculate body of the thalamus

The subsequent phase of central auditory processing involves the Medial Geniculate Body (MGB), also known as the Medial Geniculate Nucleus. This nucleus is divided into three parts: the ventral MGB (MGv), the dorsal MGB (MGd), and the medial MGB (M<sup>2</sup>G or MGm).

The MGv serves as the main relay of the primary auditory pathway, receiving inputs from the ICC and transmitting them primarily to the primary auditory cortex. On the other hand, the MGm appears to be more closely associated with the non-primary auditory pathway. Lastly, the MGd exhibits a more complex structure, which can be further divided into five subnuclei. Some of these subnuclei are part of the primary pathway, while others are part of the non-primary pathway (Winer, 1992). The MGd not only projects to the primary auditory cortex but also and mainly to the belt and parabelt.

When considering the functioning of the MGB, it is important to take into account its involvement in thalamo-cortical loops. Specifically, MGv neurons that receive information from the ICC and project to neurons in the primary auditory cortex are referred to as first-order relay nuclei. The sensory information they receive projects to layer IV of the cortices. These neurons are modulated by feedback loops originating from layer VI of the primary auditory cortex. Subsequently, neurons in the primary auditory cortex project sensory information back from layer V to nuclei primarily located in the MGd, which are designated as second-order relay nuclei. These second-order nuclei then project to the belt and parabelt regions of the auditory cortex.

A last component which is important to take into account in the functioning of MGB and the information transmitted through the thalamo-cortical loop is a inhibitory nucleus that

physically envelops the MGB : the thalamic reticular nucleus (TRN). This nucleus is composed mainly of GABAergic neurons and is thought to play an inhibitory modulatory role (gating) on the MGB neurons and auditory information. The TRN receives inputs from the MGB but also from the modulatory layer VI of the cortex and projects only to the MGB. It also receives modulatory afferences from non-auditory regions as amygdala (Rauschecker et al., 2010), raphe nuclei (Rodriguez et al., 2011). A comprehensive description of the role of the three parts MGB and how its activity can be modulated by the activity of the TRN can be found in the thesis manuscript of Nathalie Cotillon (2001).

#### 1.1.2.6 The auditory cortex

It is consensually accepted that the auditory cortex is located inside the Sylvian fissure in the Heschl gyrus (Costa et al., 2011). Except for the para-belt, its surface is not oriented facing the scalp. Additionally due to its relatively small size, measuring it using traditional EEG methods is particularly challenging. However, a recent review suggests that MagnetoEncephaloGraphy (MEG) could be a promising solution for non-invasive exploration of the human auditory cortex, especially in tinnitus research (Reisinger et al., 2023). Moreover, for animal models, ground-breaking exploration techniques such as 2-photon calcium imaging has enabled to unravel the intrinsic complexity of auditory cortex functioning and how it is influenced by behavioral context (Kuchibhotla and Bathellier, 2018).

Lastly, the auditory cortex is known to project fibers to most of the other relays of the auditory pathway as well as various subcollicular regions (Saldaña, 2015; Weedman and Ryugo, 1996; Winer et al., 1998). These corticofugal projections have probably an important modulatory role on sound perception.

#### A. The core

The primary auditory cortex (A1), also known as the core of the auditory cortex, serves as the central hub for auditory cortical activity. It is specifically characterized as the region that directly receives inputs from the MGv. Within the A1, there are distinct regions known as auditory field maps, which are organized in a tonotopic manner along at least one dimension of the cortex's surface. However, there is uncertainty regarding which sound attribute is represented in the orthogonal direction to the tonotopic axis.

Brewer and Barton, 2016 have recently proposed that the orthogonal feature to frequency would seemingly be periodotopy, defined as a gradient representation of temporal envelope variations (i.e. periodic modulations of the amplitude of the sounds). According to their hypothesis, A1 would contain 11 auditory field maps in humans and macaque. Besides, it is commonly acknowledged that neurons of A1 are heterogeneous in their peri-stimulus time histograms (PSTHs), which led Recanzone (2000) to propose categorization of these neurons according to their PSTHs.

#### B. The belt and parabelt

The belt and parabelt regions are differentiated from A1 as they do not receive afferences from primary auditory pathway MGv neurons but rather more cortico-cortical projections and projections from the subregions of the MGd. Moreover, they are differentiated because of different cytoarchitecture. Finally, the parabelt region is defined as the cortical area neighboring the belt area, receiving input from the belt and the dorsal MGB but not the core. The belt and parabelt are the likely substrates for higher order auditory processes and integration.

### 1.1.3 The non-primary auditory pathways

As mentioned on several occasions along the description of the auditory centers, it is traditionally considered that there are at least two auditory pathways (Musiek et al., 2011). Firstly, the primary auditory pathway, or lemniscal pathway or classical pathway which we have described above. This pathway is responsible for processing auditory information and extracting relevant features that can be consciously accessed. On the other hand, the non-primary auditory pathway, also referred to as the non-lemniscal pathway or the non-classical pathway, has been described to integrate non-auditory information such as somatosensory information or visual information (Moller et al., 1992) and to project to polysensory cortices.

This non-primary auditory pathway is thought to modulate the activity of the primary auditory pathway (notably at the level of the belt) by modulating the salience of auditory percepts.

There is uncertainty on the subject of where this non-primary auditory pathway would start. Some authors propose that it branches off from the primary auditory pathway at the level of the inferior colliculus (Moller et al., 1992) while others suggest that it starts at the cochlear nucleus (specifically the dorsal cochlear nucleus) and runs parallel to the primary auditory pathway, often interacting with it (Eggermont, 2021).

Yet it is important to mention that recently a second and alternative non-primary auditory pathway has been described and referred to as the non-canonical pathway or Reticular-Limbic pathway (Zhang et al., 2018). This non-canonical pathway also seems to diverge from the two other ones at the level of the cochlear nucleus, and follows a sequential route through the pontine reticular nucleus, the pontine central gray, the medial septum, and ultimately reaches the entorhinal cortex. The authors reported that this pathway specifically transmits loud noise-like aversive acoustic signals and contributes to noise-cued fear conditioning. The entorhinal cortex, its final destination, is described as a central hub that receives various sensory inputs and acts as a communication interface between the cortex and the hippocampus.

### 1.1.4 Key insights

Auditory function emerged through evolution as a byproduct of balance perception by the vestibuli. At the peripheral level, various structures filter (pinna, tympanum, ossicles), amplify (middle-ear and outer hair cells) and compress (outer hair cells) the auditory

information for optimized transduction by the inner hair cells. All components of auditory information (frequency, phase and intensity) are then transmitted through each auditory nerve. As the auditory information travels through the central auditory pathway, it is processed and refined by successive auditory nuclei. Along this journey, the receptive properties of auditory neurons become more complex and abstract. For instance, additional attributes such as stereophony are added as supplementary descriptors of auditory information in the superior olivary complex. Auditory representation gets modulated by non-primary pathways information, which integrates salience as well as other sensory information (somatosensory at the level of the cochlear nuclei, somatosensory visual and autonomic at the level of the IC). At the end of the journey, auditory information is represented at the cortical level in the auditory cortex (core, belt and parabelt). The consciousness network interacts with these representations to provide auditory perception.

## 1.2 Tinnitus

### 1.2.1 Definition(s)

While accounts of tinnitus can be traced back to ancient Egypt in the sixteenth century BC (Stephens, 1984), it is somewhat paradoxical that there is still ongoing controversy surrounding its definition. Within the three-year timeframe of this thesis, two articles were published, each proposing distinct definitions for tinnitus (De Ridder et al., 2021; Noreña et al., 2021). Although the definition put forth by De Ridder and colleagues (2021) has garnered a broader scientific consensus on an international scale, it remains a subject of debate and has faced criticism from both members of the medical and scientific community, such as Professor Mc Kenna at the Tinnitus at the Lake conference (Munich, 2022), and individuals within patient communities, like Tinnitus Talk. These ongoing debates raise questions about the medical classification of tinnitus, particularly in relation to the fields of audiology and psychology.

We will hereafter present the broad international consensus definition of De Ridder et al., 2021, while acknowledging its inherent limitations. This definition distinguishes the notion of tinnitus and tinnitus disorder and defines both as :

*“Tinnitus is the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source, which becomes Tinnitus Disorder “when associated with emotional distress, cognitive dysfunction, and/or autonomic arousal, leading to behavioral changes and functional disability.”*

### 1.2.2 Prevalence and incidence

While the definition of tinnitus remains a topic of debate, the method of measuring its prevalence in the general population is also a subject of inquiry. A recent systematic review and meta-analysis conducted by Jarach and colleagues (2022) addressed this issue. This meta-analysis made the synthesis of 113 epidemiological publications on tinnitus and identified that prevalence was measured in 6 different ways depending on studies. Here are the 6 formulations that could be found on for tinnitus assessment: “Have you experienced tinnitus?”; “Have you experienced tinnitus for more than 5 minutes?”; “Have you experienced tinnitus during the last months?”; “During the last months, have you experienced tinnitus which lasts for more than 5 minutes?”; assessment of tinnitus through a specific scale; assessment of tinnitus via other tinnitus definitions (6 studies). Interestingly, in the discussion, the authors note that *“Despite the substantial heterogeneity of estimates in the classes of any tinnitus, we did not find statistically significant differences in its prevalence across classes.”*

Their analysis concludes to a global prevalence of tinnitus in 14% of the population. They also report that 2% of the global population experience severe forms of tinnitus.

The study also examined the incidence of tinnitus in the population and found that the pooled annual incidence rate is approximately 1% (1164 per 100,000 person-years).

However, one question that remains unanswered by this meta-analysis is how the incidence of tinnitus is changing over the years in the population. This question has been addressed by Stohler and colleagues (2019) who followed a sample of 109 783 individuals in the United Kingdom between 2000 and 2016. Their study concludes that tinnitus incidence seems to be increasing over time.

### 1.2.3 Treatment options and society costs

Despite the effort of research and medicine, in the vast majority of cases, there is no curative therapeutic intervention for tinnitus aimed at making the perception disappear completely and definitively. By curative, it is meant the disappearance of the tinnitus percept as a result of whatever therapeutic intervention. Yet on the other hand, some specific forms of tinnitus can be cured. Indeed, an important proportion of vascular-caused pulsatile forms of tinnitus can now be treated by stent placement and neuro-radiological intervention (Narsinh et al., 2022). There is significant progress in the identification of new etiologies of pulsatile forms of tinnitus and how to treat them as the years pass (Cortese et al., 2021; Houdart, 2017; Lenck et al., 2012).

Yet in most cases, best available solutions to try to alleviate the burden of tinnitus in patients consist in tinnitus palliative intervention and management options. While reviews concluded that in general, cognitive behavioral therapy (CBT) appears as the best tinnitus management option available (Fuller et al., 2020; Landry et al., 2020), it may not be always the best suited in every individual situation, due to tinnitus complexity and intrinsic heterogeneity (Hoare and Hall, 2011).

A systematic review and meta-analysis of randomized controlled trials examining tinnitus management options examined the efficacy of several approaches (Hoare et al., 2011). Evaluated tinnitus management options were directive counseling, hearing aids, counseling and psychological support, relaxation therapies, cognitive behavioral therapy, sleep management, sound enrichment therapy, tinnitus retraining therapy, antidepressants, anxiolytics, and night sedation. It concludes that CBT reasonably shows good efficacy at helping tinnitus patients. It also reports that hearing aids/sound enrichment and TRT are the interventions most in need of high-level evidence studies. Recent avenues of treatment to tinnitus that were not addressed in this review were neuromodulation options (Lefebvre-Demers et al., 2021) like repetitive transcranial magnetic stimulation (Londero et al., 2018; Theodoroff and Folmer, 2013), transcranial direct current stimulation (Yuan et al., 2018), neurofeedback (Guillard et al., 2021; Güntensperger et al., 2017) and bimodal stimulation (Jones et al., 2023; Marks et al., 2018).



Despite the existence of tinnitus management options, the burden of tinnitus remains high for many individuals, affecting their daily activities and productivity, and generating health expenses. This translates in an important societal cost of tinnitus and it has been assessed in several studies. Maes and colleagues (2013) evaluated the annual societal cost of tinnitus in the Netherlands and estimated it at 6.8 billion euros and the health care costs at 1.9 billion euros. Similarly, Stockdale and colleagues (2017) estimated an average cost for tinnitus care per patient per year of £717, equating to an NHS (Great-Britain Social Security) healthcare bill of £750 million per year. Interestingly, they also estimated average health outcome per patient measured in quality adjusted life years (QALYs) gained and found that across all pathways, tinnitus therapy costs £10,600 per QALY gained. Last, a systematic review by Trochidis and colleagues (2021) concluded in a mean annual estimated cost per patient ranging between 1544 and 3429 euros for healthcare costs, between 69 and 115 euros for patient and family costs and between 2565 and 3702 euros for indirect costs, including productivity loss. Last, a recent national survey in France from Journée Nationale pour l'Audition association concluded that societal annual cost of tinnitus was at least of 11.8 billions euros in France, with an individual cost of at least 1500 euros per suffering patient per year.

## 1.2.4 Tinnitus models and proposed pathophysiological mechanisms

In this section, we are going to present succinctly some of the current proposed models accounting for the onset and/or the maintenance of the tinnitus percept. This list of models cannot be exhaustive, considering the important number of models that have been proposed.

### 1.2.4.1 Jastreboff neurophysiological model of tinnitus

Jastreboff (1990) proposed a neurophysiological model of tinnitus, which held significant historical importance in tinnitus research. Within this model, Jastreboff outlined the various stages through which tinnitus emerges: the mechanisms of tinnitus generation, the detection of tinnitus, and the perception and evaluation of tinnitus. As regards tinnitus generation, Jastreboff presented several potential pathophysiological mechanisms. The author focused mainly on cochlear dysfunctions mechanisms such as abnormal spontaneous otoacoustic emissions, heterogeneous lesions among inner and outer hair cells, ionic imbalances in the cochlea, and heterogeneous activations of type I and type II cochlear afferents. Additionally, other mechanisms related to calcium management and deficiencies in calcium channels were also considered. The detection of tinnitus was hypothesized to rely on pattern recognition in the decoding of auditory information along the primary auditory pathway.

Last, perception and evaluation were proposed to be the result of a parallel and mutually reinforcing interaction between the prefrontal areas, the limbic/emotional areas and memory areas. This last step determines if tinnitus is going to be labeled as neutral (in which case the tinnitus signal is dampened and possibly blocked, resulting in tinnitus habituation) or threatening (in which case tinnitus becomes salient and bothering, activating an autonomic nervous response). Over the years, this model has undergone evolution and successive

updates. Jastreboff later suggested that tinnitus generation could originate in the cochlear nucleus (Jastreboff and Hazell, 2008), and was summarized in a now famous boxplot figure hereafter.

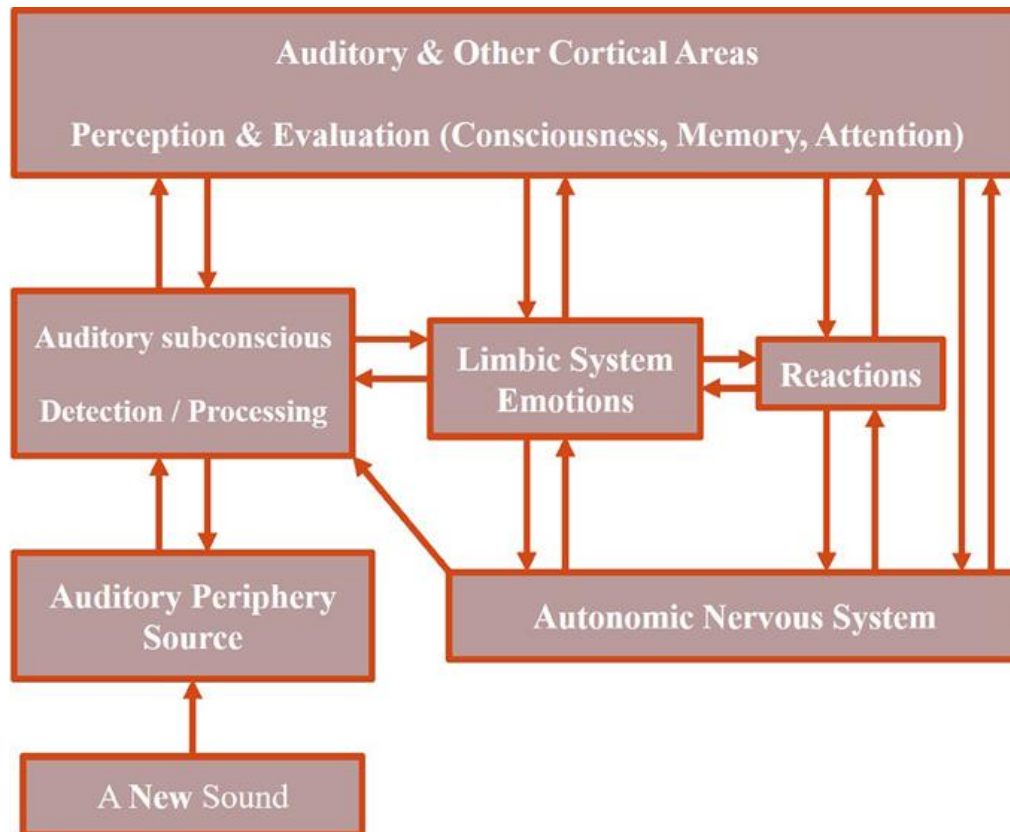


Figure 1.2.1 Neurophysiological model of tinnitus. Adapted from Jastreboff and Jastreboff (2006), published with free to share and use licence in (Ghodratitoostani et al., 2016)

#### 1.2.4.2 Thalamo-cortical dysrhythmia

Another important model accounting for emergence of tinnitus was introduced by Llinás and colleagues (1999) and is referred to as thalamo-cortical dysrhythmia (TCD). This model was proposed as a common factor in the emergence of positive symptoms in multiple neurological pathologies that were investigated through MEG imagery by this team: neurogenic pain, tinnitus, Parkinson's disease and depression. This team observed a common increase in theta rhythmicity (4 to 8 Hz) in all these patients. They propose this activity to be generated at the level of subcortical inputs (deafferented auditory input in case of tinnitus) and propagated to the cortices due to resonant interactions between the thalamus and the cortex, possibly under the inhibitory synchronizing influence of the thalamic reticular nuclei. This model is characterized by the fact that it proposes that thalamic neurons are hyperpolarized due to too much inhibition. Additionally, it postulates that as a consequence of this ongoing theta

rhythm, a faster gamma activity (25-50 Hz) is generated as an “edge-effect” which is the correlate of the observed positive symptoms.

This model was then updated by De Ridder and colleagues (2015). In this publication, the authors hold that over the years several experimental evidence have given ground to the TCD hypothesis for tinnitus. Notably, slowing of alpha to theta rhythm for auditory thalamo-cortical communication and pathological continuous gamma activity nested in the theta carrier waves were reported. A significant refinement suggested by the authors to the model is that the pattern of central reorganization varies based on the extent of auditory deafferentation.

For mild auditory deafferentation, they hypothesize that thalamo-cortical communication slows from alpha to theta, which may correspond to a reaction to the reduction of sensory information to process. Gamma activity, which is presented as a prerequisite of sensory perception, couples with the theta activity and becomes more continuously present (instead of waxing and waning as it should normally do). This would be the support of tinnitus perception.

In more severe cases of auditory deafferentation, it is suggested that sensory information from the affected frequency range no longer travels from the thalamus to the auditory cortex. Instead, this information may be retrieved from memory areas such as the hippocampal and para hippocampal regions. This communication also utilizes theta waves, as is typical for interactions between the hippocampus and sensory cortices. Similarly, gamma band activity is linked to the conscious perception of tinnitus.

Additionally, De Ridder and colleagues (2015) link the TCD model to the tinnitus as a prediction error model in the Bayesian framework. Indeed, in such context, gamma band would actually correspond to prediction error between prediction of the auditory perception and actual measure by the deafferented auditory system.

### 1.2.4.3 Homeostatic central gain increase model

Norena introduced the homeostatic central gain model in 2011. The model aims at providing an explanation for the occurrence and persistence of tinnitus based on two essential hypotheses. The first hypothesis suggests a significant decrease in sensory input, which can be caused by factors such as a very quiet or anechoic environment, conductive hearing loss, or damage to the inner ear or auditory nerve due to exposure to loud noise. The second hypothesis poses a moderate damage of the cochlea and more specifically the auditory nerve. Under this second hypothesis, the overall activity of the auditory nerve should appear reduced (Heinz and Young, 2004), but not totally silent: there should be still some functioning fibers. These fibers would still have a basal spontaneous activity, which is hypothesized to be a source of neural noise.

Under the first hypothesis, lack of auditory input should provoke a reduction of the overall central auditory activity. However, Norena mentions that a golden rule of central sensory processes is maintenance of an average neural activity around a set-point level (Turrigiano,

2008; Turrigiano and Nelson, 2004). The author proposes that homeostatic processes (structural plasticity, metaplasticity, synaptic scaling) will drive excitability of central auditory neurons upwards. This increase in central excitability is referred to as central gain.

Auditory nerve spontaneous activity could act as a neural noise source that will hence be amplified due to the hyperexcitability of central auditory neurons. This would explain the observed increase in spontaneous activity of central auditory neurons measured in sub-cortical centers such as the dorsal and ventral cochlear nucleus and the inferior colliculus (Milbrandt et al., 2000). This increase in spontaneous activity is proposed to be a correlate of the tinnitus percept.

One important limitation of this model is the boundaries it imposes on the form of auditory insults of the peripheral auditory system. Indeed, Norena admits in his paper that this model cannot account for the observed cases of tinnitus with severe or complete deafferentation (such as cases of tinnitus after auditory nerve sectioning). In such cases, the author advises to refer to the somatosensory model, in which somatosensory trigeminal excitation will become a substitute of neural noise source in replacement to auditory nerve residual spontaneous activity.

Another limit that Norena discusses is the case of acute tinnitus. Indeed, the plastic mechanism proposed to correspond to homeostatic regulation cannot account for the rapid and acute onset of tinnitus following acoustic trauma. In such cases, Norena suggests a release of cortical inhibition as the reason of the observed rapid increase in spontaneous activity in the auditory pathway.

An alternative explanation for the rapid emergence of tinnitus following acoustic trauma could be to associate it not with increased spontaneous firing in the central auditory pathway, but rather with increased firing synchrony or burst firing. This hypothesis was proposed by Norena and Eggermont (2003) after they observed very rapid changes in burst firing in the primary auditory cortex (A1) of cats, while spontaneous firing increase was only observed a few hours post trauma. In their discussion, they propose two arguments to defend that increased neurons bursting could be an alternative neural correlate of tinnitus. Firstly, they evoke that an increase in bursting in a limited set of neurons tuned to the tinnitus frequency could act as a “popping-out effect”, as what has been shown to happen in auditory steady state responses (Eggermont, 1997). Secondly, when a neuron receives synchronized inputs it presents an enhanced discharge probability (Abeles, 1991). Increase bursting in A1 could hence trigger enhanced spontaneous firing in belt and parabelt region after integration by the cortico-thalamo-cortical loop (through the MGd).

#### 1.2.4.4 Stochastic resonance model

Krauss and colleagues (2016) proposed a similar model to the latter model to explain the emergence of an increased spontaneous activity (referred to as neural noise) along the central auditory pathway following partial or complete deafferentation. Their model is based on the notion of stochastic resonance, derived from the information theory. Stochastic resonance is

the phenomenon by which weak signals that are sub-threshold for a given sensor (in our case, a synapse) still can be detected and relayed by that sensor if noise is added to the sensor input. In the case of the partially deafferented auditory system, neural noise source is postulated to be jaw and neck somatosensory information (Shore et al., 2016), and then transmitted to the cochlear nuclei. This model differs from the one of Norena (2011) for two main reasons. Firstly, stochastic resonance operates at the level prior to the detection threshold while homeostatic plasticity proposed by Norena influences processing after the detection threshold. Secondly the stochastic resonance model assigns a functional role to spontaneous activity in the auditory system in contrast to Norena's model, where increased spontaneous firing rates are simply a side-effect of the brain's attempt to cope with hearing loss. By modelling the auditory system by a neural network and by simulating auditory loss in a word recognition task, their team has shown that by adding a reasonable amount of noise to the system, the network gets twice better at recognizing words compared to the situation where no noise is added. Interestingly, they reported that it seems that discriminatory gain obtained by adding such neural noise is mainly acquired for conversational frequencies and not high frequencies. Such finding is congruent with the experimental data they report as well : in a cohort of tinnitus patients and aged matched controls (N= 39,141), tinnitus patients exhibited an average gain of 5 dB hearing thresholds on their audiograms compared to controls, particularly for conversational frequencies.

#### 1.2.4.5 Neuroinflammation model

Adcock and Vanneste (2022) proposed a model to structurally explain how central auditory pathway hyperactivity appears in case of acute tinnitus emergence. According to this model, neuroinflammation would drive the initial acute onset of tinnitus. Noise induced hearing loss or ototoxic agents would create an initial inflammation. This inflammation would then trigger the activation of microglia cells, which would intern reinforce the inflammatory response by releasing additional pro-inflammatory cytokines, which sets on a positive feedback loop. Enhanced levels of such pro-inflammatory cytokines would alter NMDA receptors expression on neurons surface and lead to increased calcium influx. In parallel, they would provoke GABA-A endocytosis and lead to decreased chloride influx and hence reduced inhibitory efficacy. Such changes in NMDA and GABA-A activity would in the end cause the emergence of the tinnitus percept as a consequence to both increased excitatory signaling and decreased inhibitory synaptic activity in the auditory pathway. It is worth mentioning that despite this model did not evoke this possibility, a recent study showed that pro-inflammatory cytokines can also alter normal functioning and expression on neurons membrane of  $K^+-Cl^-$  co-transporter isoform 2 (KCC2) resulting in GABA neurotransmission switching from inhibitory to excitatory (Parameshwarappa et al. 2023). This could also concur to tinnitus emergence.

This model is highly inspired by recent findings in animal models of tinnitus and in particular a recent study which elegantly demonstrated the important role of tumor necrosis factors (TNF) such as in particular  $TNF-\alpha$  in the initial onset of tinnitus (Wang et al. 2019).

#### 1.2.4.6 Frontostriatal gating model

Rauschecker and colleagues (2010) introduced a theoretical framework suggesting that tinnitus could manifest in individuals with damaged hearing systems due to the malfunction of a hypothesized noise-cancellation system. This theory was supported by findings from voxel-based morphometry studies conducted by Mühlau and colleagues (2006). This study discovered that subjects experiencing tinnitus had a significant reduction of volume in subcallosal area. In the present model, hearing loss (resulting from age-related damages or acoustic trauma) would lead to plastic tonotopic map reorganization in the cortex and an over-representation of the lesion-edge frequencies. Along the primary auditory pathway, this would result in a hyperactivity and/or a possible burst firing for this tonotopically-restricted range, which would constitute a “tinnitus signal”. Yet, in normal conditions, tinnitus would not emerge thanks to an inhibitory noise-cancellation system, which is proposed to be operated by the Thalamic Reticular Nucleus (TRN) at the level of the thalamus (MGB) before the tinnitus signal reaches the cortex. The inhibition provided to this signal by the TRN would be driven by paralimbic structures, notably in the subcallosal area (nucleus accumbens, driven by serotonergic input from the raphe nuclei), and the ventro-medial prefrontal cortex. This is why this model is often referred to as the frontostriatal gating model. The limbic involvement in this model provides explanations for the frequently reported tinnitus comorbidities such as anxiety and depression.

It is interesting to note for the purpose of this thesis that the authors of this model discuss the specific case of intermittent tinnitus, described as forms of tinnitus where tinnitus perception can be “switched-off” for several days, only to resume afterwards at full force. They propose two possible compatible explanations for such cases according to their theory. A first hypothesis would be that in such cases, the damages to the subcallosal area would be temporary, allowing transient filtering of the tinnitus signal. A second hypothesis would be that such patients would have fluctuating levels of central serotonin.

#### 1.2.4.7 Tinnitus in the Bayesian brain model

De Ridder and colleagues (2014b) propose that tinnitus may emerge as a byproduct of the salience network filling-in missing auditory information due deafferentation in order to minimize uncertainty. In the Bayesian framework, the brain is seen as a Helmholtz prediction machine: perception is the result of the comparison of prediction about the environment and sensory information provided by our sensory organs. The brain is consequently always making forward prediction about the states of the world and its main goal for survival is to minimize uncertainty (referred to in the information theory as Shannonian free-energy). Deafferentation provokes such uncertainty, at least for a tonotopically restricted area where it occurs. In order to try to minimize this uncertainty the brain can adopt two strategies: either to try to retrieve auditory information from tonotopically surrounding areas (when the deafferentation is not too pronounced). This can be obtained by reducing lateral inhibition from surrounding auditory cortex area and/or by plastically widening the receptive fields of the auditory neurons along the central auditory pathway. If the deafferentation is too

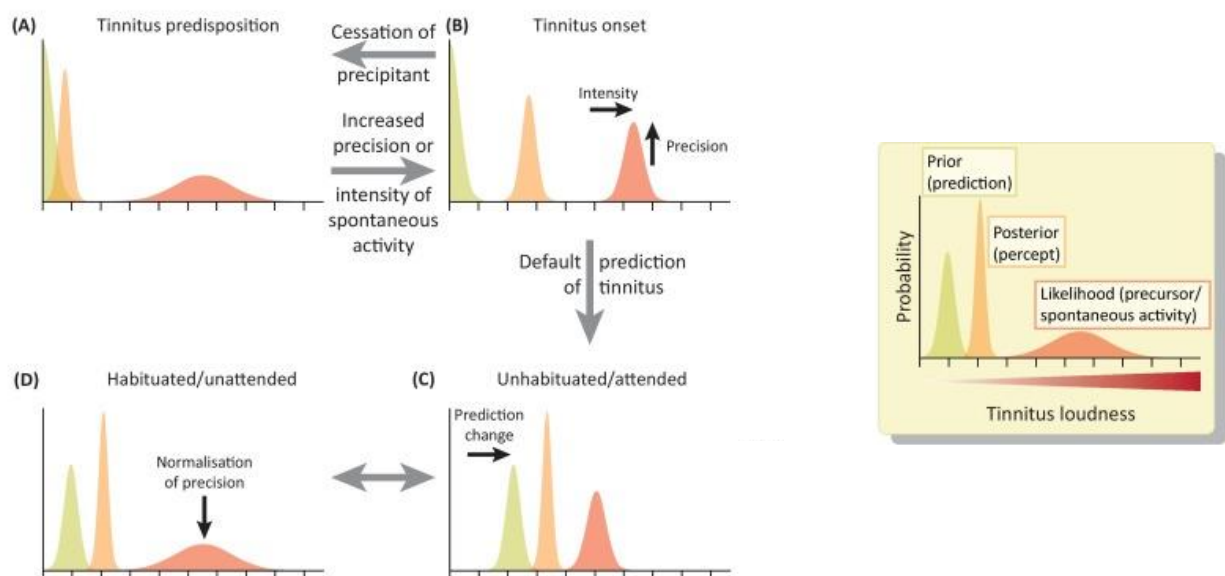
pronounced due to too much peripheral damage, a cortical map reorganization can occur and information can be retrieved and “filled-in” from memory (hence from the hippocampal and parahippocampal regions). In this context, it is proposed that the salience network (anterior cingulate cortex, anterior insula), and the auditory cortex have an abnormally high spontaneous activity, leading to bring to conscious emergence of this filled-in perception.

The theory that tinnitus appears as a filled-in perception in mirror to the central auditory deafferentation has been experimentally demonstrated by several studies. Indeed, Norena and colleagues (2002) have shown in a small sample of 10 patients that very often, the tinnitus spectral content appears as the mirror of the hearing loss of the patients, meaning that the tinnitus is loudest in the frequencies where the hearing loss was more pronounced (filling-in model presented before). Such results have been comforted by a larger retrospective study on 286 tinnitus patients (Schecklmann et al., 2012b).

#### 1.2.4.8 Predictive coding model

Sedley and colleagues (2016) proposed a model that share similarities with the Bayesian brain model of tinnitus proposed by De Ridder and colleagues (2014b). This model also refers to the Bayesian inference functioning nature of the brain but developing it within the predictive coding framework. It is interesting to note that as Friston is co-author of both this model and of the reality model adjustment through REM sleep model Hobson and Friston (2012) which we will develop in the next section on sleep. For this reason, there are obvious similarities in the concepts developed in both these models.

In the predictive coding model, sensory input and prior belief over the perception are represented as probability distributions. In this context, precision is defined as the inverse of the variance of such distributions. Perception is then postulated to be the result of a positive association between precision over the sensory input, precision over the prior belief over the perception and prediction error (difference between prior and likelihood means).



### Figure 1.2.2 Perceptual inference processes underlying tinnitus initiation, perpetuation, and modulation.

The inset box annotates perceptual inference in terms of the prior (prediction), likelihood (tinnitus precursor) and posterior (tinnitus percept) represented by Gaussian distributions over a perceptual dimension of intensity or loudness, with their widths indicating precision.

Loudness may be encoded by neuronal firing rate or be represented more abstractly. In each plot, the perceived loudness of tinnitus is indicated by the position of the posterior distribution on the horizontal axis. (A) In hearing loss alone, the tinnitus precursor has insufficient precision to override the default prediction of silence. (B) With increased precision the precursor influences perception, leading to a revised posterior percept of tinnitus. Potentially there is a window of reversibility at this stage. (C) If the default prediction is revised to expect tinnitus (generally less intense than the precursor), then the condition becomes chronic (through experience-dependent plasticity). (D) Reduction of the precision of the precursor to its pre-tinnitus level results in habituation, but not cessation of tinnitus – on account of plastic changes to prior predictions. Content in this figure was adapted from Sedley and colleagues (2016a), which was made freely available under the Creative Commons Attribution License (CC BY) (<https://creativecommons.org/licenses/by/4.0/>).

Hence, contrary to the model proposed by De Ridder and colleagues (2014b), in the present model it is not uncertainty over the sensory input that in the end makes tinnitus emerge, it is actually an increase in the precision of sensory “phantom” input that makes tinnitus emerge (at least for acute tinnitus). Additionally, according to the predictive coding model, tinnitus gets chronic when plastic changes occur and shifts the basal prediction from “silence” to “tinnitus sound”, supposedly at the level of the memory circuits -hippocampal and parahippocampal.

Interestingly, this model provides good insights on why it is hard to distinguish neural correlates of tinnitus from neural correlates of hearing loss when tinnitus is chronic. Indeed, in both cases, these tend to generate modifications in the sensory input to the auditory cortex, making it a precursor of tinnitus perception. When tinnitus is chronic, even if the sensory input has no longer enough precision on its own to drive tinnitus perception (i.e. it is identical to the case where there is hearing loss but no tinnitus, as presented in cases (A) and (D) of figure 1.2.2), then tinnitus perception is driven by the abnormal prior prediction that poses tinnitus sound as the new basal state, instead of silence.

#### 1.2.4.9 Tinnitus as an integrated multi-hub auditory phantom perception

A fruitful analogy that has been drawn concerning tinnitus is its resemblance with phantom limb pain. Møller (2011) enumerates the list of parallels that can be drawn between these two clinical phenomena. Indeed, both are occurring without any physical stimulation of the sensory receptors, both provoke some forms of suffering involving strong emotional responses and hyperacusis that often comes along with tinnitus can be compared with allodynia (pain from normally innocuous stimuli). Additionally, both seem to involve central plastic reorganization following some form of deafferentation. De Ridder and colleagues (2011) also presents these parallels and then goes one step further by proposing from a synthesis of brain imagery literature a first brain network that could be the support of tinnitus percept. This network involves not only auditory areas but also areas of the perception network / default mode network (posterior cingulate cortex, precuneus, pre-frontal cortex), memory areas (hippocampus and parahippocampus), salience network (dorsal anterior



cingulate cortex, anterior insula) which overlaps with the non-specific distress network (amygdala, subgenual anterior cingulate cortex, insula). To support this idea, they present that even though a representation of a sound can be found in the auditory cortex, it does not necessarily become conscious, if it is not bound and integrated with this network. As an example, they describe cases of patients in a vegetative state. In this condition, patients are awake but without awareness and without conscious percepts. In these patients, it was shown that activation induced by auditory stimulation is restricted to both primary auditory cortices (A1), but without any functional connectivity to the inferior parietal cortex, the hippocampus, the anterior cingulate, and the posterior cingulate (Laureys, 2007). Last, by defining tinnitus as an emergent propriety of a network of cortical and sub-cortical hubs, they hypothesize that any altered activity emerging in one of these hubs could potentially generate tinnitus. Consequently tinnitus is quite resilient as it does not rely on only one critical circuit.

In an effort to refine and consolidate this model, in a subsequent publication, De Ridder and colleagues (2014c) go further and attempt to unify it with past models such as the model proposed by Jastreboff (1990), the thalamo-cortical dysrhythmia model from Llinás and colleagues (1999) and the Bayesian brain model (De Ridder et al., 2014b). In this review, they describe tinnitus as a persistent auditory awareness entity and present neural networks of salience and awareness. Then they propose a tinnitus core subnetwork, defining it as the minimal network of cortical hubs that support the acoustic percept of tinnitus (independently of its other attributes: localization, associated distress, spectro-temporal characteristics... of which they also present the subnetworks). According to their model, this tinnitus core would be composed of the minimal areas involved in auditory awareness and auditory memory retrieval. Yet they also point out that as tinnitus is not present in dreams (De Ridder et al., 2014a), the tinnitus core should include areas that differ between REM sleep and awake state. Thus, they hypothesize that this tinnitus core network would be composed of the parahippocampus, the auditory cortex, the inferior parietal cortex and the ventrolateral prefrontal cortex.

#### 1.2.4.10 Parvalbumin neurons disinhibition model

The model proposed recently by Knipper and colleagues (2020) lies at the cross-roads between top-down and bottom-up tinnitus models. This model grounds its base in the observation that congenitally deaf people very rarely present tinnitus, in comparison to people that acquire hearing loss later in life. Starting with their premise, they postulate that a phenomenon that takes place during the auditory critical period in early life influences the auditory system in a manner that predisposes individuals to developing tinnitus following acquired hearing loss. They suggest that during our auditory critical period, a central network rooted in A1 and driven by parvalbumin (PV) interneurons becomes gradually inhibitory and driven by the excitatory activity of the high-SR auditory nerve fibers (encoding for low threshold sounds). In this scenario, in case of hearing loss that causes some damage to at least some of the high-SR auditory nerve fibers, there will be reduced stimulation to these interneurons, leading to a decrease in central inhibition. This, in turn, triggers an increase in spontaneous firing rates in the central auditory relays, ultimately resulting in the manifestation

of tinnitus. Notably, they suggest that by altering the concentration of chloride ions within the cells, PV interneurons, which utilize GABA as a neurotransmitter to inhibit downstream auditory centers, could transition from being inhibitory to excitatory, as they were prior to the critical period. This hypothesis has gained recently some ground as (Parameshwarappa et al., 2023) showed that indeed in tinnitus animal models, conditions for GABA to be excitatory were gathered in the cochlear nucleus and inferior colliculus, as  $K^+-Cl^-$  co-transporter isoform 2 (KCC2) expression was downregulated.

It is important to note that this model relies on the prerequisite of a significant amount of loss of high-SR auditory nerve fibers. Results from Vasilkov and colleagues (2023) tend to disprove this postulate. Indeed, they performed refined Auditory Brainstem Responses (ABR) testing with forward masking to test which type of auditory nerve fibers were more prone to have been damaged. Their work concluded that most probably low and medium SR were the groups of fibers with most damage, contrary to the prediction of the model by Knipper and colleagues (2020).

#### 1.2.4.11 Non-primary auditory pathway model

A crucial inquiry regarding the central neural basis of tinnitus revolves around whether tinnitus is sustained by the primary auditory pathway or the non-primary auditory pathway. Several researchers have posited that tinnitus may be supported by the non-primary auditory pathway. Moller and colleagues (1992) proposed that it may apply at least for some forms of tinnitus, by taking the example of somatosensory modulations of tinnitus (temporary modification of tinnitus pitch and/or loudness, or its silencing, elicited by movements of the temporomandibular joint, head and neck muscles, discussed further in section 1.2.6.3.C). Indeed, somatosensory information is integrated in the non-lemniscal auditory pathway (dorsal cochlear nucleus, external inferior colliculus). Hence, tinnitus can be induced or modulated by interference with the non-lemniscal auditory pathway.

Eggermont (2021) goes further in the analysis of this hypothesis, proposing that neural pathway supporting tinnitus is initiated by damage to low and medium SR auditory nerve fibers and then propagates to fusiform cells of the dorsal cochlear nucleus and then to the thalamus MGm. On the contrary, the author holds that the neural basis of hyperacusis (hypersensitivity to noise) may be rooted in the primary auditory pathway and rely on the homeostatic central gain change proposed by Norena (2011).

#### 1.2.4.12 Tonic Tensor Tympani Syndrome and acoustic shock model

Tonic Tensor tympani syndrome (TTTS) has been firstly described as a clinical entity by (Klockhoff, 1979, 1961), in which the reflex threshold for tensor tympani muscle activity becomes reduced, resulting in intermittent yet frequent contractions of the tensor tympani muscle. This syndrome often comes with other comorbidities that were later on described in a review by (Westcott et al., 2013) : tinnitus, hyperacusis, otalgia, ear-fullness, temporomandibular and/or neck pain, mild vertigo, nausea, muffled or distorted hearing, headaches. Tinnitus and hyperacusis seem to be the most prevalent associated symptoms with TTTS. Few

epidemiological studies were led to estimate the prevalence of TTTS. Tan and Lee (2023) reports a prevalence of 13% in a population of tinnitus patients seeking care.

Westcott and colleagues (2013) described that TTTS is often triggered with an initial acoustic shock (exposure to an unexpected loud sound perceived as highly threatening), and associated and/or identifiable to what is referred as the acoustic shock disorder. The pathophysiological underlying mechanisms of acoustic shock disorder has been later on described and theorized by Noreña and colleagues (2018) after thoroughly exploring a patient case described in the case report (Londero et al., 2017). Noreña and colleagues (2018) proposed that the initial acoustic shock triggers a tensor tympani overuse, which initiates a vicious circle: neurogenic inflammation, which provokes reduction of intramuscular blood circulation, then hypoxia, then nociceptor activation which loops and nurtures neurogenic inflammation. The activation of nociceptors would in turn transmit a nociceptive signal through the mandibular branch of the trigeminal nerve to the trigeminal cervical complex. This activation would elicit the symptomatic pattern of acoustic shock disorder, along with tinnitus which would identify as a form of somatosensory origin tinnitus (Shore et al., 2016). Boedts (2020) also proposed a pathophysiological explanation for these symptoms, referred to as the tympanic resonance hypothesis. According to this hypothesis, the clinical symptoms following TTTS and/or acoustic shock disorder would mainly originate from a disturbance in the tension of the tympanic membrane resulting from the chronic abnormal contraction of the tensor tympani muscle.

### 1.2.5 Tinnitus heterogeneity

To this day, as we have seen above, the complete understanding of the pathophysiology of tinnitus, its neural correlates and how to cure it is still under intense debate. A growing number of researchers align on the fact that this may be due to the fact tinnitus is intrinsically heterogeneous (Cederroth et al., 2019; Niemann et al., 2024). The younger generation of tinnitus researchers is particularly in line with this idea : we need to understand tinnitus heterogeneity, by notably exploring it through large tinnitus-specific databases if we are to solve it (Simoes et al., 2021). Several federative large-scale database projects have been launched to try to address this need : the Tinnitus Database project from the Tinnitus Research Initiative (Landgrebe et al., 2010), the Tinnitus Biobank project soon to be launched by Tinnitus UK. Moreover, to perform a standardized assessment of the complexity of the symptomatologic profiles of tinnitus patients, the European School of Interdisciplinary Tinnitus research (ESIT) created a new standardized questionnaire (ESIT-SQ, Genitsaridi et al., 2019). This questionnaire was then translated in numerous European languages (Genitsaridi et al., 2021; Haro-Hernandez et al., 2022), including French with our help (Guillard et al., 2023). Tinnitus online communities like Tinnitus Hub / Tinnitus Talk also contribute to large exploration of tinnitus samples. Finally, since 2020 we worked to create a tinnitus mutual-help community mobile app called Siopi (<https://siopi.ai>) aimed at specifically helping tinnitus patients by connecting patients with similar symptom profiles. This community helps patients also by enabling them to contribute more directly to help tinnitus

research by answering scientific surveys and promoting new clinical trials looking for recruits. Siopi has accelerated and supported several studies (Guillard et al., 2023, 2023a, 2023b) and several others soon to come.

One of the most apparent reflect of this heterogeneity is probably the immense variability of perceived sounds that tinnitus patients report. One may be tempted to infer that the timber of each and every tinnitus percept is unique to each individual. This variability may stem from the relationship that binds tinnitus to the hearing loss it is associated with. Indeed, Norena and colleagues (2002) have shown in a small sample of 10 patients that very often, the tinnitus spectral content appears as the mirror of the hearing loss of the patients, meaning that the spectral content of the tinnitus percept matches the hearing loss pattern in the audiogram (Bayesian filling-in model presented before).

Besides, another important aspect of tinnitus heterogeneity is the variety of causes that can act as a trigger on the emergence of tinnitus. Here is a non-exhaustive list of often reported initial causes of tinnitus emergence:

- Age-related hearing loss
- exposure to loud sounds (acoustic trauma)
- exposure to change in ambient pressure (e.g. flight or diving)
- flu, common cold or other infections,
- feeling of fullness or pressure in the ears
- Stressful event or stressful period
- Head trauma
- Neck trauma
- Drugs (ototoxicity)

Additionally, patients self-report other possible causes for initial tinnitus onset, such as over-exposure to magnetic fields.

More generally, heterogeneity in tinnitus patient profiles project on a vast number of tinnitus-specific and non-tinnitus specific attributes. A comprehensive list of such attributes was attempted by Genitsaridi and colleagues and presented hereafter in Figures 1.2.3 and 1.2.4.

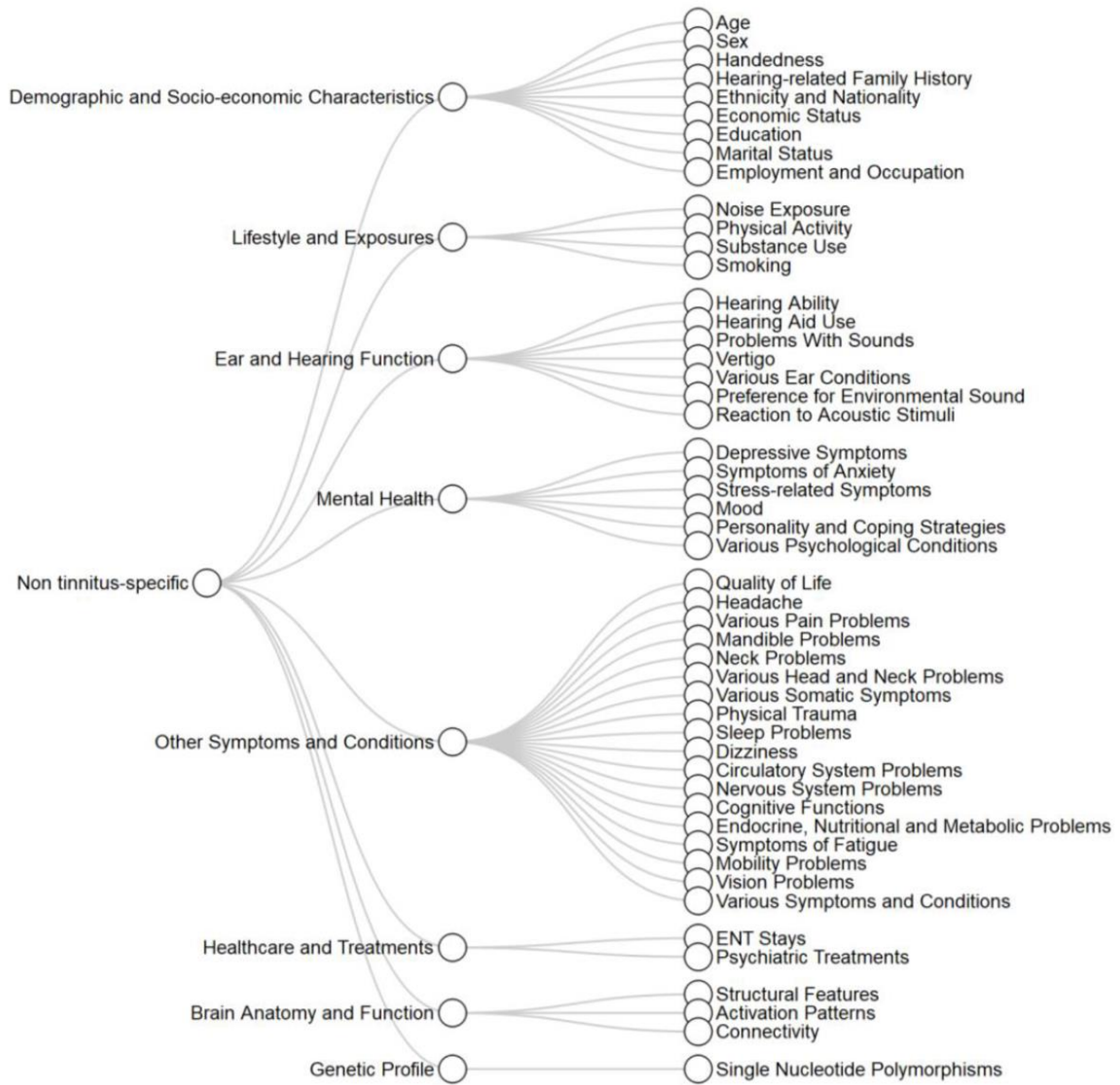


Figure 1.2.3 List of non-tinnitus-specific attributes, reproduced from (Genitsaridi et al., 2020) under CC BY License

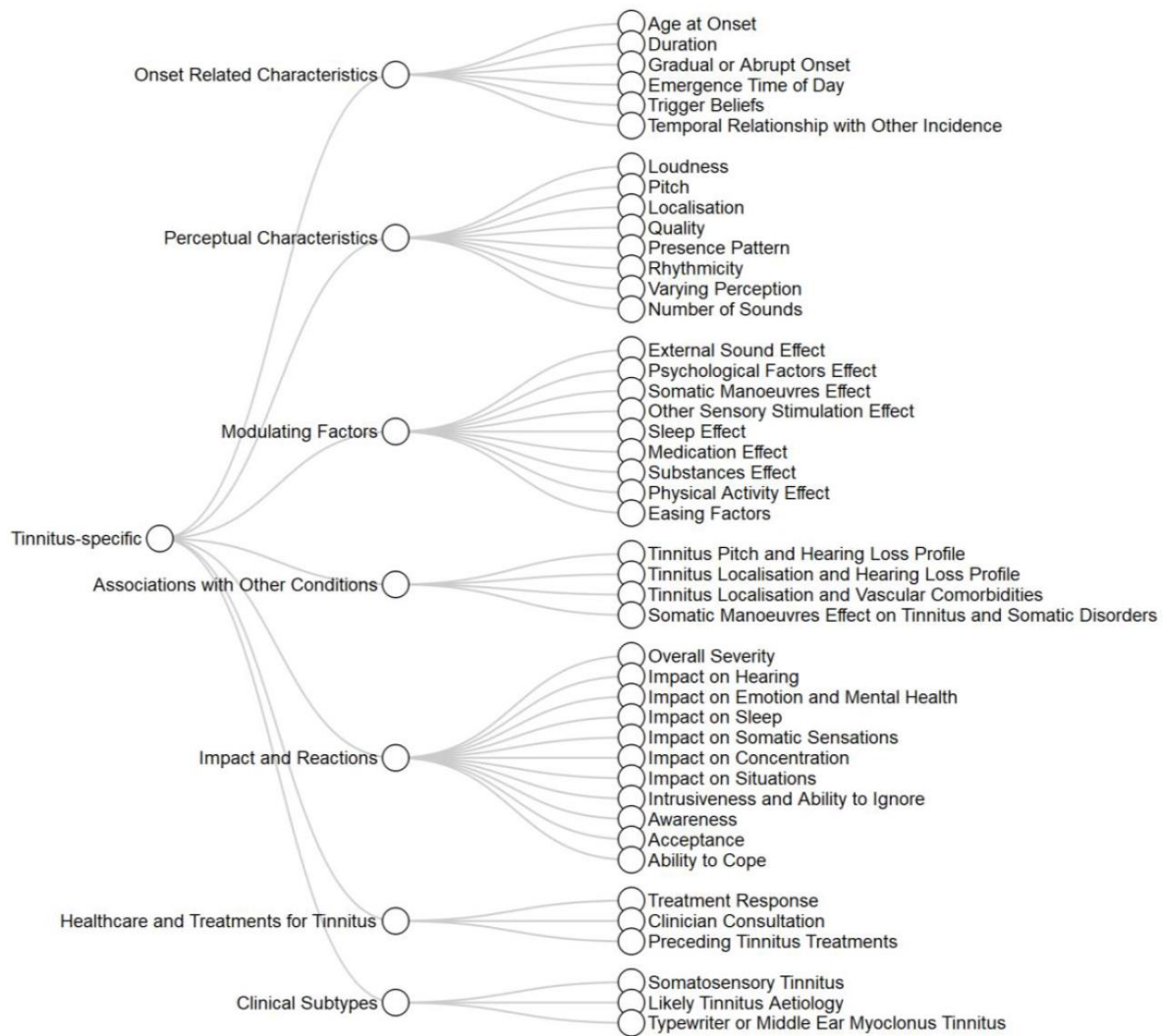


Figure 1.2.3 List of tinnitus-specific attributes, reproduced from (Genitsaridi et al., 2020) under CC BY License

Exploration of such heterogeneity across multiple dimensions requires to define a conceptual framework according to which the tinnitus population can be segmented. On this matter, an interesting framework of thought has been proposed by Genitsaridi (2021) in her thesis. The author proposed a framework on how to explore tinnitus heterogeneity by introducing the three concepts of subphenotyping, subtyping and endotyping with the definitions given hereafter in figure 1.2.1.

Term	Definition
Subgroup	A part of a population (generic term)
Subphenotype	A part of a population with a distinct set of observable characteristics (based on Lötvall et al., 2011)
Subtype	A part of a population with a condition that can be used to guide treatment decisions (based on Saria and Goldenberg, 2015)
Endotype	A part of a population with a condition with distinct underlying mechanisms (based on Anderson, 2008; Lötvall et al., 2011)

Figure 1.2.1 Conceptual distinctions between segmentations of one pathology. From Genitsaridi (2021) reproduced with authorization, ref: (Anderson, 2008; Lötvald et al., 2011; Saria and Goldenberg, 2015)

The core idea of such conceptual distinction lies in the fact one should not take for granted the hypothesis that they are identical. There may not be a bijective relation between such segmentations Each subphenotype of tinnitus may not correspond to a unique endotype of tinnitus, and maybe multiple different treatments can have efficacy for it.

Concerning the question of tinnitus subtypes and hence how different tinnitus subgroups may respond differently to different treatments, this was defended with the formula “one size does not fit all” (Hall et al., 2019; Kim, 2022) and results from another study which tends to confirm such point of view (Niemann et al., 2024).

Concerning the search of homogeneous subphenotypes of tinnitus, several studies have tried to perform algorithmic segmentations (clustering) of tinnitus patients on various databases (Baloi, 2020; Langguth et al., 2017; Niemann et al., 2020; Schecklmann et al., 2012a; Tyler et al., 2008; van den Berge et al., 2017). Most of these attempts were reviewed by Genitsaridi and colleagues (2020) who gave methodological recommendations for future clustering studies, as well as a comprehensive list of tinnitus specific and non tinnitus-specific variables to optimize such a clustering attempt. A similar comprehensive list of dimensions to investigate tinnitus heterogeneity was also proposed (Mohan et al., 2022).

## 1.2.6 Tinnitus intra-individual variability

The perception of tinnitus, and its associated burden, can vary over time in the same patient, whether he or she is seeking medical care or not (Dauman et al., 2015).

Recently, a major project was launched to measure longitudinal assessments of tinnitus in a large cohort of patients. This endeavor was titled the TrackYourTinnitus project (Schlee et al., 2016). It consisted in a mobile crowdsensing platform in the form of a smart phone app that enabled tinnitus patients to record ecological momentary assessment of their tinnitus on several symptom scales. Such longitudinal acquisitions demonstrated an important panel of tinnitus variability patterns in different patients, on different time scales and often in association with different tinnitus symptoms. For example, an analysis of such dynamics showed that increases in tinnitus loudness were associated with increases in tinnitus distress (Probst et al., 2016). Moreover, Pryss and colleagues (2019) highlighted a positive correlation between self-reported stress and tinnitus (loudness and distress).

Moreover, patients tend to report, retrospectively, that either their tinnitus is naturally varying or not varying. The study from Pryss and colleagues (2019) with the TrackYourTinnitus app showed that there was no significative difference in prospective variation of tinnitus loudness between users who retrospectively rate tinnitus loudness as “varying” and the ones who retrospectively rate it as “non-varying”. Hence, studying such variations require to perform prospective longitudinal assessments of tinnitus cohorts.

Chen and colleagues (2020) demonstrated that when such longitudinal measurements of tinnitus were reported, its variability tended to diminishes with increasing number of repetition of its assessments. This suggests that at least a part of tinnitus variability that is reported in longitudinal studies is due to some form learning or habituation process of patients to the measurement tool. Yet, depending on patients, a residual variability can remain even after an important number of consecutive measurements. What are the reasons for such intra-individual variability of tinnitus over time ?

For this section, we are going to decompose possible variability patterns depending on their time scales. Indeed, tinnitus can vary over several days (infradian variability), or can have 24h patterns of variation (circadian variability) or can vary within a shorter time span (tinnitus modulations).

### 1.2.6.1 Infradian variability

On long time-scales, a study suggested a seasonal variability of tinnitus burden by studying the seasonal pattern of evolution of Internet search engine query data of the term “tinnitus” (Plante and Ingram, 2015). According to this study, “tinnitus” was browsed on Internet significantly more in winter than in summer. Moreover, another study has shown that chronic tinnitus patients were often prone to seasonal affective disorder and that uncomfortable seasons were associated with higher tinnitus burden (Kim, 2016).

Little research has been performed on trying to link menstrual cycles and tinnitus variations. A case study by Schwartz and colleagues (1994) reported that in a female subject tinnitus varied with menstrual cycles and its frequential characteristics varied in correlation with the frequency of spontaneous otoacoustic emissions of one of her ears. Besides, another study by Yu and colleagues (2019) showed that women with menstrual cycle irregularities had higher chance of presenting tinnitus.

Last, in some patients tinnitus can be intermittent (Koops et al., 2019). Such patients are not able to perceive their tinnitus at some moments and unable to silence it at others. Such intermittent forms of tinnitus can oscillate between presence and disappearance of the tinnitus percept at different time scales. In the present thesis, a specific focus will be made to analyze and understand tinnitus patients that present an intermittent form of tinnitus that switches from one state to the other due to the occurrence on sleep. Such patients will be designated as Sleep Intermittent Tinnitus (SIT) patients (Guillard et al., 2023b). Such patients have irregular cycles of several days with or without tinnitus, tinnitus intensity being settled at their awakening, and potentially reset after naps.

### 1.2.6.2 Circadian variability

Several studies have tried to understand whether or not tinnitus was subjected to circadian variations. A first and evident question regarding circadian cyclicity of tinnitus is : does tinnitus depend on time-of-day? A study by Probst and colleagues (2017) with the TrackYourTinnitus app showed that on subjective scales of tinnitus loudness and distress,



tinnitus appeared milder between 8am and 8pm and louder in the evening and above all during the night between midnight and 8am. Yet, this study has some methodological limitations as between 9am and 9pm, tinnitus metrics were calculated as an average on more than 500 records, while between midnight and 8am, tinnitus metrics were calculated as an average on only 100 records or less. Average scores between midnight and 8am may hence appear as data points collected by a minority of participants suffering from insomnia, and hence, more prone to provide outliers measures.

In a survey on Siopi, the question “Is your tinnitus varying over time?” was submitted, with possible answers: “From one second to the other without clear reason”, “Depending on the day I observe very different intensities, potentially disappearances, it generally gets decided when I wake up”, “It is very frequently clearly more intense on waking”, “It is very frequently clearly more intense in the evening”, “No, my tinnitus is constant or varies very little”. 1361 people with tinnitus responded to this question. 256 (18,8%) responders selected “It is very frequently clearly more intense on waking” and 478 (35,12%) selected “It is very frequently clearly more intense in the evening”. Hence, according to our collected data, it seems almost twice as many people report tinnitus is stronger in the evening than in the morning.

Two other questions on the subject of circadian regulation of tinnitus are: is tinnitus more a burden for individuals of morning chronotype or evening chronotype ? When is tinnitus more a burden for individuals depending on their chronotype (peak of alertness in the morning or the evening) ? A study by Zacharia and colleagues (2014) on a small cohort of 20 patients showed that patients that tended to have a moderate morning chronotype (peak of alertness rather in the morning) tended to experience higher tinnitus in the morning compared to evening. In comparison, intermediate chronotype patients did not show differences between morning and evening evaluations of tinnitus. This study hence suggests that circadian chronotype may affect tinnitus variability. Additionally, another study by Toplu and colleagues (2014) identified that evening chronotype patients reported higher burden of tinnitus (measured by visual analog scales on tinnitus severity) than morning chronotype patients.

Last, the research led by the team of Pr Barbara Canlon, including Pr Christopher Cederroth, over the last decade had made significant progress on the question of the influence of the circadian rhythm in the auditory system. Basinou (2016) has recently dedicated his thesis on this subject under their supervision. They notably identified a circadian clock inside the inferior colliculus (Park et al., 2016). Moreover, Cederroth and colleagues (2017) present how circadian rhythmicity could interplay with tinnitus according to current models, and how the methodology of protocols should adapt to take this parameter into account. Last, the article concludes that taking advantage of circadian influences on tinnitus could be an avenue to new therapeutic approaches.

### 1.2.6.3 Tinnitus modulations

Variations of tinnitus that occur on a time scale shorter than a day reported in the literature are often elicited forms of variations, classically designated as tinnitus modulations.

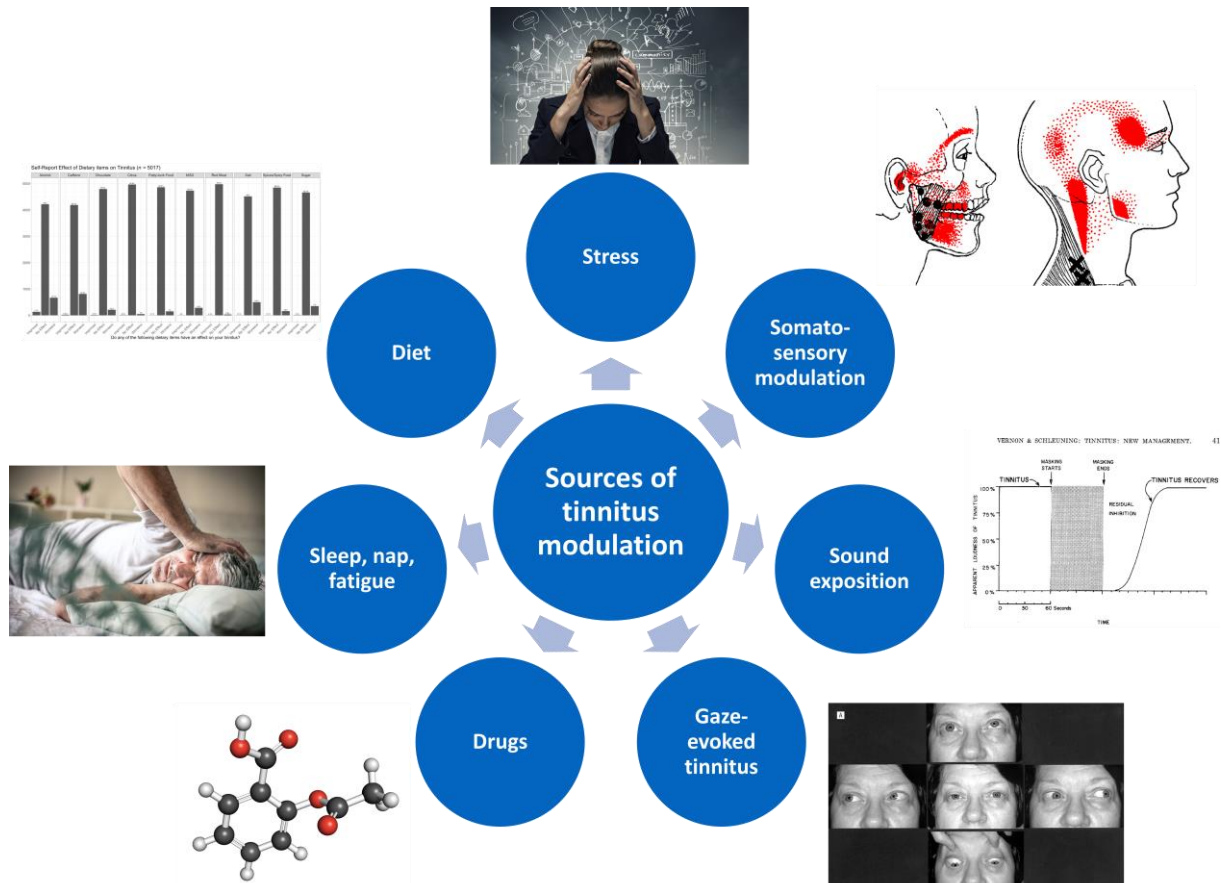


Figure 1.2.2 Sources of tinnitus modulation. Sound exposition illustration from Vernon and Schleeuning (1978), diet illustration from Marcrum and colleagues (2022)

#### A. Tinnitus modulation by stress

Stress has long been known to modulate tinnitus and above all tinnitus burden. A review by Elarbed and colleagues (2021) demonstrated from a synthesis of 50 studies that tinnitus patients tend to report louder and more bothersome tinnitus when they are stressed, although not all patients identify stress as the initial cause of the onset of their tinnitus. Another review by Mazurek and colleagues (2015) digs in the question of what pathophysiological mechanisms may create an interaction between emotional stress and tinnitus. In this review, they present the physiologic changes provoked by emotional stress: flip from homeostasis to allostatic load, central release of acetylcholine and glucocorticoids (in particular cortisol), epigenetic modulations, activation of the sympathetic nervous system... Multiple studies have shown associations between tinnitus and several of these physiological markers of stress. Notably Hébert and Lupien (2007) have shown thanks to salivary cortisol measurements that

tinnitus patients have a blunted cortisol response to psychosocial stress in comparison to a matched control group. Moreover, a study from Jackson (2019) highlighted that tinnitus patients had a disturbance in their cortisol awakening response. Both of these examples illustrate as Mazurek and colleagues (2015) concludes that tinnitus is associated with significant hypothalamic–pituitary–adrenal (HPA) axis dysregulation as found in other stress-related diseases.

## B. Tinnitus modulation by sound and “silence”

Sound exposure is also a very well-known cause of modulation of tinnitus. Yet, sound relation to tinnitus is complex. Sound exposure can trigger tinnitus and yet sound is often used to try to alleviate it. Tinnitus modulations by sound are heterogeneous with positive and negative outcomes depending on sound and individual characteristics. On the one hand, silent and non-ecological very silent environments such as anechoic rooms are generally reported to have a negative impact on tinnitus (Colagrosso et al., 2019). Even healthy individuals can experience tinnitus by staying in silent and/or anechoic environments (Tucker et al., 2005), and especially if they are engaged in an auditory attention experiment (Knobel and Sanchez, 2008).

On the other hand, rich sound environments can have mixed effects on tinnitus, depending of the characteristics of the sound and the symptomatologic profile of the patient. As an example, in a survey by Pan and colleagues (2015), 256 patients were asked what made their tinnitus worse or better. 31% of them reported that noise improved their tinnitus, while 32% patients reported that noisy places made their tinnitus worse. Interestingly, this study highlighted that patient whose tinnitus is not worse in quiet, report generally tinnitus reduction by noise. On the contrary, for those whose tinnitus is not worse in noise, it is usually not reduced in quiet.

In some forms of tinnitus, often when it is associated with debilitating hyperacusis, sound exposure can worsen tinnitus perception. This has notably been reported in patients affected by what has been referred to as tensor tympani syndrome (Westcott et al., 2013). This phenomenon has been referred to by PJ Jastreboff as “winding-up” effect and led him to a classification of tinnitus patients in five categories (Jastreboff, 1999). In this classification, patients presenting such exacerbation of tinnitus following prolonged sound exposure in association with hyperacusis, were described as having the highest impact on their quality of life and requiring specific treatment approaches.

Numerous therapeutical approaches, referred to as sound therapies have been tested to try to alleviate or cure tinnitus by sounds (Hoare et al., 2014; H. Wang et al., 2020). Examples of such sound therapies are : hearing aids, white noise generators, enriched sound environments and specific sound therapies. Studies report that these approaches generally elicit positive outcomes at least for some tinnitus patients. Patients with more severe initial tinnitus seem to respond better to such approaches. Customized sound therapies appear to generate better outcomes than non-customized sound therapies.

General mechanisms of action of sound-based therapies for tinnitus are tinnitus masking and residual inhibition. Tinnitus masking is by definition an acoustical suppression of tinnitus by another sound. Residual inhibition is the phenomenon of temporary suppression of the tinnitus percept following the offset of a tinnitus masking sound (Roberts, 2007). This phenomenon generally last less than a minute and is not present in all individuals.

### C. Somatosensory modulations of tinnitus

Another well-documented source of tinnitus modulations are somatosensory modulations of tinnitus (Ralli et al., 2016). Somatosensory modulations of tinnitus are temporary modification of tinnitus pitch and/or loudness, or its silencing, elicited by movements of the temporomandibular joint, head and neck muscles. Such tinnitus modulations are reported to be present in two thirds of tinnitus patients. A standardized list of jaw and head maneuvers have been proposed by Ralli and colleagues (2017b) to explore patient's susceptibility to present somatosensory modulations of tinnitus. In the same review, the authors report that jaw movements most often trigger tinnitus increase, while mixed outcomes can be observed for neck movements.

Pathophysiological mechanisms accounting for somatosensory modulations of tinnitus have been described by Shore and colleagues (2016). Findings of their team over more than a decade of research concluded that jaw-dependent modulations of tinnitus were most probably initiated by proprioceptive signaling by sensory nerve fibers of the mandibular branch of the trigeminal nerve. This signal is then received by the caudal part of the spinal trigeminal nucleus (Sp5), which has been identified to have excitatory glutamatergic projections towards the dorsal cochlear nucleus. In case of auditory nerve deafferentation, maladaptive plastic changes seem to occur at the level of the cochlear nucleus, which becomes particularly excitable by somatosensory information coming from Sp5. This tends to increase spontaneous firing activity at its level. This increased spontaneous activity then propagates downstream in the central auditory pathway, triggering an increase of the tinnitus percept.

A similar mechanism is proposed to explain tinnitus modulations by signals coming from the cervical area. In this case the proposed anatomical substrate of such an interaction are the projections that have been identified between the dorsal root ganglion of the upper cervical area and the cochlear nucleus (Zhan et al., 2006).

It is important to specify that depending on authors, some believe that somatosensory interactions with tinnitus are just the cause of tinnitus modulations while some other believe that this subgroup of patients form a different etiological homogeneous endotype on its own, referred to as somatic tinnitus, that should be investigated and treated separately to other forms of tinnitus (Ralli et al., 2017a). For this reason, this section could also have been placed in the section 1.2.4 "tinnitus models" as well. Additionally, tinnitus patients presenting important modulations mainly elicited by the cervical area are described as cervicogenic somatosensory tinnitus patients (Michiels et al., 2015). For these patients, it seems that

physical therapy coordinated by a physiotherapist has shown efficacy to alleviate their symptoms (Michiels et al., 2017).

#### D. Gazed-evoked tinnitus

A curious source of modulations of tinnitus that is only observed in a minority of tinnitus subject is gaze-evoked modulations of tinnitus. In such cases, eyes rotation in some directions (upward, laterally, downward) tend to trigger, modulate or stop the tinnitus percept (Lockwood et al., 2001). This phenomenon seems to appear most frequently after acoustic neuroma resection with posterior fossa / cerebellar–pontine angle surgery (Biggs and Ramsden, 2002). Subjects typically describe tinnitus in the deaf ear on the side of the surgery that can be modulated by peripheral eye gaze. Van Gendt and colleagues (2012) report that in such cases fMRI imagery highlights a hyperactivity of cochlear nucleus and inferior colliculus. A reduction of activity in MGB and of inhibition in the auditory cortex activity was also observed.

#### E. Tinnitus modulation by sleep and fatigue

Another source of modulation of tinnitus, that will be thoroughly explored in this thesis are sleep modulations of tinnitus, specifically tinnitus modulations by naps. This topic is here cited but will be exhaustively developed later on. It is worth mentioning that in relation with sleep, fatigue is known to increase tinnitus (Colagrosso et al., 2019).

#### F. Tinnitus modulation by dietary items and drug intake

Patient often report tinnitus modulation after consumption of specific substances: food, drinks or drugs. A survey led by Marcrum and colleagues (2022) analyzed records from a cohort of 5017 responders on how a list of dietary items could elicit modulations of tinnitus. Investigated dietary items were alcohol, caffeine, chocolate, citrus, junk food, monosodium glutamate, red meat, salt, spicy food and sugar. Their study concluded that the majority of patients did not report any modulation of tinnitus after consuming any of these products. Additionally, reported effects were most commonly mild. Yet, they identified that intake of caffeine, alcohol and salt tended to elicit negative effect on tinnitus severity. Curiously, alcohol was also the dietary item that elicited most often improvements of tinnitus, although it was only for 2.7% of the sample.

On the other hand, an important list of drugs are known to have ototoxic proprieties and tend to trigger tinnitus as a side effect (Cianfrone et al., 2011). Notoriously, antibiotic gentamicin is particularly well known for its ototoxicity (Ahmed et al., 2012), and is now used as ablative treatment that provoke definitive cophosis in case of highly bothersome Meniere disease (Pullens and Benthem, 2011). Additionally, at high concentrations, common aspirin/salicylate is well-known to trigger tinnitus. This is why a lot of studies used aspirin as trigger for tinnitus in animal models (Jastreboff and Sasaki, 1994). Tinnitus induction by salicylate has been thoroughly investigated and models have been proposed to explain how it could cause tinnitus emergence (Stolzberg et al., 2012).

## 1.2.7 Key insights

Tinnitus is a quite prevalent condition for which there is still no cure in the majority of cases. Scientific and medical communities are still gradually converging to define it properly. The quest for a cure for tinnitus is probably hampered by its interindividual and intraindividual variability. An abundance of models have been proposed to try to explain the pathophysiology of tinnitus as well as its physiological correlates. Due to the heterogeneous nature of tinnitus, it is maybe possible that several and potentially incompatible models of tinnitus will result to be true for different endotypes of tinnitus. Models of tinnitus can be classified in three types :

- Bottom-up models which propose candidates and/or mechanisms that lead to the emergence of a “tinnitus signal” within the auditory pathways. Such models diverge on the nature of the tinnitus signal: is it related to increased spontaneous activity (Norena, 2011), increased synchrony (Noreña and Eggermont, 2003) or alteration of the communication between the thalamus and the auditory cortex (Llinás et al., 1999) ? Is it due to only altered auditory signal or its interference with cross-modal somatosensory inputs coming from the jaw and/or neck (Shore et al., 2016) or even the middle ear muscles (Noreña et al., 2018) ? Is it transmitted through the primary or non-primary pathways (Eggermont, 2021) ?
- Top-down models which propose that damage to hearing necessarily generates a predisposition to tinnitus (precursor of tinnitus) and that the difference between patients experiencing tinnitus and patients experiencing hearing loss without tinnitus lies in the efficiency of the gating mechanisms within the auditory pathway. Yet again different models have been proposed, notably on the locus of such inhibition: at the level of the thalamus due to the thalamic reticular nuclei (Rauschecker et al., 2010) or at the level of the auditory cortex because of the PV neurons (Knipper et al., 2020)?
- Bayesian inference models: in such models the question of tinnitus perception is raised at the interface between the auditory cortex and consciousness network. In these cases, it is assumed that at least for a tonotopically restricted range the information present at the level of the auditory cortex is altered, whether it is due to alteration of the auditory signal itself and/or because of insufficient gating. Such models assume that the brain has prior predictions, confronts them to the altered sensory input and that a prediction error emerges from it. This prediction error leads to the emergence of tinnitus. Such models additionally provide a framework in which modulation of salience translates to modulation of tinnitus perception. Yet, divergence exist between models on the question of distribution of which areas of the brain are associated with tinnitus. Is everything mainly occurring at the level of the auditory cortex (Sedley et al., 2016) or is it distributed among numerous regions of the brain, within a tinnitus network, with a core and auxiliary attributes (De Ridder et al., 2014c) ?

## 1.3 Sleep

We all know what is to sleep. From before we are even born to our oldest days we will experience it (almost) every day. We feel tired, we rest, we enter this strange state and after a couple of hours we emerge from it, and after a short period of confusion (awakening), we feel fresh to go on for another day. Sleep evolves with us as we evolve through life, its characteristics changing over time, especially in our early days. Then, over the years it takes less and less space, and gets more fragmented as we get older.

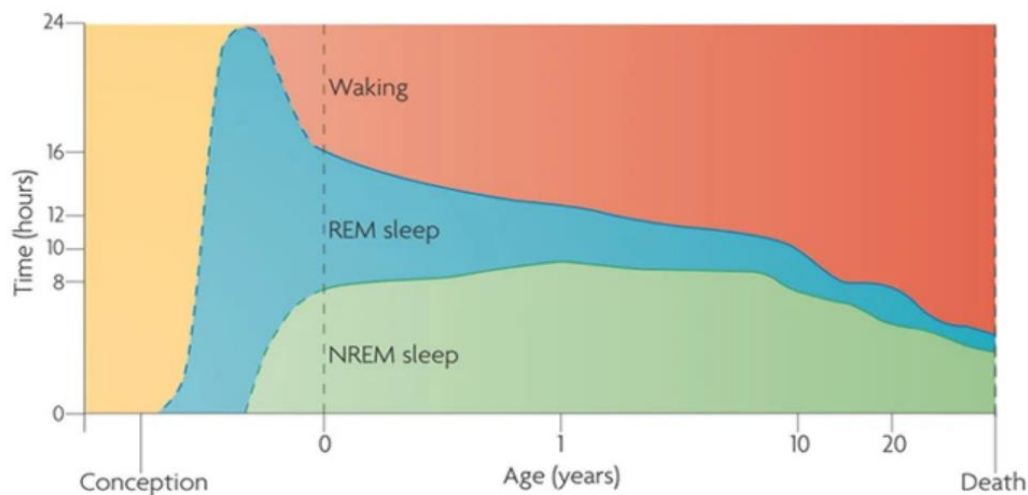


Fig 1.3.1 Sleep and wake proportions across life, reproduced with authorisation from (Hobson, 2009)

Sleep has adapted its attributes to the characteristics of Earth specific rhythms. Earth revolution cycles bring rhythm to our existence, referred to as circadian rhythm. As a diurnal specie, we have associated activity with light and sleep with darkness. But earth revolutions cycles seem more important to us than cycles of light and dark : individuals above the polar circles still live and sleep in 24 hours circles, despite in some periods of the year, summer, they do not experience night, and in some others, winter, they do not experience day.

Circadian alternances of periods of activity and rest are a general rule with only rare exceptions in all forms of life on Earth, from bacteria to mammals (Bhadra et al., 2017). Yet sleep as we experience it seems to have appeared quite recently in the great tree of life, although this question is still highly disputed as sleep does not leave a mark in fossils. Indeed, current hypothesis tracks back sleep to around 280 millions years ago, in the common ancestors to mammals, birds and reptiles, cotylosauria (Nicolau et al., 2000). This hypothesis was emitted by studying which current species sleep and observing that most current reptiles experience what is designated as behavioral sleep, which is comparable to some extent with mammal's sleep. It appears that sleep appeared in birds and mammals' ancestors coincidentally with thermoregulation and telencephalic development.

Alongside evolution, it seems that two distinct types of sleep have appeared : Non-Rapid eye movement (Non-REM) sleep, which contains light and deep sleep and Rapid Eye Movement (REM). It seems rapidly following its appearance, Non-REM sleep appeared as a bare necessity for staying alive, as 2-3 weeks without it leads to death (Rechtschaffen and Bergmann, 1995). In humans, sleep deprivation is also known to put our health greatly at risk (Orzeł-Gryglewska, 2010). It is currently disputed whether or not REM sleep has appeared simultaneously or after Non-REM sleep. Signs of REM-like sleep have been identified in some reptiles suggesting that maybe it was also present in our common ancestors (Libourel and Barrillot, 2020). Unlike Non-REM sleep, it is apparently questionable that we rely on REM sleep to survive, above all in adulthood. Indeed, on the one hand, it has been shown in adult animals and adult humans that REM sleep deprivation leads to limited health disturbances (Vogel, 1975). It was even shown that REM sleep deprivation can have positive effects in depression (Crişan et al., 2023). On the other hand, it was shown that REM sleep deprivation leads to a rebound of REM sleep on next sleep occurrences, suggesting that the brain tries to compensate such deprivation (Beersma et al., 1990), and REM sleep seems to be critical for human brain development, above all in our early life (Shaffery and Roffwarg, 2009).

### 1.3.1 Why do we sleep ?

Considering sleep as an essential process necessitates assigning one or several purposes to it. However, identifying the exact function of sleep continues to be a major obstacle in the field of sleep research. While researchers have made significant progress in comprehending the characteristics, mechanisms, and regulation of sleep, its ultimate purpose remains unclear. The difficulty lies not in the scarcity of possible explanations, but rather in the numerous functions that sleep seems to fulfill and the challenge of determining its specific role in each of these functions.

Here are few examples of processes that has been identified to mainly occur during sleep. Sleep seems also very important for the conservation of energy (Berger and Phillips, 1995), the cleansing of metabolic waste in the central nervous system (Eugene and Masiak, 2015; Xie et al., 2013), and it appears as the price the brain has to pay for plasticity (Tononi and Cirelli, 2014). An extensive literature has also assessed the function of sleep in memory (Diekelmann and Born, 2010).

Yet, the functions attributed to sleep should be specific to the act of sleeping itself. Among the aforementioned functions, which ones require an individual to be asleep and disconnected from their environment? For most of them, as for example for metabolic recovery or the consolidation of immune memory, it does not necessitate to occur in a state of disconnection.

#### 1.3.1.1 The synaptic homeostasis hypothesis

An important hypothesis on the question of why do we sleep has been emitted by Tononi and Cirelli (2006) and is referred to as the synaptic homeostasis hypothesis or the synaptic downscaling hypothesis. According to the hypothesis, synaptic strength in numerous brain circuits is believed to undergo a net increase as a result of plastic processes that take place



during wakefulness. This synaptic strength increase is referred to as synaptic potentiation. The purpose of sleep, on the other hand, seems to be to reduce (i.e. downscale) synaptic strength to a baseline level that is sustainable in terms of energy, gray matter space utilization optimization, learning and memory.

It is worth noting that evidence has been provided that such a downscaling process mainly happens during Non-REM sleep and more specifically during Slow Wave Sleep (SWS). As a result, this hypothesis mainly accounts for the explanation of the importance of Non-REM sleep and not REM sleep. We will try to present the utility of the latter in the following sections. Moreover, this hypothesis centers the importance of sleep around its critical role for the brain and the nervous system and not any peripheral organ.

### 1.3.1.2 Ontogenetic hypothesis of REM sleep

The ontogenetic hypothesis on the function of REM sleep has been proposed by Roffwarg colleagues (1966). It was proposed after this team made the discovery that REM sleep (or at least a sleep stage comparable to REM in many aspects) was of greater proportion in the late-fetal and early postnatal period than at any other time point later in life. It was later shown that REM sleep proportion within a 24h timespan tend to diminish gradually through life (as shown in figure 1.3.1). This finding led this team of researcher to posit that REM sleep may have an important role in brain development or brain maturation. More precisely, they proposed that REM sleep may help to shape neural pathways. More generally, this hypothesis gives an explanation on why humans devote a larger part of their days asleep during the postnatal period.

More than forty years later, Shaffery and Roffwarg (2009) wrote an updated review on the topic of this hypothesis. They presented the consequent number of results that had comforted this hypothesis through the years. Notably, these results illustrated that REM sleep appears necessary for normal brain maturation, especially for the maturation of the hippocampus. A strong argument to their hypothesis was that an interruption of REM sleep in animals (either experimentally-induced or because of congenital sleep disorders) during the critical periods of synaptic plasticity of early life contributes to abnormal brain maturation (Lopez et al., 2008; Mirmiran, 1995; Mirmiran et al., 1983).

### 1.3.1.3 Reality model adjustment through REM sleep

Hobson and Friston (2012) proposed an additional and potentially complementary hypothesis on the function of REM sleep. This hypothesis notably gives explanations on why we continue to experiment REM sleep throughout our life, despite the fact that in adulthood our brain maturation has been completed. Notably, they highlighted that it should serve an important purpose for it to be selected by evolution as it comes with costs. Not only are we not responsive during REM sleep as in Non-REM sleep, but also and curiously, REM sleep is the only normal human state in which homeothermy is not preserved (Parmeggiani, 2003).

The function Hobson and Friston proposed for REM sleep concerns brain representations optimization. For it to be properly understood, Bayesian formalism in brain functioning must be introduced. An important framework that has been proposed to explain how the brain

handles sensory information is the Bayesian framework which states that our perception of the world may not be the perception that our sensory organs are continuously transmitting to us but rather more the prediction of the state of the world that our brain creates, continuously adjusted by incoming sensory information. This conceptual jump is of great importance. It hence means that the brain is constantly making predictions about the state of the world, inventing it. Then in parallel sensory organs measures the states of the world and transmits information about it to the brain. Then, last step, the brain adjusts its perception of reality according to the differences between its predictions and the sensory information it received, what we call prediction error.

The Bayesian framework is a suitable hypothesis to explain how the brain works as it is intrinsically cost-effective. Indeed, if the brain has good prediction capabilities on the states of the world, prediction error is low and there is little adjustment to be done to provide an accurate experience of reality. To illustrate this process, one can conceive a television or computer screen. Let's assume that such a screen display one image per millisecond and let's assume that each image is composed of 10 000 pixels. It would consume much more energy for a computer to refresh the color content of each of the 10 000 pixels each millisecond that it would cost it to refresh only the pixels that have changed since the last image. Bayesian brain theory applies the same idea for our brain and how we see the world : from one millisecond to the next, the brain saves energy by only adjusting the pixels that have changed in what we see (or at least for what we devote interest to seeing).

Consequently, Bayesian formalism implies that we are making continuous iterative infinitesimal jumps in time to update our predictions of the state of the world. This update process consists in starting from a prior prediction on the states of the world and making a posterior prediction on the states of the world by adjusting the prior prediction with prediction error.

Here comes with more formalism the hypothesis defended by Hobson and Friston on the function of REM sleep. They propose that during the day as we are interacting with our environment and sampling information from it with our sensory organs, our brain works in optimizing our posterior predictions, based on fixed priors and measured sensory data. On the other hand, during sleep, we are isolated from the sensory information of the world and confined in a reality of our own, created by us as a playground for another type of optimization. Indeed, in REM sleep, they propose that starting from posterior predictions (what has been observed) and taking into account what sensory data has been measured (or by simulating it) the brain then start to optimize its prior predictions. This means it tries to adjust retrospectively what it should have assumed in the first place, thanks to the new experience it has collected during the day.

## 1.3.2 How do we sleep ?

### 1.3.2.1 The circadian and homeostatic processes

The circadian and homeostatic processes are two processes that are hypothesized to regulate sleep in mammals. This two-process model proposes that the regulation of sleep is determined

by the interaction between two processes: Process S, which is influenced by sleep and wakefulness, and Process C, which is controlled by the circadian pacemaker (Borbély et al., 2016). Process S, also known as homeostatic process or sleep pressure, accumulates during wakefulness and decreases during sleep. Its value-range oscillates in accordance with the day and night cycle, which is regulated by the circadian pacemaker. When Process S approaches its lower boundary, it triggers awakening, while nearing the upper boundary triggers sleep. During sleep, the principal marker of Process S is non-REM sleep electroencephalography (EEG) slow wave activity (delta waves). On the other hand, markers of Process C include core body temperature and melatonin rhythms.

### A. Circa diem:

“Around a day”. A meaning both referring to one turn on the sphere we live on and the notion of an approximative duration. It conveys indeed the idea of its meaning. Circadian rhythms are time keepers for biologic processes and metabolic activities in most life forms. Such time keepers are strategically approximative: they rely on synchronizing events referred to as zeitgebers (German for “time-giver”) to adjust the clock to environmental changes. The light-dark cycle, temperature, feeding, and social interactions are all factors that influence biological rhythms. The light-dark cycle is particularly important as it serves as a major zeitgeber, or time cue, for organisms. In mammals, light-dark response is mediated by the secretion of melatonin. The light-dark cycle response is considered the most significant factor in evolution because it provides explicit predictions of the daily and seasonal cycles. For example, it helps organisms anticipate changes in the length of daylight throughout the year. However, even in the absence of environmental cues, the biological clock, which is an endogenous timing system, is capable of generating biological rhythms. This means that physiological functions can continue to occur even in temporal isolation, ensuring the organism's survival and well-being.

A major seminal discovery in this field was the discovery by Shearman et al. (1997) of the 3 proteins Per1, Per2 and Per3 that organize the circadian rhythm at the level of each cells in mammals. This circadian clock is regulated by suprachiasmatic nucleus that act as a pacemaker. It receives information from the retina which serves as a direct recipient of photic information, and then in turn coordinates the synchronization of peripheral oscillators located in various brain regions and peripheral tissues. This synchronization process, known as entrainment, is facilitated through autonomic innervation, humoral signals, hormones, as well as the regulation of body temperature and feeding.

### B. Sleep pressure / homeostatic process

Sleep pressure is the mechanism by which the need for sleep increases as the day progresses. It is hence at its lowest in the morning at the awakening and appear as an increasing function in time. Different physiological markers of this process have been identified, as notably the progressive accumulation of adenosine in the organism during wake (Porkka-Heiskanen et al., 2002), and the increase in synaptic weights (synaptic potentiation) in the brain described by Tononi and Cirelli (2006).

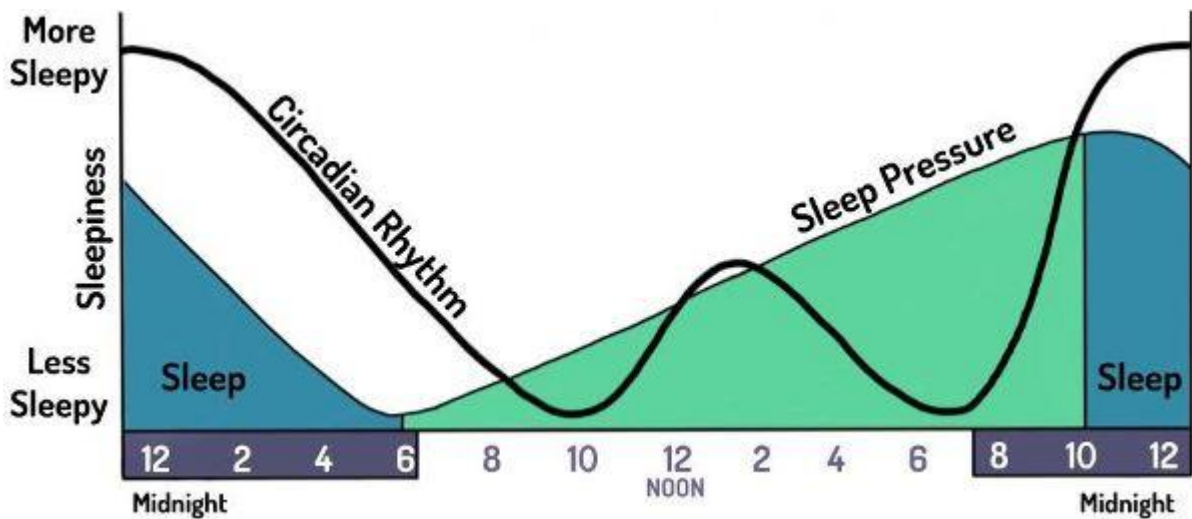


Fig 1.3.2 Circadian rhythm and sleep pressure along the day cycle, from Libretexts social sciences, Pr Sheryl Shook, Kapi'olani Community College

Traditional observations led to the belief that circadian rhythm and homeostatic pressure are two distinct processes, but recent research has shown that these processes may be linked (Franken and Dijk, 2009). In fact, this review highlights that induced lesions in the functioning of circadian regulation has consequences over the homeostatic process as well.

### 1.3.2.2 From wake to sleep, the sleep onset

Sleep onset appears as a quite straightforward process. As mentioned before, the transition from wakefulness to sleep in normal physiological conditions is influenced by two factors: sleep homeostatic pressure and intrinsic circadian oscillation. It is believed that the increasing sleep need or pressure during prolonged wakefulness leads to the activation of sleep-regulating neurons. These neurons inhibit the multiple arousal systems facilitating the transition from wakefulness to sleep. This arousal system comprises hypocretin (orexin) neurons in the lateral hypothalamus and aminergic centers like Locus Coeruleus for noradrenaline, Raphé nuclei for serotonin and tuberomammillary nucleus for histamine. Sleep-regulating neurons are found in various subregions of the preoptic hypothalamus, with a high concentration in the ventral lateral preoptic area (VLPO) and the median preoptic nucleus (MnPN) (Gvilia, 2010). These neurons are GABAergic or use the neurotransmitter galanin and exhibit elevated discharge rates during both non-REM and REM sleep compared to waking.

### 1.3.2.3 Stages of sleep

The following parts will consist in describing the characteristics of the conventional stages of sleep which are N1, N2 and N3 sleep stages composing Non-REM sleep and finally REM sleep. These are the usual sleep stages that are used for sleep scoring in sleep medicine and that are recommended by the American Academy of Sleep Medicine (AASM). It worth noting that such classification of sleep is a convention and that other scoring conventions exist,

notably a scoring method proposed by Hideki and colleagues (1996) that proposes to classify sleep in 9 sleep stages (referred to as Hori scoring).

### A. N1 sleep stage

N1 sleep stage is at the transition between wake and light sleep N2. It corresponds to the moment of progressive transition to sleep. This stage is distinguished by distinct electroencephalogram (EEG) patterns, namely bursts of theta band rhythm (4 to 8Hz) replacing the alpha band rhythm (8 to 12 Hz) that is typically observed when an individual is awake with closed eyes. Yet it is important to note that such theta band occurrence present themselves as short bursts, of duration of around 1 second or less. Moreover, when the theta bursts are not present, the EEG activity is characterized by a significative decrease in the alpha band compared to wake, the amplitude of the signal is generally low and mixed frequencies can generally be present.

In addition, a transient characteristic of N1 sleep stage is the presence of vertex sharp waves. These waves manifest as brief, prominent negative deflections lasting around 500 ms and are observable in the raw EEG data. They typically exhibit maximum amplitude over the central areas of the scalp. Vertex sharp waves can occur spontaneously or approximately 300 to 350 ms after a stimulation during the onset of sleep period (Campbell and Colrain, 2002). It is believed that these waves represent an incomplete form of K-complexes, which are more commonly observed during the N2 sleep stage. N1 sleep stage is also characterized by slow eye movements and a lower level of muscle activity (EMG tonus) compared to wakefulness.

### B. N2 sleep stage

N2 sleep stage is commonly called light sleep and is generally the most prevalent kind of sleep during a normal night's rest, especially in adulthood. Similarly to N1, N2 sleep stage is characterized by low amplitude EEG comprising mixed frequencies. Theta bursts can happen as well but are less frequent. Key landmarks to N2 sleep stage are the presence of K-complexes and sleep spindles.

The K-complex is identified by a temporary negative peak with a high voltage, usually exceeding 100  $\mu$ V. This is followed by a slower positive complex lasting between 350 and 550 ms, and finally, a negative peak is observed at 900 ms. Although K-complexes can occur spontaneously, they can also be triggered by external stimuli such as sounds or touches on the skin, as well as internal stimuli like breathing interruptions. It is believed that K-complexes serve two main purposes: to maintain sleep continuity by suppressing cortical arousal in response to non-threatening stimuli perceived by the sleeping brain, and to facilitate memory consolidation during sleep. These complexes are generated in various regions of the cortex, with a tendency to be more prominent in the frontal areas of the brain. K-complexes typically occur approximately every 1 to 2 minutes during normal N2 stage and are often accompanied by sleep spindle bursts. For more specific information, see Cash and colleagues (2009).

Sleep spindles are transient burst-like signals in the Sigma power band, within the 7-16 Hz bandpass region, more frequently between 10 and 15 Hz. They are visible in the electroencephalogram (EEG) of the sleeping brain in humans and more generally mammals.

They serve as electrical surface correlates of neuronal rhythmic activity in the thalamus, and especially the thalamic reticular nuclei (TRN). These sleep EEG signatures, known to be highly heritable, likely indicate the robustness and adaptability of thalamocortical circuits that play a fundamental role in shaping individual cognition. Notably, they play an essential role in both sensory processing and long-term memory consolidation. For a complete review on general knowledge on sleep spindles, see Fernandez and Lüthi (2020). Moreover, for epidemiological data of sleep spindle characteristics in a large population sample, see Purcell and colleagues (2017).

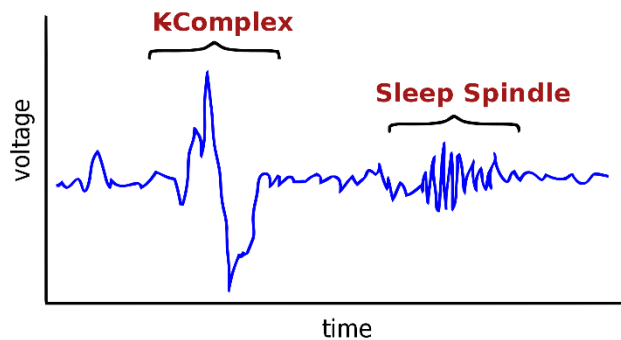


Figure 1.3.3 Schematic view of the signature of a K-complex and a sleep spindle on a single channel EEG signal, adapted from Neocadre, [https://commons.wikimedia.org/wiki/File:Stage2sleep\\_new.svg](https://commons.wikimedia.org/wiki/File:Stage2sleep_new.svg)

### C. N3 sleep stage

N3 sleep stage is also called deep sleep and is often considered the most restorative and deepest stage of sleep. Indeed, it is during deep sleep that the arousal thresholds are the highest to sound stimulations (Bruck, 2001). It is most prevalent in the beginning of the night during the first sleep cycles and its proportion within the night is highly correlated with how much sleep deprived the individual is. It is more important in proportion in younger individuals. Many healing and restorative functions occur during N3 sleep stage: growth hormone secretion, which is hypothesized to facilitate the healing of muscles as well as repair damage to tissues (Payne and Walker, 2008), sugar fueling of detoxifying glia cells to provide energy for the brain (Frank, 2019). Last and as presented before, it is during this sleep stage that the process of synaptic downscaling is believed to mostly occur (Tononi and Cirelli, 2006).

N3 sleep main landmark is synchronized EEG activity across the whole scalp which manifests as high amplitude slow waves (delta band power, between 0,5 and 4Hz, or sometimes even below). Formerly, there used to be a differentiation when slow waves were sparse and cover only for 20% of 30 second epochs (this was the previous N3) or dense, a state that used to be referred to as N4 in the past (deepest state of sleep). Now both stages have been fused into one.

During the negative portions of slow waves, there is a significant decrease in the spike rates of most cortical neurons, often referred to as a down state. Inversely, positive portions of slow waves are characterized by concomitant elevation of neuronal fire rate in the cortex.

Last, N3 sleep stage is also characterized by important reduction in muscle tone.

#### D. REM sleep stage

Rapid-Eye Movement (REM) sleep is also called paradoxical sleep. The paradox of this state of sleep is the concomitance of an apparent state of high activity in the brain, generally associated with wake, with the fact that the muscle tone is at its lowest. In fact, except for “saw-tooth” theta wave bursts that occasionally appear, an important landmark of REM sleep is the fact that the EEG signal sensibly looks like the one of wake. This may be explained by the fact that one main activity of the brain during REM sleep is dreaming, which has been associated to a state of proto-consciousness (Hobson, 2009) and that there was an evolutive need to refrain the individual to act its dreams in real life, which translated in a strong gating of any muscular activity at the level of the brainstem. Yet, it is worth noting that not all muscle activity is shut down during REM sleep. First, of course, respiratory system and associated muscles still function to enable breathing (Kubin, 2016). Second, REM owes its name to the fact that during this sleep stage, eyes can rapidly move, which has been associated with visual content inside dreaming and visual stimuli internal generation through Ponto-Geniculo-Occipital (PGO) waves (Gott et al., 2017). REM often happen continuously during segments of REM sleep and remain still during the rest of the time. This bi-phasic nature of REM sleep led some researchers to propose a distinction between two sub-stages of REM sleep : phasic REM sleep during which REM occur and tonic REM sleep during which the eyes are still (Simor et al., 2020). Last and less known, middle-ear muscles also spontaneously activate during REM sleep (Pessah and Roffwarg, 1972). These events are referred to as Middle-Ear Muscle Activity and seem to be the equivalent of REM for the auditory modality (Benson and Zarcone, 1979). Besides, despite a seemingly continuous inhibition of all muscle tone during sleep, it not common to observe very brief bursts of EMG activity during REM which are referred to as twitches.

REM sleep function is still debated, although some hypotheses have been emitted such as the reality model adjustment theory of (Hobson and Friston, 2012). Despite the fact it has long been considered that dreaming only happened during REM sleep, studies have shown that it also happened during other stages of sleep (Oudiette et al., 2012; Zimmerman, 1970).

Last, it is important to mention that during REM sleep aminergic neurons activity is inhibited : locus coeruleus noradrenergic neurons, Raphe Nuclei serotonergic neurons, tuberomammillary histaminergic neurons are all virtually silent, while cholinergic neurons activity remains similar to wake (Hobson and Friston, 2012).

#### E. Non-REM/REM transitions

The transition between Non-REM and REM sleep has been described by Lu and colleagues (2006) and referred to as the flip-flop model, in which one of the mutually inhibitory REM-off and REM-on areas in the mesopontine tegmentum inhibit the other or vice et versa.

This transition is not instantaneous and the transitory sleep stage between Non-REM sleep and REM sleep has been named intermediate sleep (Carrera-Cañas et al., 2019; Gottesmann, 1996). According to Gottesmann (1996), during this intermediate sleep stage, thalamocortical

responsiveness and thalamic transmission level, which are controlled by brainstem activating influences, are the lowest of all sleep–waking stages. It seems this stage is characterized by the apparition of PGO waves, although some slow waves delta band activity are still present. The author also proposes that barbiturates and benzodiazepines extend this intermediate stage at the expense of REM sleep, and Carrera-Cañas and colleagues (2019) draws an analogy between this sleep stage in cats and the one induced in cats by injection of cholinergic agonist Carbachol in the peri-locus coeruleus  $\alpha$  nucleus.

### 1.3.2.4 Sleep cycles

The human sleep structure adheres to a pattern of cycles lasting between 90 to 120 minutes. Typically, healthy adults experience around 7 to 8 hours of sleep, which consists of approximately 5 sleep cycles. These cycles commence with a transition from wakefulness to N1 sleep, followed briefly by a shift from stage N1 to stage N2 (light sleep). After a period of N2, individuals enter stage N3 (deep sleep). Following deep sleep N3, there is often a short period of N2 sleep before entering REM sleep. The REM sleep phase concludes with a brief awakening, leading to either another sleep cycle or morning awakening. Throughout the night, the structure of sleep cycles undergoes changes.

The initial cycles of the night are characterized by a significant proportion of restorative deep sleep (stage N3) and a smaller proportion of REM sleep at the end. In some cases, REM sleep may even be absent at the end of the first cycle. As the night progresses, REM sleep gradually becomes more prominent in the sleep cycles and may dominate towards the end of the night. Conversely, the proportion of deep sleep N3 progressively decreases and may disappear in the final sleep cycles, giving way to light sleep N2.

Graphical displays of the sequence of sleep cycles across the night for sleep diagnosis is called an hypnogram. Here is an instance of hypnogram:

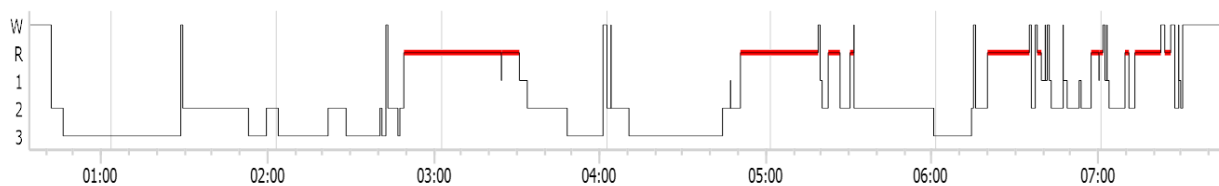


Figure 1.3.3 Example of an hypnogram acquired during our polysomnographic comparative study on sleep-intermittent tinnitus patients. W: Wake, R: REM, 1: N1, 2: N2, 3: N3,

To have an idea of the quantitative normal sleep stage proportions across life, a meta-analysis was performed by Ohayon and colleagues (2004) and can serve as a good reference.

### 1.3.2.5 Naps

Individual can also decide to rest during the day, this habit is referred to as napping. Due to its not optimal occurrence in the circadian and homeostatic processes, nap sleep is generally shallower and of shorter duration than night sleep. Naps have been suggested a public health tool to counteract the negative effect of sleep debt which becomes quite common in our



modern societies (Faraut et al., 2017). Yet, depending on the nap duration, some studies have suggested that this habit was associated with negative effects such as an association with obesity, chronic diseases and overall mortality (Guo et al., 2017; Li et al., 2022; Wang et al., 2020). Nap sleep is generally composed of N2 sleep and can potentially contain N3 sleep if they are more than 30 min and performed later during the day. REM sleep is uncommon during naps, except during morning naps (Endo et al., 1981) or at the end of long afternoon naps of more than 45 min duration (Lewis, 1969). While short naps are generally associated with greater alertness upon awakening (so called “power” naps), longer naps can lead to a transitory period of grogginess and impaired performance upon awakening, referred to as sleep inertia (Hilditch et al., 2017).

### 1.3.3 Sleep disorders

Sleep can sometimes be disturbed in some individuals, chronically or occasionally. Most often sleep disorders consists in alterations of sleep, except for pathologies like narcolepsy, where it is wake that can be disturbed by the irruption of sleep, either spontaneously or triggered by events such as laughter. There are a variety of sleep disorders but in the scope of this thesis we are going to limit their description to sleep disorders that have been described to potentially interplay with tinnitus.

#### 1.3.3.1 Snoring

Snoring is most probably the most prevalent and commonly considered less harmful form of sleep disorder. Simple snoring, or primary snoring was defined in 2014 by International Classification of Sleep Disorders as the ‘audible vibrations of the upper airway during respiration in sleep’. It is often considered as the first step in sleep breathing disorders that leads to chronic obstructive sleep apnea (OSA). Besides, when OSA manifests, it comes most often with snoring. Snoring is believed to be caused by loss of muscular tone in the uvula and soft palate zone, most probably due in insufficient tensor veli palatini and tensor levi palatini muscle tonus. This reduction in muscle tone reduces the upper airway section and results in creations of loud vibrations of the soft palate that create snoring characteristic sounds.

Primary snoring does not have diagnostic criteria in terms of number of event occurrence or acoustic intensity (in dB) but its diagnostic is often opposed to the diagnostic of sleep apnea by the fact that less than 5 sleep apnea episodes per hour are present in polygraphic or polysomnographic explorations.

Snoring has been associated or defined as an aggravating risk factor of several severe health conditions like strokes (Bai et al., 2021), coronary artery disease (Liu et al., 2021), hypertension (Niu et al., 2021) and metabolic syndrome (Ma et al., 2020). Yet, individuals do not always try to treat it for their own sake but rather more for the disturbances it creates for their bed partners. Several solutions exist to limit snoring or at least the sound of snoring: positioning therapy, weight loss, mandibular protrusion splints, rhinological or rhinosurgical treatment or minimally invasive surgical procedures (Stuck and Hofauer, 2019).

### 1.3.3.2 Sleep apnea

Sleep apnea events are pauses in breathing of more than 10 seconds or more during sleep while “sleep hypopnea events” are periods of 10 seconds or more of shallow breathing during sleep. Both events are often associated with events of blood oxygen desaturation. When an individual presents a significant amount of apnea events and hypopnea events with desaturation per hour, a ratio often referred to as “Apnea Hypopnea Index” (AHI), he or she is diagnosed with sleep apnea. Cut-off number of AHI for diagnosing sleep apnea depends on countries and conventions. Moreover, AHI relevance as main diagnostic criteria has recently been questioned, as recent research points out the heterogeneous nature of sleep apnea (Pevernagie et al., 2020).

Among sleep apnea, an important distinction should be made between events which are caused by physical obstruction of the upper airways due to a collapse of pharyngeal walls. Such events are referred to as obstructive sleep apnea events. Exploration of pharyngeal collapse site is commonly assessed through drug induced sleep endoscopy. Koo and colleagues (2013) reported on 69 cases that in 84% cases there was a multilevel obstruction (both retrolingual and retropalatal), with 91% cases of retropalatal obstruction when the obstruction was only at one level. On the other hand, it can happen that the cause of a sleep apnea event is not an obstruction but rather more an absence of central drive to perform one or several breathing cycles. In such scenario, we refer to these apnea events as central apnea. Central apnea syndrome appears much rarer than obstructive sleep apnea syndrome as a recent study on 5804 participants showed 0.9% of the sample had solely central apnea syndrome, while 47.6% had solely obstructive sleep apnea and 2.7% had both (Donovan and Kapur, 2016).

A systematic review of the prevalence of OSA concluded that by placing an AHI threshold at 5 events per hour, 9 to 38% of the population was concerned by it, with higher prevalence as individuals get older. By placing the AHI threshold to 15 events per hour, the prevalence was between 6% and 17% (Senaratna et al., 2017).

In terms of repartition of sleep apnea events across sleep stages, it has been commonly reported that mild forms of sleep apnea mostly happen during REM sleep (Alzoubaidi and Mokhlesi, 2016; Mokhlesi and Punjabi, 2012), then in moderate and severe cases, all sleep stages are affected, resulting in fragmented sleep, mostly composed of light sleep with intermittent arousals triggered by resolution of sleep apnea events.

Sleep position is an important factor on the question of sleep apnea : obstructive apnea events are known to happen more often when sleeping in the supine position (Penzel et al., 2001). This is why the most basic form of intervention to help treat mild sleep apnea consists in positioning therapy. Similarly, weight loss can also be advised. In case of moderate to severe apnea, golden standard treatment are continuous positive airway pressure (CPAP) devices. Oral appliances can also be advised to treat sleep apnea in case of retrolingual obstruction site assessment.

### 1.3.3.3 Sleep bruxism

According to the American Academy of Sleep Medicine, sleep bruxism consists in a movement disorder characterized by grinding or clenching of the teeth during sleep, associated with sleep arousal activity. A prevalence study performed on a sample of 1024 patients has concluded that it is present in 5,5% of the population (Maluly et al., 2013).

Sleep bruxism episodes during sleep have been hypothesized to happen under the influences of brief and transient brainstem arousal. On such occasions, reticular ascending system may contribute to an increase of activity in autonomic-cardiac and motor modulatory networks resulting in jaw muscles activations (Lavigne et al., 2007).

The golden standard method to diagnose bruxism consists in a combination of questionnaires and polysomnographic exploration, with specific interest on the EMG activity of the jaw, notably of the masseter muscles (Lavigne et al., 1996). It can also be completed by a dental visual examination. Polysomnographic scoring criteria for diagnosing sleep bruxism, according to Lavigne et al., are : (1) more than 4 bruxism episodes per hour, (2) more than 6 bruxism bursts per episode and/or 25 bruxism bursts per hour of sleep, and (3) at least 2 episodes with grinding sounds. Generally, in bruxism scoring practice, sleep technologists distinguish three types of events : tonic events, phasic events and mixed events, depending of the temporal pattern of jaw activations. Treatment options for sleep bruxism are occlusal splints, stomatology intervention and/or hyaluronic acid injections in the masseter muscles.

### 1.3.3.4 Exploding head syndrome

Exploding head syndrome (EHS) is a rare parasomnia which consists in the perceptions of loud noises when going to sleep or awakening. These loud noises manifest themselves suddenly and are of brief duration. Though not often associated with pain, such episodes result in a great deal of fear, confusion, and distress. It is usually a benign and infrequent experience, but can manifest in more chronic forms and engender clinical consequences. Few prevalence studies of this parasomnia exist. A study is reported on small cohorts of psychiatric patients, sleep disorder patients and healthy controls that : 13.8% of psychiatric patients, 10.0% of patients with a sleep disorder, and 10.7% of healthy controls screened positive for EHS symptoms on a self-report measure, total N = 180 (Fulda et al., 2008). Treatment approaches that were tested, if deemed necessary, were clomipramine (Sharpless, 2014) or oral appliance in case of concomitant sleep apnea (Nakayama et al., 2021).

## 1.3.4 Key insights

Although naturally selected since its apparition in the tree of life, sleep's core function remains the topic of intense debate. Multiple essential biological and metabolic functions are attributed to sleep but can occur without it, questioning its bare necessity. In this section we presented several current models that try to answer to this problematic (synaptic homeostasis for Non-REM sleep, ontogenetic origin of REM sleep and reality model adjustment through REM sleep), which are among current plausible answers, but remain to be further demonstrated in the future.

The characteristics of sleep and its regulation by circadian and sleep pressure processes are more clearly understood. Sleep comprises cycles of specific sleep stages (N1, N2, N3 and REM) which gradually evolve through the night to contain less deep N3 sleep and more REM sleep. Sleep stages are characterized by polysomnographic and specifically EEG activity landmarks which are indirect signs of ongoing brain processes specific to sleep.

Pathological disturbances of sleep are called sleep disorders, among which most prevalent are sleep breathing disorders such as snoring and sleep apnea. Such sleep disorders can lead to important damage of quality of life and ought to be diagnosed and treated.

## 1.4 Auditory system in sleep

### 1.4.1 Auditory gating during sleep

#### 1.4.1.1 Auditory awakening thresholds

An established attribute of sleep is the decrease in responsiveness of individuals to external stimuli compared to wake. In the auditory modality, this translates to the fact that in appearance individuals will not respond to sounds while they are sleeping and that only sounds of significance (baby crying heard even from afar) or of significant loudness may provoke awakening.

The question of which sound intensity is necessary to trigger awakening has been addressed by several studies. Such sound intensities are generally referred to as auditory awakening thresholds or auditory arousal thresholds (AAT). These studies analyzed dependence of AAT upon various parameters. For example, Bruck and colleagues (2009) tested different types of sounds to determine which sound characteristics elicits most easily awakening. Upon a set of sound patterns, the authors showed that low-frequency (520 Hz) square wave seem to be most efficient to wake people up from deep sleep with the lowest sound intensity. Interestingly, they mention that such sounds are known to be also the ones that trigger the lowest thresholds of response when individuals are awake.

Studies investigating associations between sleep stages during which patients are waken up and AAT have reached mixed conclusions. Rechtschaffen and colleagues (1966) and Zimmerman (1970) observed that AAT were rather similar during N2 and REM sleep, while it was higher during N3/N4 deep sleep. On the other hand, Rosenthal and colleagues (1996) reported that AAT were higher during N2 sleep than during REM sleep across all these groups.

Besides, Ermis and colleagues (2010) investigated the difference of AAT between tonic and phasic REM sleep. They found that AAT were different between these phases of REM sleep, enhancing the belief that REM sleep should not be regarded a uniform state. Indeed, they reported that AAT were similar between N2 and tonic REM and significantly less elevated than those of phasic REM sleep, which were more comparable to those found during N3 deep sleep.

However, it is crucial to approach these findings with caution, as the studies consistently reported an intriguing characteristic of AAT: its levels tend to decrease as the night progresses (Rechtschaffen et al., 1966; Rosenthal et al., 1996; Zimmerman, 1970). This suggests that probably they are correlated with homeostatic sleep pressure, which decreases as well as the night progresses. As N3 and N4 deep sleep are mostly present during the beginning in the night and N2 sleep and above all REM sleep rather more at the end, this may explain at least partially the observed and reported results except for the case of phasic REM sleep).

Last, another study from analyzed the effect of age on AAT (Zepelin et al., 1984). This study identified that for all sleep stages but even more for deep sleep, AAT tend to be lesser as age progresses, meaning that elder people can more easily get awakened. This led the authors of this study to postulate that this supports that intensity of sleep is lighter in elder people.

#### 1.4.1.2 Thalamic gating hypothesis

These past results have led to the long-lasting theory that sensory information and in particular auditory information is not granted access to the cortex and blocked at the level of the thalamus by the thalamic reticular nucleus during sleep. This theory has been referred to as the thalamic gating hypothesis and has been first proposed by McCormick and Bal (1994). More precisely, the defended idea is that the above-described neural synchronization events of sleep, such as sleep spindles and slow waves, may prevent the correct coupling of cortical activity with external events and thus disfacilitate sensory processing during sleep. Indeed, functional Magnetic Resonance Imagery (fMRI) studies have shown that slow waves and above all sleep spindles distort the transmission of auditory information to the cortex, therefore isolating the brain from external disturbances during sleep (Dang-Vu, 2012; Dang-Vu et al., 2011). This theory is still currently supported by Coenen (2022) despite several breaches that we will present hereafter.

#### 1.4.1.3 Evidence that the cortex processes sound during sleep

Contrary to what is postulated by the thalamic gating hypothesis, there is experimental evidence that sound processing, cortical interpretation, decision making from auditory input and even learning can happen during sleep, above all through the auditory modality.

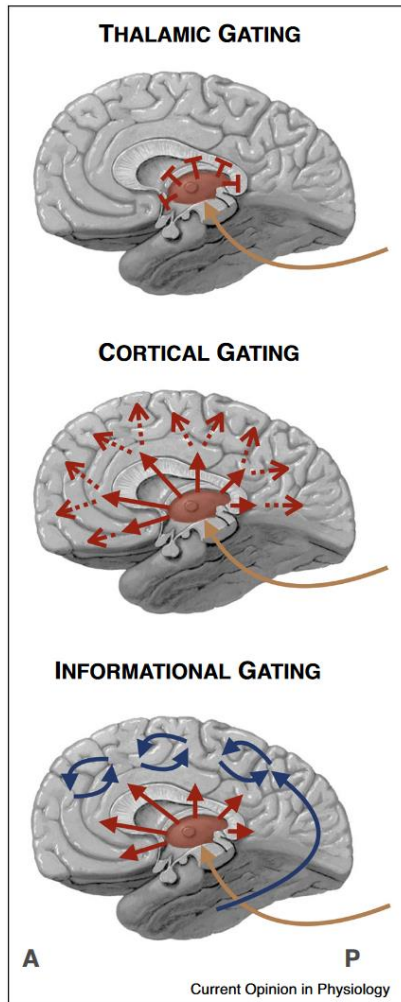
While sounds may need higher sound intensities to elicit overt responses during sleep than during wake, several studies from Andrillon and Kouider have consistently shown during nap (Kouider et al., 2014) and full night protocols (Andrillon et al., 2016) that the brain is still able to process sounds and project motor decisions from the sounds it heard. Moreover, they demonstrated that some form of auditory learning was possible during sleep (or at least during light sleep N2 and REM sleep). Indeed, participants in one of these studies were able to extract regularities within short white noises tracks when exposed during sleep and performed better the next morning at recognizing them compared to new sounds they were never exposed to (Andrillon et al., 2017).

Another set of examples that tend to disprove the isolation of the cortex from auditory input during sleep by the TRN is the fact we preferentially awaken to sounds we evaluate as relevant (hence salient). For example, we more likely awake to our own name than its reversed version (Langford et al., 1974) or to other people first names (Oswald et al., 1960). In addition, it has been shown that mothers react more during their sleep to their baby cry than to other babies cries (Formby, 1967). Last, it has been shown that we are able to detect and label sounds like screaming as threatening while asleep (Legendre et al., 2022). This shows that the brain is able to process roughness during sleep.

In a review by Andrillon and Kouider (2020), the authors also present several additional examples of complex auditory processing during sleep : some studies demonstrated that

sleepers can detect not only the violation of simple auditory rules (Perrine Ruby, 2008; Strauss et al., 2015), but also semantic incongruencies in sentences (Brualla et al., 1998), and even arithmetic violations (Strauss and Dehaene, 2019).

#### 1.4.1.4 Alternative models to thalamic sensory gating



In the same review, Andrillon and Kouider (2020) present alternative models to try to explain how gating would work during sleep. An important conceptual leap that they propose is that gating may work differently depending on sleep stages. Indeed, they propose that during Non-REM sleep, auditory information may reach the auditory cortices but not propagate in the cortex from it, notably because of the alteration of the awareness network and consciousness hubs during sleep. This gating is referred to as “cortical gating”. On the other hand, during REM sleep, the information may also reach the auditory cortex, but in this case the cortex may be actively distracted by the internal generation of oneiric content. This internal content generation is assumed to be materialized by PGO waves for visual content. This would disfacilitate the processing of external auditory information to the profit of internally-generated representations. This model is referred to as “informational gating”. Figure 1.4.1 from Andrillon and Kouider (2020) offers a comparison view between these three models.

Figure 1.4.1 the three models of auditory gating, reproduced with permission from Andrillon and Kouider (2020)

Another possible model for Non-REM auditory gating is proposed by the recent study from (Legendre et al., 2022). Their research indicates that screams are processed with equal priority during wakefulness and Non-REM sleep. The primary acoustic feature of screams is their inherent roughness. Recent studies have demonstrated that they recruit salience aversive networks probably through the non-canonical auditory pathway (Arnal et al., 2019; Schneefeld et al., 2022). This is their interpretation of the non-linear component they observed when modulating sound envelope between 10Hz and 250 Hz.

Such a similar conservation of scream processing during sleep may suggest that the non-canonical auditory pathway functioning may not be altered between wake and Non-REM sleep, contrary to the primary (and possibly non-primary) auditory pathways. This would be evolutionary coherent with our need to get awakened in case of danger. These observations open the conceptual door that auditory gating during sleep may not be similar depending on the auditory pathway that we consider.

## 1.4.2 Auditory neuronal firing during sleep

In this section we will focus on presenting current knowledge on neuronal behavior transitioning from wake to sleep and across sleep stages, in the different relays of the central auditory pathway. We will present as much as we can results over changes in spontaneous activity and evoked activity.

Evoked activity is neuronal activity that is induced by a stimulus. In auditory research, stimuli used are generally clicks or short tone burst (pure or wideband). To measure such evoked activity, there must be a precise synchronization between the sound temporal signal and the associated brain measurement. Often, we add a supplementary channel to our EEG recording setup and we record the onset of the sound stimulus and refer to this additional signal as the “trigger”. It defines the origin of time of the evoked response.

Evoked responses are generally noisy and to visualize them properly, the usual method is to perform an important number of measurements (several hundreds) and then average all the evoked responses after aligning all the responses similarly relatively to the trigger.

In this section we will often present individual neuronal evoked activity to a sound stimulus. Whole scalp EEG responses to sound stimuli are often referred to as Auditory Evoked Potentials (AEP). We usually segment these AEPs in three categories: early/short latency responses (0-10 ms) which we often call auditory brainstem responses (ABR), middle latency responses (10-50 ms) and late latency evoked responses (more than 50 ms), which can be referred to as event related potentials (ERP). The later the signature, the more cortical the activation is and the stronger its signature on EEG.

It is important to mention that most of the work that will be presented for subcortical auditory relays unitary activity during sleep has been performed by a single research team under the supervision of Velluti and, nowadays, Pedemonte.

### 1.4.2.1 Auditory nerve activity across sleep

Several studies have tried to analyze auditory nerve activity evolution between wake and sleep stages. Baust and colleagues (1964) first observed evoked response (auditory compound potential) to clicks in unanesthetized cats by measuring electrical potential on the middle ear round window (electro-cochleo-graphy). They did not observe any changes in the auditory nerve activity between wake and different sleep stages, only that there was a reduction in evoked activity when there was an activation of middle-ear muscles during REM sleep. Irvine and colleagues (1970) reproduced and refined the protocol of Baust and colleagues and performed averaged measurements of auditory compound evoked potential on the middle ear round window. They also performed a cochlear microphonics test (echo response of the outer hair cells). They observed a maximal amplitude of response during slow-wave sleep (SWS) and similar (and reduced) amplitudes during wake and REM sleep. Likewise, they observed some relations between middle-ear muscle activity and these evoked potentials. These results could not be reproduced in a later study (Irvine and Webster, 1972). Last, a study by Velluti and colleagues (1989) confirmed the results found by Irvine and colleagues (1970), showing that peak responses on auditory compound potential and cochlear microphonics were at its



highest during slow-wave sleep (N2-N3) and that responses during wake and REM were lower and comparable.

#### 1.4.2.2 Cochlear nucleus activity across sleep

Pena (1992) conducted a single unit activity study on ventral cochlear nucleus neurons of guinea pigs across wake and sleep stages. Recordings from 32 neurons from 28 guinea pigs were analyzed across wake, slow-wave sleep (SWS) and REM sleep. The middle ear muscles and ossicles were removed. Spontaneous discharges were collected from 11 neurons and evoked responses from 21 neurons to 40 to 50 dB clicks

Firing rate	Increased	Decreased	No Change
<b>Spontaneous firing</b>			
Wake -> SWS (n=11)	n=8 (73%)	n=0 (00%)	n=3 (27%)
SWS -> REM (n=9)	n=0 (00%)	n=6 (67%)	n=3 (33%)
Wake VS REM (n=5)	n=0 (44%)	n=1 (11%)	n=4 (44%)
<b>Evoked firing</b>			
Wake -> SWS (n=21)	n=10 (48%)	n=6 (29%)	n=5 (24%)
SWS -> REM (n=10)	n=5 (50%)	n=2 (20%)	n=3 (30%)
Wake VS REM (n=10)	n=4 (40%)	n=2 (20%)	n=4 (40%)

Figure 1.4.2 Comparisons of ventral cochlear neurons units firing rates modification in spontaneous and evoked responses, adapted from (Pena, 1992)

Globally, it appeared that in the ventral cochlear nucleus the spontaneous activity raised in most of neurons measured when transitioning from wake to SWS, which is matching observations concerning the auditory nerve during SWS. For the rest of transitions results were more heterogeneous (Velluti et al., 1989).

It is important to note that for the purpose of this experiment, a complete ablation of the middle ear muscles and ossicles was performed on the animals when setting the electrodes in place. This reason, and the fact that these measurements were only performed within the ventral cochlear nucleus could explain the fact that results from another study from Reivich and colleagues (1968) are quite different. Indeed, in this study on cat models, the experimenters did not remove the middle ear muscles and measured the blood flow through the whole cochlear nucleus. They observed a slightly significant increase in blood flow passing from wake to SWS, but above all a spectacular increase of 173% of the blood comparing wake and REM (which was as well significantly higher than the blood flow during SWS).

#### 1.4.2.3 Superior olivary complex activity across sleep

Pedemonte and colleagues (1994) conducted a single unit evoked activity study on lateral superior olive neurons of 28 guinea pigs across wake and sleep stages. Recordings from 53 neurons were analyzed across wake, slow-wave sleep (SWS) and REM sleep. The middle ear muscles and ossicles were removed. One goal of the study was to better understand if the

sound localization function of the lateral superior olive is preserved through the different stages of sleep. Evoked responses to 50ms pure tone bursts were collected at the neuron's characteristic frequency with an intensity varying between 40 to 60 dB. To study binaural processing of these neurons, stimulation were either binaural, ipsilateral or contralateral to the measured neuron.

Figure 1.4.2 results of lateral superior olive unitary evoked activity, adapted from (Pedemonte et al., 1994)

These observations led to the conclusion that the lateral superior olive neurons do not follow the same change of pattern of firing activity than cochlear nuclei neurons. No clear pattern is yet remarkable.

#### 1.4.2.4 Inferior colliculus activity across sleep

Tortorolo and colleagues (2002) analyzed the changes in single unit activity of neurons of the inferior colliculus (IC) of guinea pigs across sleep-waking stages and under pentobarbital effect. Recordings from 29 guinea pigs were analyzed across wake, slow-wave sleep (SWS), REM sleep and under pentobarbital. The middle ear muscles and ossicles were removed. Sound stimulation consisted in 50ms tone bursts, 10 to 20 dB above each neuron unit threshold.

	Wake Mean (Std)	N	SWS Mean (Std)	N	REM Mean (Std)	N
Spontaneous firing rate (spk/s)	17.8 (1.7)	134	19.9 (2.4)	81	22.7 (3.4)	19
Evoked firing rate (spk/s)	83.7 (7.0)	134	86.5 (10.7)	81	58.9 (13.4)	19

Figure 1.4.3 Spontaneous and tone-evoked IC unitary activity, adapted from (Tortorolo et al., 2002)

It is noteworthy to mention that 84,2% of recorded neurons showed a significant increase in spontaneous firing when transitioning from SWS to REM, while 70,4% did not change their spontaneous firing rate when transitioning from wake to SWS. Additionally, a reduction in the ratio between the evoked and the spontaneous frequency of discharge was observed during REM. Thus, during this state, there was a reduction in signal to noise ratio, and evoked sound

response is partially lost in the increased spontaneous background activity, which has also been observed to be the case in the auditory thalamus (Edeline et al., 2000).

Such an increase in spontaneous activity during REM sleep is explained by the authors as a potential consequence of changes of neuromodulation influences during REM sleep. They refer to past studies presenting that cholinergic drive which is increased during REM sleep is excitatory to IC neurons, while serotonergic and noradrenergic neurons which decrease their activity during REM sleep were at least partially inhibitory to IC neurons.

Concerning evoked activity, a slight amplification of the firing rate was observed in SWS compared to wake, and a reduction during REM sleep. Meeren and colleagues (2001) performed a local field potential click-evoked study of IC neuronal firing during wake and sleep stages on WAG / Rij rat models. They observed a more important amplification of the IC evoked response during SWS compared to active and passive wake. Similarly, REM sleep responses were intermediate between active and passive wake.

#### 1.4.2.5 Medial geniculate body activity across sleep

Edeline and colleagues (2000) conducted a single unit spontaneous, bursting and evoked activity study on medial geniculate body (MGB) neurons of guinea pigs across wake and sleep stages. Recordings from 102 neurons were analyzed across wake, slow-wave sleep (SWS) and 53 also with REM sleep. Neurons were randomly sampled from MGv, MGm and MGd regions. One goal of the study was to better understand the evolution of the receptive fields of MGB through the different stages of sleep. Consequently, for each neuron tested, the receptive field map was created from a frequency and intensity variation paradigm. 100ms pure tone bursts were used with 1s inter-tone interval.

	Wake	SWS	REM
Spontaneous firing rate (spk/s)	5.29	3.29	6.8
Evoked firing rate (spk/s)	15.59	7.46	8.82
Signal to Noise Ration (Evkd/Spont)	5.35	4.51	2.05

Figure 1.4.4 Changes in physiological parameters for 44 cells tested in each vigilance state at the intensity eliciting the strongest evoked responses in Wake, adapted from (Edeline et al., 2000)

Along with other studies of MGB neurons across the wake and sleep stages (Bizzi 1966; Maffei et al. 1965; Marks et al. 1981; McCarley et al. 1983; Mukhametov and Rizzolatti 1970; Mukhametov et al. 1970; Sakakura 1968), this study consistently showed that for most of the cells, spontaneous activity was decreased during SWS and increased during REM sleep. Interestingly this study observed that for all neurons measured, the signal to noise ratio between spontaneous and evoked activity was reduced during REM sleep, while it was globally unchanged during SWS compared to wake. Similar to previous studies, evoked responses were decreased in the MGB during SWS, which gives credit to the thalamic gating theory. On the other hand, the results were more heterogeneous for REM sleep where two

groups of cells were observed: some that exhibited strongly decreased evoked response (60%) and others that had a comparable pattern to wake (40%). Bursting index was also modified depending on the state: it was increased relative to wake during SWS and reduced for tone presentations during REM sleep. Meeren and colleagues (2001) measured evoked local field potentials activity in a larger population of MGD neurons in the WAG / Rij rat models and reported on the contrary a slight increase in evoked activity compared to wake for SWS, parts of this activity, negative, was associated to inhibition according to them. REM evoked potentials were slightly decreased but still comparable to wake potentials.

Edeline and colleagues (2000) also observed the evolution of the receptive field (RF) of MGB neurons across vigilance states. They report that RF width was significantly decreased during SWS compared to wake, meaning that MGB neurons were more finely tuned to their best frequency during SWS compared to wake. On the contrary, RF were significantly broader during REM sleep compared to SWS, and were found not significantly different between REM and wake.

#### 1.4.2.6 Auditory cortex activity across sleep

A study of auditory cortex activity changes between wake and sleep stages was performed by Edeline and colleagues (2001). They explored the change of characteristics of 56 neurons recorded at different depth in the core of the auditory cortex of adult unanesthetized guinea pigs between wake and SWs and 12 neurons also during REM sleep. While at the level of the whole group of neurons no changes seemed to be apparent between wake and SWS, looking closely at individual neurons behaviors, an important heterogeneity of changes was observed. An interesting finding that they observed as they were the same team that investigated earlier the changes of activity in the MGB was that contrary to what happened in the thalamus, auditory cortex activity was not reduced when transitioning from wake to SWS.

	Wake	SWS
Spontaneous firing rate (spk/s)	4.73	3.93
Evoked firing rate (spk/s)	15.33	12
Signal to Noise Ration (Evkd/Spont)	9.58	7.14

Figure 1.4.6 Changes in physiological parameters observed for the 56 cells tested during slow-wave sleep and waking, adapted from (Edeline et al., 2001)

Edeline and colleagues (2001) analyzed the evolution of the receptive field (RF) of A1 neurons across vigilance states. Like for MGB neurons, they report that RF width was decreased in a lot of A1 neurons during SWS compared to wake, yet this tendency was not strong enough to be significative.

Due to the limited number of neurons measured for REM sleep (n=12) no dominant effect was observed on any statistics between REM and wake in this study. The authors note that spontaneous activity was significantly increased for six cells and decreased for two cells; the

evoked activity was increased for five cells and decreased for three cells. No significant change in RF properties compared to wake were reported.

Investigating auditory cortex activity across vigilance states hence appears as a complex question that was the subject of a whole PhD thesis (Issa, 2008). This author investigated the changes of neuronal activity in larger samples of the superficial layers of the core of the auditory cortex (A1) but also their changes of activity in the belt and parabelt regions. We will try to summarize his findings hereafter.

In A1, the author found that spontaneous firing rates were significantly different between wake and SWS on a large number of neurons (N=384). Disparities in their behaviors could be observed. On the other hand, generally, spontaneous activity was increased during REM sleep in A1 compared to wake (from 4 spike/s to 5.4 spike/s) even if for the 332 neurons measured it did not reach statistical significance. In belt and parabelt, SWS did not lead to changes in spontaneous rate, and an increase in spontaneous activity was observed during REM.

Concerning evoked activity, for SWS in A1 and belt and parabelt, on all neurons tested, behavior was divergent between neurons : 44% units decreased activity and 34% increased their activity, resulting in average gain decrease of only 5%. During REM, evoked activity was also modulated in both directions in A1 with a similar 6% average decrease in gain in A1 compared to wake, yet an average decrease in gain of 12% was observed in belt region compared to wake.

Additionally, Issa mentions that one third of the 382 neurons tested (135) showed opposite changes between SWS and REM illustrating the important difference of sound processing during these two sleep stages.

Issa shares the following insights from his work: low intensity sounds (20-30 dB) do not seem to be processed by the auditory cortex during SWS, while high intensity sounds are processed similarly that what is happening during wake.

Issa concludes that globally the auditory cortex does not seem to have a higher inhibition during SWS, it has both a lower excitation and a lower inhibition, hence less range of excitability. On the contrary, REM sleep dynamic range did not seem to be different from wake.

#### 1.4.2.7 Auditory evoked potentials evolution across sleep

##### A. Auditory brainstem response evolution across sleep

Auditory brainstem responses (ABR) seem to be little affected by sleep. While some studies reported no changes between wake and any stage of sleep (Campbell and Bartoli, 1986; Deacon-elliott et al., 1987), some others noticed a slight delay in the wave V appearance during Non-REM sleep and specifically deep sleep (Harvey et al., 2020; Litscher, 1995). The most consistent effect reported does not specifically concern sleep : several studies report that ABR latencies are delayed when body temperature decreases, which happens during sleep were homeothermy is no longer always maintained (Harvey et al., 2020; Litscher, 1995).

## B. Auditory middle latency evoked responses evolution across sleep

Concerning middle latency evoked responses across wake and sleep, three studies found rather congruent results (Deiber et al., 1989; Erwin and Buchwald, 1986; Jones and Baxter, 1988). Indeed, middle latency responses during wake are marked by three complexes Pa-Na (Pa, 30-40 ms), a Pb-Nb (Nb 45-55 ms) and a P1-N1 (P1, 55-80 ms) component. It seems that Pa component is preserved during Non-REM sleep, yet reduced and delayed. Yet P1 is largely reduced and sometimes disappears during Non-REM sleep. Yet, it seems that Pa as well as P1 reappear during REM sleep. Jones and Baxter (1988) report that the Nb component sometimes disappears during Non-REM sleep, replaced and dominated by a positive peak of latency intermediate between Pa and Pb peaks.

Interestingly, a study focused on assessing if sleep inertia could alter middle latency responses following a night sleep (Hulse et al., 2011). In this study, 12 subjects performed an auditory oddball paradigm test before sleeping and 30 min after awakening. Their results show a reduction in amplitude of the middle latency complex N1-P2 response. The authors suggested that it mirrored homeostatic reduction in synaptic strength as suggested by the theory of Tononi and Cirelli (2006). This also gives ground to the theory of residual sleep homeostasis effects following awakening.

## C. Auditory late latency evoked response evolution across sleep and following awakening

Colrain and Campbell (2007) reviews the use of auditory late latencies evoked responses (evoked related potentials, ERP) in probing and understanding auditory processing through sleep. Such cortical evoked potentials are the signature associated with the averaged responses to deviant sounds in the context of an oddball paradigm. Their conclusions are that ERP pattern change depending on the vigilance state of the individual: peaks and latencies vary and traduce the level of auditory processing of each sleep stage. For example, P300 which is normally present during wake is gradually dampened at sleep onset (when the subject is no longer able to give overt responses and theta band activity rises), and is abolished during Non-REM sleep (except when the subject is presented with his/her own name). P300 is altered and delayed (becoming a delayed P400 and with more occipital source) but often present during tonic REM sleep and absent during phasic REM sleep. A study from (Sallinen et al., 1996) confirms this difference between tonic and phasic REM sleep. During Non-REM sleep, ERP consists in large response which are generally independent of the stimuli administered and result in a K-complex evoked response with a notably marked N350 peak. The N350 appears to reflect activation of the generator responsible for vertex sharp waves of the K-complex and is supposed to be an indicator of an active inhibition of auditory information processing during Non-REM.

### 1.4.2.8 Theta-band coupling with hippocampal regions

Velluti (2018) described in his book “the auditory system in sleep” that their team along with other researchers consistently found a phase-locking between hippocampal theta activity and neuronal discharge at the theta band frequencies in different nuclei of the primary auditory

pathway (CN, SOC, IC and A1). Velluti described this association as an internal clock (zeitgeber) of the auditory system. Although it was less present during SWS, both at the hippocampal and auditory level, it was robust during wake and REM sleep. This association was above all observed during evoked activity, when exposed to continuous sound stimulation, but could be noticeable as well during spontaneous activity. It seemed that this coupling was all the more present in case of higher attentional focus on the auditory modality.

### 1.4.3 Auditory activations during sleep

An important landmark of REM sleep which is often neglected compared to the most apparent rapid eye movements are middle ear muscle activations (MEMA) during REM sleep. They were first discovered in cats concomitantly and independently by Baust and colleagues (1964) and by Dewson and colleagues (1965). They were later identified in humans subjects through non-invasive impedancemetry (Pessah and Roffwarg, 1972). Several subsequent papers explored characteristics of MEMA events during REM sleep (Benson and Zarcone, 1979; Ferrara et al., 2000; Slegel et al., 1992, 1991). These studies added refinements in the understanding of these muscular events during sleep. Notably, it was found that 80% of all MEMA events during the night occurred during REM sleep and 10% of them occurred in the minutes before the occurrence of REM sleep. It was also found that they were associated with rapid eye movements and mostly present during phasic REM sleep, yet they were not always concomitant with rapid-eye movements. Last, Ferrara and colleagues (2000) identified that a 2h pure tone 90 dB 1000 Hz tone before sleep onset reduced the number of MEMA events during the following night.

### 1.4.4 Sleep apnea and auditory processing

#### 1.4.4.1 Sleep apnea and auditory evoked responses

Two studies reported that patients submitted sleep respiratory disorders and in particular to obstructive sleep apnea have degraded auditory evoked responses during sleep (Paquereau et al., 1994; Wetmore et al., 1988). Notably they reported that ABR were delayed in apneic patients with respiratory insufficiency compared to patients only experiencing sleep apnea syndrome, and that after obstructive sleep apnea syndrome treatment, the ABR response were shorter than before treatment. Another study analyses ABR responses in controls, mild, moderate and severe obstructive sleep apnea patients (Matsumura et al., 2018). The authors reported an association between the presence of obstructive sleep apnea and changes in absolute latency of wave V ( $p = 0.03$ ). and notably among the moderate obstructive sleep apnea group ( $p = 0.01$ ).

#### 1.4.4.2 Sleep apnea and hearing loss

Chronic sleep apnea has been consistently reported as to be associated with hearing loss. For this reason, a meta-analysis assessing the relationship between them was recently conducted by Wang and colleagues (2022) and concluded on a basis of 10 articles gathering data from 7867 subjects that the incidence of hearing loss in patients presenting obstructive sleep apnea

is significantly higher than in the control group, and that generally, the hearing thresholds in the obstructive sleep apnea group was higher than in the controls.

Several scenarios are mentioned to try to explain the pathophysiological mechanism that could explain such an association: damage to the cochlea and auditory pathway neurons due to chronic intermittent hypoxia, snoring noise, alteration in the Eustachian tube function, metabolic disorders and neuro-cognitive impairment related or caused by obstructive sleep apnea.

### 1.4.5 Key insights

A partial gating of auditory information is present during sleep. Indeed, auditory awakening thresholds are higher than auditory detection thresholds during wake. While several studies supported that auditory information was gated at the level of the thalamus during sleep, recent research has provided multiple demonstrations that the cortex is porous to incoming exterior sounds during sleep. In fact, cognitive and potentially complex cortical tasks can be performed during sleep, both during Non-REM and REM sleep. Yet, distinct physiological characteristics of Non-REM and REM sleep as well as specific divergence of evoked and spontaneous activity of neurons between these states in the firing properties of central auditory pathway neurons tend to demonstrate that as Andrillon and Kouider (2020) hypothesized, gating mechanisms may be different between Non-REM and REM sleep.

During Non-REM/SWS sleep, compared to wake, spontaneous activity of auditory neurons from cochlear nuclei to inferior colliculus were not very different from wake, yet it is then reduced in the MGB and slightly reduced in the auditory cortex. Concerning evoked activity, auditory neurons displayed enhanced activity from auditory nerve to inferior colliculus and then decreased in the MGB and slightly decreased in A1. Receptive fields were sharper in MGB and slightly in A1. Bursting activity of neurons was higher in SWS compared to wake in MGB and during evoked activity in A1. Concerning global auditory evoked potentials, ABR are maintained during Non-REM with wave V sometimes reported slightly delayed. Middle latency potentials are reduced and late latency potentials (ERP) sometimes disappear.

These results show that for SWS indeed a reduction of activity is observed at the level of the thalamus, but information at the level of the auditory cortex is less affected. As Issa summaries in her thesis : during SWS, globally the auditory cortex does not seem to have a higher inhibition, it has both a lower excitation and a lower inhibition, hence less range of excitability.

Auditory neurons behave differently during REM sleep. A key mark of REM sleep seems to be an increase of the spontaneous activity along the auditory pathway, notably in the MGB and auditory cortex (A1, belt and parabelt), while evoked activity remains unchanged at the first stages and then even decreased compared to wake in the inferior colliculus, MGB and auditory cortex. This results in a lower signal to noise ratio for the transmission of auditory sensory information during REM sleep starting at the level of the inferior colliculus up until the belt and parabelt. Information seems to be drowned in noise for these relays during REM



sleep. Additionally, AEP during REM sleep seem to be preserved during tonic REM sleep while ERP seem to be absent during phasic REM sleep.

These observations lead to the question of the source of such increased spontaneous activity in the auditory pathway during REM sleep. The question remains open with two potential candidates. First, one could posit it is caused by the integration of PGO waves and acoustomotor proprioceptive information derived from MEMA activity along the auditory pathway. Alternatively, it could be the result of a potentially enhanced influence of the hippocampal regions on auditory processing through phase-locking with the increased theta activity observed during REM sleep. All in all, such observations give ground at the theory of an informational gating of auditory information during REM sleep (and above all during phasic REM sleep), as presented by Andrillon and Kouider (2020).

Last, several studies illustrate that chronic sleep apnea can have damaging effects on auditory processing and hearing abilities.

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# **Chapter 2**

# **Tinnitus & Sleep**

## 2. Tinnitus and sleep

Poor sleep quality is a recurrent complaint in the tinnitus population and sleep disturbances are the second most frequent comorbid condition among tinnitus patients (Asplund, 2003). It has been indeed shown that sleep is deteriorated in many aspects in the tinnitus population, as illustrated by a recent review and meta-analysis (Gu et al., 2022). Notably, particularly in the elderly, it was shown that tinnitus was associated in deteriorated sleep compared to aged matched controls (Hébert and Carrier, 2007). Another study has even demonstrated that tinnitus severity was correlated with poor sleep quality prior to tinnitus onset (Lu et al., 2020).

Taking into consideration the time dimension of sleep, tinnitus can interact with it in three different ways. Sleep and tinnitus can interact at sleep onset resulting in sleep onset insomnia. Tinnitus and sleep could potentially interact during sleep, endangering sleep continuity. Lastly, tinnitus can interact with the end of sleep, that is to say the awakening. The core of this thesis will be devoted on the two latter types of interactions, yet we will develop in this introduction the subject of tinnitus and insomnia.

### 2.1 Tinnitus and insomnia

#### 2.1.1 Prevalence and manifestation

Insomnia appears as one of the most frequent comorbidities experienced by tinnitus patients. Several studies have shown and described the association between subjective insomnia and tinnitus (Crönlein et al., 2007; Folmer and Griest, 2000; Miguel et al., 2014). In a review which included these studies, Asnis and colleagues (2018) reports that the prevalence of insomnia in tinnitus patients ranges from 10% to 80% (with the majority of studies reporting a prevalence above 40%). Such disparity would be due to the majority of studies inadequately defining insomnia as a diagnosis and only describing it as a symptom. Notably, too few studies give enough details on which sleep characteristics are more typically affected by tinnitus (difficulty falling asleep, awakenings during the night and early morning awakening). When such dimensions are reported, often all aspects of insomnia were found present in tinnitus patients, with difficulty in falling asleep as the most severe (Axelsson and Ringdahl, 1989; Hallam, 1996).

#### 2.1.2 Hyperarousal as a potential underlying mechanism

Hyperarousal, in the context of insomnia, refer to a state of high sympathetic activation which has been often associated with increased high-frequency EEG activation, abnormal hormone secretion, increased whole body and brain metabolic activation and elevated heart rate. It manifests as a state of increased psychological and physiological tension marked by anxiety, exaggerated startle responses, reduced pain tolerance, insomnia, fatigue, and accentuation of personality traits (Bonnet and Arand, 2010).

It is often associated with the cognitive focus and rumination that insomniac patients tend to devote on their insomnia. It initiates a vicious circle of “learned sleep preventing associations” that fuel the chronicity of the disorder (Riemann et al., 2010). As such, it is of the major perpetuating factors associated with insomnia, as theorized by the “3P” model of (Spielman, 1986). According to this model, insomnia emerges on the base of Predisposing conditions (anxiety, depression, alcohol/coffee/tobacco consumption, obesity, irregular working hours), and is triggered due to Precipitating circumstances (professional or social stress, illness) and gets chronic because of Perpetuating factors (prolongation of bedtime, daytime napping, hyperarousal).

In a theoretical review Wallhäusser-Franke and colleagues (2013) interrogate the possibility that tinnitus and insomnia may both have hyperarousal as potential initial cause. Indeed, both conditions seem to have stress episodes as precipitating circumstances, activating limbic networks, both tend to become more frequent with age, both are associated with hyperarousal attributes, such as dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic hyperactivation. Additionally, in this review the experimenters collected 4705 records of participants to a survey exploring sleep onset and sleep maintenance characteristics of tinnitus patients. They found that patients reported problems with sleep maintenance more often than sleep onset, some of them reporting being wakened up because of their tinnitus, which questions the role of tinnitus during sleep.

### 2.1.3 Treating one alleviates the other

It is important to mention that treating sleep complaint or tinnitus often results in improving the other. For example, recent work in adapting cognitive behavioral therapies for insomnia applied to tinnitus patients demonstrated remarkable results in terms of efficacy (Marks et al., 2023). For a review, see Curtis and colleagues (2021). Conversely, treating tinnitus results in a reduction of sleep disorders such as insomnia (Wakabayashi et al., 2018).

## 2.2 Tinnitus and sleep interactions during sleep

### 2.2.1 Sleep architecture of tinnitus patients

In addition to the delayed sleep latency, early awakening in the morning and nocturnal awakenings reported by questionnaire (Alster et al., 1993), various studies tried to assess more objectively sleep deterioration in the tinnitus population by performing polysomnographic assessment of tinnitus samples.

A first study was conducted by Burgos and colleagues (2005) and compared three groups : 10 patients with tinnitus, 20 patients with primary insomnia and 20 age and gender matched controls. All patients underwent two nights of polysomnographic clinical assessment (first night of adaptation and then a second night of assessment). Results show that tinnitus group

and primary insomnia group both displayed decreased sleep efficiency, reduced total sleep time and increased frequency of nocturnal awakenings.

Eysel-Gosepath and Selivanova (2005) carried out a polysomnographic assessment on 26 patients with tinnitus and sleep disturbances. They reported increased index of arousal as well as a reduction of N3 sleep and REM sleep phases (yet, without pairing these observations with controls). Additionally they noted a high prevalence of sleep disorders in their tinnitus cohort : 10 patients with obstructive sleep apnea syndrome, 4 with insomnia and 3 with pathological movements of the legs.

Hébert and colleagues (2011) conducted a comparative one-night polysomnographic study on 22 tinnitus patients and 22 matched controls. They did not report significant differences in the objective polysomnographic architecture parameters between the two groups. They additionally conducted analyses on the spectral power differences between the two populations. Interestingly, they observed and reported a significant reduction of EEG delta band power (1-4 Hz) in the tinnitus group as compared to the control group and a marginal correlation between absolute delta power and tinnitus reaction questionnaire scores. This suggests that sleep depth in tinnitus patients is impaired and the extent of sleep depth deterioration is associated with tinnitus severity.

A similar study was conducted by Attanasio and colleagues (2013) comparing 18 tinnitus patients to 15 healthy subjects on a one-night polysomnographic assessment. They reported a significant decrease of N3 sleep and REM sleep proportion in the tinnitus group compared to the control group and a higher combined proportion of N1 and N2 sleep in the tinnitus group compared to the control group. Additionally, they observed a significant correlation between the increase of light sleep (N1 + N2) and the THI score reported by the tinnitus group, but not between REM sleep proportion and THI.

A similar study was conducted by Teixeira and colleagues (2018b) involving 25 tinnitus patients and 25 controls. In this study, the authors report a significant decrease of REM sleep proportion in tinnitus patients as compared to controls ( $p < 0.05$ ), a marginal decrease in N3 stage sleep proportion and an increase in N1+N2 sleep proportion in tinnitus as compared to controls.

A study performed on a selected tinnitus patient population that concomitantly suffered from Post-Traumatic Stress Disorder (PTSD) concluded that REM sleep proportion and duration were inversely correlated with Tinnitus Functional Index (TFI) scores (Madhulika, 2019).

As Teixeira and colleagues (2018a) proposed in their review, all these studies converge on the fact that polysomnographic characteristics of tinnitus patients seem to display lighter, shallower and more fragmented sleep, with decreased N3 deep sleep, decreased slow waves, as illustrated by the reduction of delta band power observed by Hébert and colleagues (2011) and, above all, reduced REM sleep, which would suggest a decreased homeostatic sleep pressure drive as it can be observed in primary insomnia.

## 2.2.2 Auditory local arousal in the tinnitus sleeping brain

In a theoretical review, Milinski and colleagues (2022) proposed that tinnitus neural attributes deteriorate sleep quality and continuity. This would manifest as a degradation of sleep maintenance resulting in fragmented sleep. In their model, tinnitus is associated with increased spontaneous activity in the central auditory pathway, as postulated by models such (Krauss et al., 2016; Norena, 2011; Shore et al., 2016) and a general state of hyperarousal of the central auditory pathway. Sleep maintenance would become cumbersome in such a context since a main attribute of Non-REM sleep is the ability of exhibiting synchronized activity across the whole brain. Disturbed auditory activity, appearing as a local remanence of wake in the sleeping brain would disfacilitate the emergence of slow waves and their propagation. Reciprocally, if important homeostatic sleep pressure drives the emergence of synchronized slow waves, with “off” periods on neuronal firing, the authors presuppose that it may result in perturbation of the tinnitus-related activity and potentially its alleviation. Hence, the authors hypothesize that tinnitus and homeostatic sleep drive have a competitive mutually exclusive relation: deeper sleep, associated with synchronized slow waves would be associated with lower tinnitus neural correlates and the end of the night with dimer sleep drive would lead to higher tinnitus level

Moreover, the authors propose that tinnitus signal and the associated percept are maintained during sleep and could act as an arousal trigger that could wake patients up. Indeed, they defend this idea arguing that sleep architecture deterioration in tinnitus patients is similar to sleep architecture of healthy subjects exposed to white noise during their sleep (Terzano et al., 1993).

They also proposed that sleep may play a role in anchoring acute tinnitus into becoming a chronic condition. Indeed, sleep has been identified to play a role in cortical map plasticity and tinnitus has been associated with such reorganizations following auditory deafferentation. Moreover, sleep could contribute to the consolidation of the memory of the tinnitus percept resulting in its anchoring. Last, homeostatic gain changes described by Norena (2011) could preferentially happen during sleep resulting in hyperexcitability of central auditory pathway neurons.

## 2.2.3 Tinnitus and dreams

In partial opposition to the theory developed by Milinski and colleagues (2022), two studies provide evidence that tinnitus may not be present during sleep. Indeed, Aazh and colleagues (2021) and De Ridder and colleagues (2014a) both report that a quasi-unanimous majority of tinnitus patients do not experience tinnitus within their dreams. Aazh and colleagues (2021) present the symptomatologic characteristics of the 7 out of 148 patients that reported hearing tinnitus during their dreams. They highlight that these patients seem to be younger and to experience severe and distressing forms of tinnitus compared to the rest of the sample, although the small size of this subgroup in the sample surveyed does not enable to perform consistent statistical analyses.

On the other hand, De Ridder and colleagues (2014a) put forward the observation that 97% of their 76 tinnitus patients sample do not report hearing their tinnitus within their dreams in favor of the Bayesian brain model of tinnitus (De Ridder et al., 2014b). Yet, it is important to mention that as the Bayesian brain model shares common bases with the predictive coding model (Sedley et al., 2016), the latter is also compatible with the finding that tinnitus is not perceived during dreams. Indeed, Hullfish and colleagues (2019) argue that the predictive coding model is indeed compatible with tinnitus. They also refer to the hypothesis of Hobson and Friston (2012) on the role of REM sleep and that during this state there is an intact body representation, despite hearing loss. They postulate that in such context of simulation, the proto-consciousness has learned to attenuate signals from the external world, leading to low evidence of abnormal deafferentation signal and attenuated prediction error, leading to no tinnitus perception within the dreams.

## 2.2.4 Tinnitus and sleep disorders

As presented hereafter, several co-prevalence studies have assessed what kind of sleep disorder is associated with tinnitus. Most published research has focused on the association between tinnitus and sleep apnea and, to a lesser extent, bruxism.

### 2.2.4.1 Tinnitus and sleep apnea

The association between sleep apnea and tinnitus was recently reviewed in a meta-analysis (Gao et al., 2024). This study yields an odds ratio of 1.65 (95% confidence interval: 1.14-2.39) for the comorbidity of tinnitus with sleep apnea ( $p < .001$ ). They made their observation on the base of seven studies gathering 132,292 adults in which 1556 had sleep apnea. More precisely, tinnitus was associated more with severe sleep apnea than mild or moderate forms. It is important to note that out of the seven studies used for this review, most of the data comes from the study of Koo and Hwang, (2017) which included 130,788 patients. In the discussion of the meta-analysis, the authors examine the different pathophysiological mechanisms that could explain such interactions. Indeed, in both pathologies chronic systemic inflammation and abnormal sympathetic activity have been reported. As reported before in the section on auditory system in sleep, chronic sleep apnea induces chronic hypoxia which is particularly damaging for the fine structure of the inner ear and to sustain the demanding needs of the auditory nerve (which has critically high firing rates). Moreover, most apneic patients have an obstruction site at the level of the soft palate (Koo et al., 2013). The muscle of the soft palate crucially involved in apnea events is the tensor veli palatini, which is innervated by the trigeminal nerve. Tinnitus and sleep apnea interaction could therefore come from a dysfunction of this muscle, resulting in some somatosensory form of tinnitus. Last, the authors evoke a potential involvement of the serotonergic system, which has been proposed to be involved both in apnea and in tinnitus. To the best of our knowledge, no study analyzed if tinnitus is associated more with obstructive sleep apnea or with central sleep apnea.

### 2.2.4.2 Tinnitus and bruxism

Various studies has examined the potential relation between tinnitus and bruxism (Camparis et al., 2005; Fernandes et al., 2014; Peleg et al., 2022; Saltürk et al., 2015). Camparis and

colleagues (2005) analyzed the prevalence of tinnitus in a group of 100 sleep bruxism patients. 54 patients out of 100 complained of tinnitus in addition to sleep bruxism. Comparing the characteristics of the two groups, the authors describe higher prevalence of chronic facial pain, a number of areas that are painful to patients to palpation in the masticatory and cervical muscles, myofascial pain in the masticatory muscles and indices of depression in the tinnitus group as compared to sleep bruxism patients without tinnitus. Inversely, Peleg and colleagues (2022) analyzed the prevalence of sleep bruxism in a tinnitus sample of 51 tinnitus patients seeking clinical care. In their sample, thirty-four participants (66.7%) were diagnosed with bruxism and Temporo-mandibular disorder was found in 14 (27.5%) of the cases. Patients with sleep bruxism and temporo-mandibular disorder were found having the highest level of anxiety. Saltürk and colleagues (2015) compared the tinnitus characteristics between a group of sleep bruxism patients with tinnitus and a group of patients experiencing tinnitus only. They concluded that when tinnitus is associated with sleep bruxism it tends to present with higher pitch and a lower loudness. Lastly, Fernandes and colleagues (2014) have investigated the association between sleep bruxism, tinnitus and temporo-mandibular disorders, analyzing a sample of 261 women. They found a greater association between painful temporo-mandibular disorders and tinnitus than between sleep bruxism and tinnitus, although both were significantly associated. The concomitant presence of painful temporo-mandibular disorder and sleep bruxism was associated with a higher degree of tinnitus severity.

#### 2.2.4.3 Tinnitus and snoring

The potential association between tinnitus and snoring has been investigated in Lu and colleagues (2022). In this study, the 50 participants who presented tinnitus underwent a polysomnographic exploration in which intra-ear canal snoring sound energy was measured with an intracanal microphone. The experimenters found that the 33 tinnitus patients had higher intra-ear canal snoring sound energy than non-tinnitus patients on the 851-1500 Hz frequency band, which means that tinnitus patients had snores containing power on higher frequencies than the other patients. The authors hypothesize that high-frequency tissue vibration of such snoring sounds may cause tissue damage to the inner-ear and bring about subsequent tinnitus. In fact, a guinea pig model demonstrated that temporal bone vibration from an external electromagnetic shaker could cause hearing threshold shift, and particularly in case of higher frequency vibrations (Sutinen et al., 2007).

#### 2.2.4.4 Tinnitus and other sleep disorders

Aazh and colleagues (2023) explored potential association of exploding head syndrome and tinnitus in a sample of 148 tinnitus and/or hyperacusis patients. They identified 12 cases (8.1%) of exploding head syndrome within this sample, which is a similar prevalence for this syndrome as in the general population. On the other hand, Levine (2013) associated exploding head syndrome manifestations to the clinical reports of tinnitus patients who hear a brief loud sound when dozing off. This questions the absence of link between tinnitus and this syndrome. The authors note that the rather small size of the cohort, due to the rarity of the syndrome, does not enable a refined prevalence analysis. Hwang and colleagues (2021) analyzed potential co-prevalence of tinnitus with night terrors, as well as walking and/or



talking during sleep in a sample of 1937 patients without and 970 patients with chronic tinnitus. They identified that a significantly higher proportion of patients experienced sleep terror in the tinnitus group as compared to the other, especially in young adults. The percentage of patients reporting sleep walking was slightly higher in subjects with tinnitus than in those without, with marginal significance ( $p = 0.063$ ). The percentage of patients experiencing sleep talking did not differ significantly between the groups. Hwang and colleagues (2020) assessed if tinnitus was associated with periodic limb movements in a sample of 2849 adult patients and did not find any association.

## 2.3 Tinnitus and awakening

Tinnitus can have interactions with the end of sleep, that is to say, the awakening, on different modalities. First, there is the question of when the tinnitus appears regarding the awakening: is tinnitus waking patients up, is it appearing at the instant the patients open their eyes or is it appearing gradually or abruptly some time after the patients have woken up ? Then, there is the question of the tinnitus modulation following the awakening: are the psychoacoustic attributes of tinnitus (spectral content, loudness, localization...) upon wake up different from the ones just before sleep onset ? Last, it also depends on the circumstances of the awakening: is it awakening from a nap, in the morning after a long night or during the night (nocturnal awakening) ? Is it awakening from sleep stages N1, N2, N3 or REM ? Is it awakening with a high or low remaining sleep debt ? Is it awakening in a situation of sleep inertia ? Lastly, and as we will see, outcomes of such situations can differ from patients to patients because of tinnitus heterogeneity.

As previously presented, a few studies have tried to understand the relation of tinnitus with time of day. Some of these studies analyzed physiological characteristics of tinnitus patients in the morning and how tinnitus was perceived at this time of day. As a brief reminder, firstly, it was found that tinnitus patients seem to have an abnormal cortisol awakening response (Jackson, 2019). Secondly, a study by Probst and colleagues (2017) with the TrackYourTinnitus app described that tinnitus patients experienced a “morning roar” as tinnitus loudness and distress ratings were highest during the night between midnight and 8am. Yet, this study has some methodological limitations. First, this effect was called a morning roar but it referred to measurements performed between midnight and 8am, which most probably refer to nocturnal awakenings and not morning awakenings. Moreover, between 9am and 9pm, tinnitus metrics were calculated as an average of more than 500 records, while between midnight and 8am, tinnitus metrics were calculated as an average of 100 records at most. Average scores between midnight and 8am may hence appear as data points collected by a minority of participants suffering from insomnia, and hence, more prone to provide outliers measures.

### 2.3.1 Tinnitus increase after naps

A subgroup of tinnitus patients describes modulations of their tinnitus loudness perception upon awakening from a nap sleep. Hereafter, we will refer to this phenomenon as Nap-

Induced Tinnitus Modulations (NITM). The minority of such patients describes a reduction of tinnitus loudness perception following a nap, but the majority the opposite effect, an increase of tinnitus loudness upon awakening. We will refer at the latter subgroup as the Tinnitus Increases After a Nap (TIAN) subgroup. TIAN phenomenon has been described in the tinnitus literature by different authors.

Newman (1998) develops the theory that in some cases tinnitus may be linked to hyperuricemia (abnormally high level of uric acid in the blood). To defend this theory, the author mentions that in clinical practice often some tinnitus patients can complain that involuntary sleeping or napping (narcolepsy) can rapidly induce severe tinnitus attacks. The author links such sleep onsets as provoking abrupt drop of circulation in the very fine capillaries of the auditory system, causing hypoxia. Hypoxia in tissues could then provoke overproduction of urate by purine nucleotide degradation, resulting in hyperuricemia, which is hypothesized to be related to tinnitus.

A marking event in the consideration of NITM was the acknowledgment of its clinical reality following the Tinnitus Research Initiative meeting in 2006. Indeed, following this meeting emerged a consensus for tinnitus patient assessment in the form of a questionnaire. This questionnaire created from this meeting is referred to as the Tinnitus Sample Case History Questionnaire, TSCHQ. It is a 35 items questionnaire which includes this question :

22) Does taking a nap during the day affect your tinnitus?

A) worsens my tinnitus B) reduces my tinnitus C) has no effect

Since then, several studies refer to NITM due to the fact they use TSCHQ as a questionnaire and analyze this item.

Levine (2013) described the phenomenon of TIAN and presented it as a sign of somatic form of tinnitus. Indeed, in his publication, the author reports that patients most often experience TIAN when they are performing their nap in the seating position. The author hypothesizes that it may relate to somatic factors such as the stretching of the neck muscles when the head of the patient passively falls forward while dozing in a sitting position. Ralli and colleagues (2017a; 2017b) both refer to NITM and link it to somatosensory forms of tinnitus evoking the same reasons as Levine.

Van den Berge and colleagues (2017) worked on tinnitus heterogeneity by proposing a clustering analysis in order to find homogeneous subphenotypes of tinnitus in a database containing 1783 patients. In this study, the database was constituted of records of patients visiting the tertiary referral tinnitus care group at the University Medical Center Groningen. The questionnaire they filled included the question of whether or not tinnitus increased following naps and the authors thought it was important to include this question for the clustering analysis as it could be characteristic of a specific tinnitus subphenotype. Yet, in the 4-cluster solution they propose following the execution of their clustering algorithm (k-means) no subgroup contains specifically the TIAN patients.

Likewise, Kojima and colleagues (2017) reports the clinical characteristics of 584 tinnitus patients who completed the TSCHQ questionnaire. In this study sample, they note that tinnitus patients presenting concomitant hyperacusis were more concerned by tinnitus increase following naps, although in the discussion they mention that future research should investigate the reason of this link without providing a hypothesis for it.

More recently and following the impulsion of the TRI consensus of 2006, the European School for Interdisciplinary Tinnitus research (ESIT) created a new standardized questionnaire to perform a complete anamnesis initial questionnaire for tinnitus patients, designated as the ESIT-SQ (Genitsaridi et al., 2019). This anamnesis questionnaire also includes a question on tinnitus potential modulation by naps (potential increase or decrease).

### 2.3.2 Sleep intermittent Tinnitus

Another rarer form of tinnitus manifestation that has been described in some cases is what will be here designated as sleep intermittent tinnitus (SIT). Such SIT patients will describe complete intermittence of their tinnitus perception. In their case, any sleep occurrence acts as a random switch. These patients report that on some days, they can wake up after a night sleep and experience a full day without any experience of tinnitus, until the next sleep episode (nap or night sleep). On such days, some of them report that even while staying still in a very silent room, they cannot hear their tinnitus. In clinical reports, such patients describe that on tinnitus-free days, dozing off for a few seconds or making a nap can switch on their tinnitus. Interestingly, the effect of nap is not often symmetrical: on days in which they wake up with intense tinnitus, making a nap will not switch off their tinnitus perception, only night sleep seems to be able to activate a switch off. These tinnitus patients have rarely been described in the tinnitus scientific literature. Nicolas-Puel and colleagues (2002) proposes a classification of tinnitus types depending on the time course of tinnitus variation. SIT patients are classified in a separate group referred as “intermittent” tinnitus. Interestingly, the authors associate NITM phenomenon as being part of another category referred to as fluctuating tinnitus by mentioning “*All patients who described their tinnitus as fluctuating in intensity described a very clear increase in intensity of their tinnitus after periods of sleep (whether nighttime or siesta)*”.

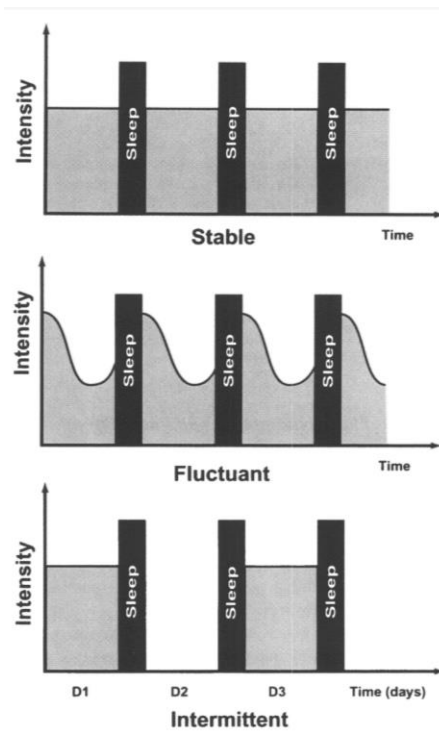


Figure 2.1 Tinnitus classification depending on temporal variability of its intensity. SIT patients are patients of the “intermittent” category (Nicolas-Puel et al., 2002)

Rauschecker and colleagues (2010) mention the case of SIT patients while elaborating their frontostriatal gating model. They describe such patients as having tinnitus sensation disappearing completely for days or weeks, only to resume at full force. In their model, they hypothesize that such situation “*may occur during a stage at which damage to the subcallosal area is still temporary: fluctuating activity (and corresponding neurotransmitter) levels allow transient filtering of the tinnitus signal*”.

## 2.4 Principal questions and thesis outline

Although TIAN and SIT patients’ subphenotypes have been described in the tinnitus literature, to our knowledge, no epidemiological study tried to assess the prevalence of these subphenotypes in the tinnitus population, nor their associated symptomatologic specificities. Moreover, no study aimed at understanding the physiological mechanisms behind night sleep-induced tinnitus modulations or NITM, neither through sleep exploring techniques such as polysomnography nor through longitudinal follow-up of such patients.

**In this thesis, we question the epidemiological characteristics of the TIAN and SIT populations and the physiological mechanisms at the origin of such sleep-induced tinnitus modulations.**

**In Chapter 3** we explore the heterogeneity of tinnitus and interrogate if TIAN and SIT patients constitute separate subphenotypes within the tinnitus population. To this end, we produced a validated French translation of the ESIT-SQ questionnaire which notably includes

question items on nap sleep and night sleep tinnitus modulations and we conducted a first survey with this questionnaire on a French tinnitus patient sample population. This questionnaire will help future research acquire more standardized information about tinnitus patients depending on NITM. Then, we tried to perform an optimized segmentation of the tinnitus population in subphenotypes with regards to known endotypes. For this purpose, we performed a diagnostic-driven benchmark of different clustering methods applied on a large database of tinnitus questionnaire records, within a semi-supervised framework.

**In Chapter 4** we perform a symptomatologic exploration of the TIAN patients to better understand the profile of symptoms associated with NITM. To this end, we performed a cross-sectional study across two databases in order to analyze the prevalence and symptomatologic characteristics associated with NITM, and by analyzing the specific symptomatologic profiles of the TIAN patients and the tinnitus decreases after naps patients.

**In Chapter 5** we present two polysomnographic studies of the TIAN and SIT population. In a first one night-sleep study, we compare the symptomatologic and polysomnographic characteristics of the SIT population in comparison to a control group of tinnitus patients that do not present any variation of their tinnitus level with regards to sleep. Then we present a longitudinal nap-sleep analysis of a sample of TIAN population. Within this study, each participant is his/her own control, within a framework of six naps of polysomnographic measurements along with pre and post nap audiological and kinesiological measurements.

# Chapter 3

## Tinnitus heterogeneity

# 3. Tinnitus heterogeneity

In this chapter, we will review our contribution to tinnitus research on the matter of tinnitus heterogeneity. Indeed, studying tinnitus heterogeneity has been a recent growing interest in tinnitus research as it has been identified as an obstacle to finding physiological correlates of tinnitus and new treatments (Cederroth et al., 2019; Niemann et al., 2024). There may not be only one treatment that will help all tinnitus patients but probably instead several treatments that will be most suited for several distinct subtypes of tinnitus patients as stated by (Hall et al., 2019; Kim, 2022) with the formula “one size does not fit all” for tinnitus. In fact, results from the study of (Niemann et al., 2024) tend confirm such point of view.

## 3.1 Validated French translation of the ESIT-SQ standardized tinnitus screening questionnaire

Among the initiatives launched to better understand tinnitus heterogeneity and complexity, European School of Interdisciplinary Tinnitus research (ESIT) was launched under the coordination of Pr Winfried Schlee and aimed at improving tinnitus treatment and research in Europe through interdisciplinary teaching and training for young researchers. 15 students received funding to perform a PhD within this program. They devoted a specific common interest for the subject of tinnitus heterogeneity, as they presented in a common publication on their perspective as early stage researchers (Simoes et al., 2021).

Among the projects led by the ESIT was the creation of a new standardized screening questionnaire, ESIT-SQ, to perform a unified anamnesis of tinnitus patients (Genitsaridi et al., 2019). This questionnaire was produced as a replacement of the Tinnitus Research Initiative’s 2006 Tinnitus Sample Case History Questionnaire (TSCHQ) questionnaire (Langguth et al., 2007). It enabled administration to subjects free of tinnitus, with more ecological assessment, it explored more broadly pathologies and symptoms associated with tinnitus, as well as chronological relations between tinnitus and such pathologies. This questionnaire was originally inspired from the anamnesis questionnaire of Dr Alain Londero and administered in the Georges Pompidou European Hospital in Paris.

The goal of such questionnaire was its administration to large scale cohorts within the European population in order to collect an extensive database of records of such questionnaire within the Tinnitus Database project (Landgrebe et al., 2010). With such extensive database, fine epidemiological analyses could be led to identify subphenotypes, endotypes and subtypes segmentations of tinnitus patients. To this end, the ESIT-SQ questionnaire was published and then translated into various European languages : English, Flemish, German, Italian, Polish, Spanish, Swedish, Albanian and Spanish (Genitsaridi et al., 2021, 2019; Haro-Hernandez et al., 2022). Yet, no validated French translation of the ESIT-SQ questionnaire existed to this day.



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Original article

## Validated French translation of the ESIT-SQ standardized tinnitus screening questionnaire

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### Info

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 Siopi

### Article Abstract

**Objectives.** – The heterogeneity of tinnitus in terms of etiology, presentation and sometimes severe impact on quality of life hinders treatment and clinical research. The European School for Interdisciplinary Tinnitus Research Screening Questionnaire (ESIT-SQ) collects standardized tinnitus characteristics for patient subtyping. A validated French translation of the ESIT-SQ is presented here.

**Method.** – On the initiative of the French Interdisciplinary Tinnitus Association (AFREPA), 3 translators (1 professional translator, 1 clinician and 1 researcher) were missioned to translate the English version of the ESIT-SQ into French, adhering to good practice guidelines. Nine patients were recruited with the help of the France-Acouphènes patient association, to test and validate the translation. Lastly, an exploratory survey of responses to the French questionnaire was conducted online via the Siopi mobile phone application.

**Results.** – The French translation of the ESIT-SQ was successfully validated. 105 patients responded to the exploratory survey, and their characteristics are presented here.

**Conclusion.** – This new validated French translation of the ESIT-SQ will enable epidemiological and clinical data to be collected in French-speaking populations, and thus compiled and compared with data collected with other versions of this questionnaire already published in other languages.

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### Introduction

Tinnitus is defined as an auditory sensation without external acoustic stimulation or meaning which may be experienced as disagreeable and impacting quality of life [1]. Prevalence is high, at 10% of the population [2], and impact can be severe [3]. Tinnitus remains a scientific and clinical challenge that is only partially understood, largely due to its intrinsic heterogeneity [4]. To elucidate this heterogeneity, the European School for Interdisciplinary Tinnitus Research (ESIT) was set up, one aim being to collect epidemiological data in a centralized database at European level [5]. This extended the Tinnitus Database project (<https://tinnitus-database.eu>), launched in 2010 by Landgrebe's and colleagues [6]. The first step in

patient follow-up through the Tinnitus Database was a screening step, for which ESIT developed a standardized screening questionnaire, the ESIT-SQ [7].

This questionnaire replaced the the Tinnitus Research Initiative's 2006 Tinnitus Sample Case History Questionnaire [8], and enabled administration to subjects free of tinnitus, with more ecological assessment, more broadly including pathologies and symptoms associated with tinnitus and the chronological relations between tinnitus and such comorbidities [7,9].

The ESIT-SQ was published in English, Flemish, German, Italian, Polish, Spanish, Swedish and Albanian [7,10,11]. Despite its having been largely founded on a French questionnaire used in the Georges Pompidou European Hospital in Paris (see Appendix A [7]), no French translation of ESIT-SQ was previously available.

In France, the French Interdisciplinary Tinnitus Association (AFREPA, <https://www.afrepa.org>) brought together medical and paramedical professionals to improve the standard of care in

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tinnitus via a multidisciplinary approach, and seeks to contribute to clinical research [12,13]. To improve and harmonize practices in each of its teams, AFREPA sought to standardize initial assessment. The ESIT-SQ, which had the further advantage of making data available for European-level research, was chosen as the optimal candidate.

The main aim of the present study was therefore to translate the ESIT-SQ into French, following the good practice guidelines laid out in [14], so that it could be made available to all French-speaking health practitioners managing tinnitus patients, and allow interested patients to contribute to European-level research. The secondary objective was to conduct an exploratory survey of results on the French ESIT-SQ, administered online via the Siopi tinnitus sufferers' community mobile phone app (Siopi, <https://siopi.ai/fr>).

## Method

The translation was made between April and December 2020, and the exploratory survey data were collected between September and December 2021.

Translation adhered rigorously to the good conduct guidelines laid out by Hall et al. [14]. Thus, 3 translators were recruited: 1 professional translator, 1 neuroscience PhD student specializing in tinnitus, and 1 ENT specialist (respectively, F. Decobecq, R. Guillard and A. Londero). They were all graduates, and native French speakers, with a good level of English. After a first meeting to explain the procedure, F. Decobecq and R. Guillard produced 2 independent translations, which A. Londero then combined in a version that was discussed and validated in a dedicated meeting including all 3 translators. The France-Acouphènes tinnitus patients' association (<https://www.france-acouphenes.fr>) was then contacted to recruit experienced volunteer patients for real-life validation. Nine tinnitus patients were thus asked to fill out the questionnaire, reading it closely so as to screen for:

- spelling or grammatical mistakes and;
- problems in the formulation of the questions and responses that might lead to ambiguity and thus difficulty in answering.

This test phase revealed some minor spelling and grammatical mistakes, leading to one change in wording to avoid ambiguity: in question 5, at the beginning of the question, "comment" ("how") was replaced by "quelle" ("what") regarding the subject's economic situation. The translation team then validated this revised and final version of the questionnaire.

The secondary study objective involved an exploratory online survey in a sample of volunteers. The Siopi platform is a community mobile phone app enabling mutual aid between patients with comparable symptom profiles and introducing those who wish to the ecosystem of clinical research. Before medical data, such as responses on our survey, are collected by the application, users are informed of the procedure and accept the general conditions of use, including anonymized export of the database for public-sector research purposes. Responses were collected in a database hosted by an approved health-data host, and separated from personal data so as to ensure strict anonymity.

Siopi developed a specific module for the survey, and users were informed by email of the possibility of participating: information about tinnitus communities had been posted on social media was shared by the France-Acouphènes patient association with the members of its network.

In total, 105 users responded to the survey between September and December 2021. The dataset had no missing data. Respondents reported no particular difficulties in filling out the questionnaire.

**Table 1**

Demographic data for respondents to the exploratory survey ( $n = 105$ ). Sample demographics. 42 female, 63 male.

	Mean	SD	Median	Min	Max
Age (years)	45.03	14.4	45	18	77
Height (cm)	172.8	9.2	174	149	196
Weight (kg)	76.42	16.25	75	50	140
Time since onset (years)	5.05	8.12	2	0	54

Abbreviations: SD: standard deviation

Respondents were informed that the data would be used for research purposes via Siopi's data management policy and directly on the survey homepage. Moreover, on filling out the questionnaire, respondents received a notice about the nature of the study, enabling them to apply their data privacy rights and decline use. Siopi, in charge of data processing, exported the anonymized survey responses for analysis from the secure database in comma separated value (CSV) using the Jupyter Notebook module under Anaconda Python 3.7 software to obtain the visualizations reported below in the Results section.

## Results

### French-language version of the ESIT-SQ

The final French-language version of the ESIT-SQ is provided here as [Appendix A](#), "Validated French translation of the ESIT-SQ questionnaire". It is complete and includes all the optional fields of ESIT-SQ, in 2 parts, the first of which can be filled out by anyone, whether suffering from tinnitus or not.

### Exploratory survey

The results of the exploratory survey are presented in three Tables: [Table 1](#) shows demographic characteristics of the sample of respondents, [Table 2](#) general characteristics of the sample, and [Table 3](#) characteristics of the tinnitus and comorbidities. The sample comprised 42 women and 63 men, with a mean age of  $45.03 \pm 14.4$  years, and a mean time since tinnitus onset of  $5.05 \pm 8.12$  years. The general characteristics show an international French-speaking population with varying lifestyle and diet. 102 of the 105 respondents reported experiencing tinnitus, the characteristics of which illustrated the heterogeneous presentation of this symptom. Other oto-neurological symptoms were often associated: 49.52% of respondents reported episodes of vertigo at least once a year, 76.19% at least mild hyperacusis, 73.33% at least mild hearing loss, and only 1 person (0.95%) reported no painful syndrome. [Fig. 1](#) presents causes of change in tinnitus level (aggravation or reduction), showing that many factors can increase or decrease severity in some subjects. Some tended to increase severity rather than reduce it: stress aggravated tinnitus in 65.69% of cases and decreased the level in only 6.68%; likewise, clenching the teeth aggravated tinnitus in 28.43% of cases and decreased the level in only 1.96%. [Fig. 2](#) shows previous treatments attempted by respondents: 51.96% had not sought help from any of the health professionals listed (hearing aid professional, physiotherapist, psychologist, psychiatrist, "other practitioner").

### 1.1. Discussion

The present study produced a validated French translation of the ESIT-SQ. It was made by 3 translators then validated in 9 tinnitus sufferers, following good practice guidelines [14]. It can be used in France for tinnitus research and epidemiological surveys and in current practice. It can probably be used in other French-speaking

**Table 2**  
General characteristics of respondents to the exploratory survey (n = 105). General sample characteristics (N = 105).

Criterion	Number of responders	Percentage	Criterion	Number of responders	Percentage	Criterion	Number of responders	Percentage
Handedness:			Meat consumption			Phone use		
Right	89	84.80%	Never / Vegetarian	4	3.81%	< 1 h per month	15	14.28%
Left	14	13.30%	Occasional	6	5.71%	1 h per month	8	7.61%
Ambidextrous	2	1.90%	1 time per week	12	11.40%	2-3 h per month	19	18.09%
Country:			2-3 times per week	43	40.95%	1h per week	14	13.33%
France	93	88.60%	4-5 times per week	22	20.95%	2-6 h per week	16	15.23%
Belgium	6	5.70%	≥6 times per week	18	17.14%	1h per day	14	13.33%
Canada	3	2.85%	Fish consumption			>1 h per day	19	18.09%
Other	3	2.85%	Never / Vegetarian	5	4.76%	Use of headphones		
Sport:			Occasional	30	28.57%	Never	47	44.76%
<2h / week	59	56.20%	1 time per week	41	39.05%	<1 h per month	16	15.23%
2-4h / week	30	28.60%	2-3 times per week	29	27.62%	1 h per month	4	3.81%
4-7h/week	9	8.50%	Fruit consumption			2-3 h per month	7	6.67%
>7h/week	7	6.70%	Never	1	0.95%	1h per week	5	4.76%
Sleep			Occasional	14	13.33%	2-6 h per week	10	9.51%
<6h	20	19.04%	1-6 times per week	33	31.42%	1h per day	4	3.81%
6h	27	25.71%	1 time a day	28	26.66%	> 1 h per day	12	11.43%
7h	38	36.19%	2-3 times a day	23	21.90%	Night or shift work		
8h	15	14.29%	≥4 times a day	6	5.71%	Never	70	66.67%
≥9h	5	4.76%	Vegetable consumption			Before	33	31.40%
Smoking			Occasional	9	8.57%	Now	2	1.90%
Non-smoker	50	47.62%	1-6 times a week	32	30.47%			
Ex-smoker	38	36.20%	1 time a day	36	34.28%			
Smoker	17	16.20%	2-3 times a day	21	20.00%			
			≥4 times a day	7	6.67%			

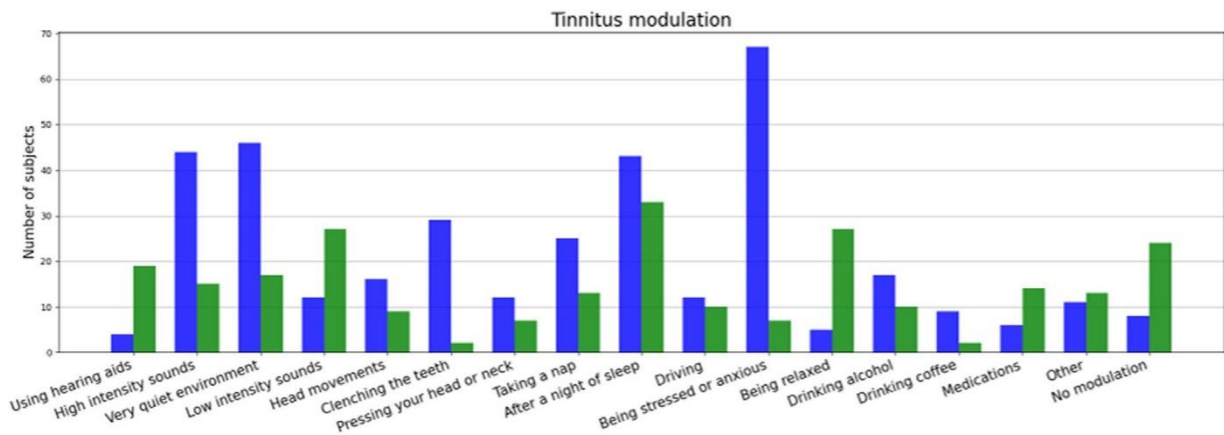
**Table 3**  
Symptom characteristics of respondents to the exploratory survey (n = 105). Symptom characteristics (N = 105).

Criterion	Number of responders	Percentage	Criterion	Number of responders	Percentage	Criterion	Number of responders	Percentage
Tinnitus			Lateralization*			Vertigo		
Never	3	2.86%	Left	17	16.19%	Never	53	50.48%
Not last year	2	1.9%	More left than right	25	23.81%	< 1 per year	20	19.05%
Sometimes	10	9.52%	Both ears / head	25	23.81%	≥1 per year	32	30.48%
Very often	8	7.62%	More right than left	7	6.67%	Hyperacusis		
Always	82	78.1%	Right	1	0.95%	Never	25	23.81%
Bother			Other	27	26.47%	Mild	31	29.52%
None	4	3.81%	Diurnal variation *			Moderate	25	23.81%
Slight	11	10.48%	Stable	16	15.24%	Severe	14	13.33%
Moderate	33	31.43%	Sometimes fluctuating	64	60.95%	Very strong	10	9.52%
Severe	57	54.29%	Always fluctuating	25	23.81%	Hearing loss		
Number of sounds*			Description *			None	28	26.67%
1 only	51	50.00%	Pure tone	44	43.13%	Mild	28	26.67%
Several	51	50.00%	Melodious tone	2	1.96%	Moderate	24	22.86%
Onset *			Noise	11	10.78%	Severe	20	19.05%
Progressive	38	36.19%	Crickets	10	9.80%	Deafness	5	4.76%
Sudden	67	63.81%	Other	35	34.33%	Pain syndrome		
Type*			Pitch*			Migraine	23	21.90%
Subjective	95	90.48%	High	85	80.95%	Neck pain	25	23.88%
Objective	10	9.52%	Medium	16	15.24%	Ear pain	8	7.61%
Rhythm*			Low	4	3.81%	Jaw pain	3	2.85%
No	89	87.25%	Consultations *			Facial pain	3	2.85%
Cardiac	6	5.88%	Never	27	25.71%	Other	42	40.00%
Respiration	1	0.98%	1 consultation	19	18.1%	None	1	0.95%
Head or jaw movement	4	3.92%	2-4 consultations	38	36.19%			
Other	3	2.94%	≥5 consultations	21	20.0%			

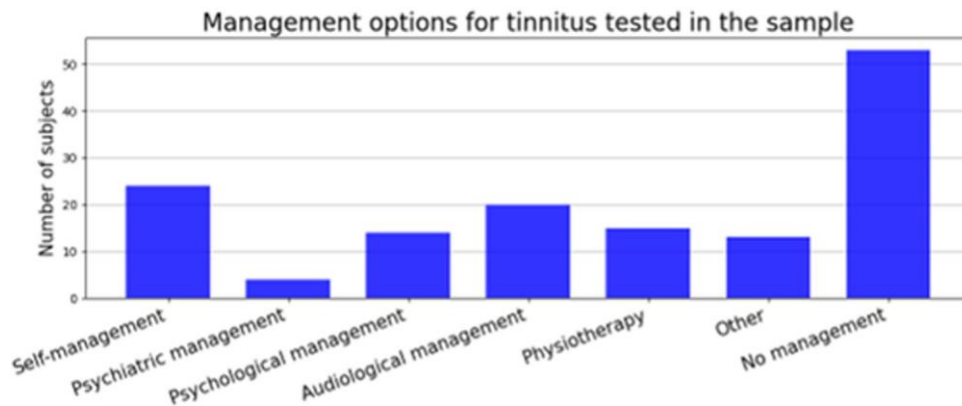
\*: For these questions, 102 responses were taken into account, excluding the subjects that declared not experiencing any tinnitus.

countries after checking compatibility with local linguistic particularities; it is noteworthy that Belgian, Swiss and Canadian subjects were able to respond to Siopi's online survey with no apparent difficulty. The exploratory survey provided some initial information on the epidemiological characteristics investigated by the questionnaire in a French-speaking sample. The results showed wide disparities in symptom profiles, tinnitus presentation and subjective experience. Results concerning factors modulating tinnitus were in agreement with previous reports. Stress modulated tinnitus, with

aggravation during stress episodes and decrease during relaxation, as frequently reported elsewhere; a review can be found in [15]. Somatosensory modulation was also frequently reported, notably in the review by Ralli et al. [16], and may depend on particular pathophysiological mechanisms, on which light has recently been shed [17]. There was great intersubject variation in response to acoustic level: very quiet environment, low intensity sound and high intensity sound; in each case, some subjects reported increased or decreased tinnitus loudness, but with a tendency for aggravation in quiet and high intensity stimulation and for decrease with lower intensity sound. This finding was not surprising,



**Fig. 1.** Tinnitus modulation as reported by responders to the exploratory survey ( $n = 102$ ). For “No modulation”, the blue bar represents those who experienced no increase in any of the proposed situations, and the green bar those who experienced no decrease.



**Fig. 2.** Tinnitus treatments tried out by respondents ( $n = 102$ ).

considering the beneficial effect of acoustic masking reported by some patients [18].

Several remarks can be made concerning the management of the sample subjects. Table 3 shows that, while 54% of respondents suffered greatly from their tinnitus and that 74% had sought at least one medical consultation (5 or more consultations in 20% of cases), many failed to adhere to the prescribed treatment and preferred to manage their tinnitus themselves (Fig. 2). It would thus seem that a large number of respondents either had not received treatment proposals or were not satisfied with them and decided not to continue. Another possible explanation is that the sample include both patients who were and patients who were not seeking help, as described in [19].

We did not undertake a back-translation in to English, which may be considered to be a limitation, although there is no consensus on the benefit this would provide [20]. We adhered to a rigorous translation procedure (see [14]) intended to reduce the risk of error in three ways: firstly, two translators made two independent translations which a third translator combined, thus minimizing the risk that the final translation might be colored by the translator’s personal style. Secondly, the translators’ native language was French, ensuring that the translation would be linguistically and culturally adapted for the target population. And thirdly, the questionnaire was validated in 9 experienced tinnitus patients, to ensure that it was clear and non-ambiguous.

The exploratory survey had certain limitations. Data were collected via a digital platform open to all-comers with no supervision of response entry by a health professional. Responses were self-reported by platform users, who may have had problems with

certain medical terms and in self-assessing medical criteria such as degree of hearing loss. Also, some items referred to past events, memory of which could be defective.

Notably, a large number of respondents chose the response “Other” in the question about the sound of their tinnitus, suggesting that the range of possible responses failed to match the experience of many patients.

Moreover, the sample was too small to represent the exact characteristics of the French tinnitus population as a whole.

Finally, although the questionnaire was validated to some extent in reports of previous translations in other languages [10,11], it would still be useful to complete the validation by test-retest analysis and extensive psychometric tests. We hope that this will soon be done in studies of the international data-sets collected by the Tinnitus Database project.

The Tinnitus Database aims to collate epidemiological data such as those collected using ESIT-SQ at European level. Adding this new French version will broaden the sample to include French speakers. Questionnaire administration via a Siopi-type free and freely available mobile phone application is also an advance in mass collection of epidemiological data in French-speaking countries. And the French translation of ESIT-SQ is a step forward for good quality standardized screening for epidemiological studies and current clinical practice, as advocated by the AFREPA for its teams. An interesting future project would be to develop a digital tool allowing practitioners to collect data from questionnaires such as the ESIT-SQ as part of their day-to-day practice so as to assess their patients’ symptom profiles and also to centralize the data they collect so as to advance our understanding of tinnitus in the hope of soon being able to shed light on the mystery of its heterogeneity.

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## Disclosure of interest

R. G. and A. F. are employed by Siopi; R. G. holds shares in Siopi. The other authors declare that they have no competing interest.

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The French version of ESIT-SQ is in open access.

The exploratory survey data are available on request.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.anorl.2022.12.007](https://doi.org/10.1016/j.anorl.2022.12.007).

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## 3.2 Comparing Clustering Methods Applied to Tinnitus within a Bootstrapped and Diagnostic-Driven Semi-Supervised Framework

Concerning the methods to perform a segmentation of the tinnitus population into homogeneous subphenotypes, several studies have tried to perform algorithmic segmentations (clustering) of tinnitus patients on various databases (Baloi, 2020; Langguth et al., 2017; Niemann et al., 2020; Schecklmann et al., 2012a; Tyler et al., 2008; van den Berge et al., 2017). Most of these attempts were reviewed by (Genitsaridi et al., 2020) who gave methodological recommendations for future clustering studies, as well as a comprehensive list of tinnitus specific and non-tinnitus specific variables to optimize such a clustering attempt. A similar comprehensive list of features to investigate tinnitus heterogeneity was also proposed by (Mohan et al., 2022). Among the methodological recommendations advised by (Genitsaridi et al., 2020) on how future studies should perform such clustering analysis, they recommended to perform data-driven and not hypothesis driven studies, and to evaluate clustering stability. In the study we will present hereafter, we applied these recommendations and we addressed another limitation of past clustering studies which was the absence of supervision of such approaches to mathematically estimate the quality of an obtained clustering. We hence designed a diagnostic-driven semi-supervised framework using the partially labelled endotypes of known tinnitus endotypes such as Menière disease, otosclerosis, neurinoma etc... to guide the clustering algorithm in its work of segmentation. Transposing the clustering framework from non-supervised to semi-supervised enabled us to perform a benchmark of different dimensionality reduction techniques as well as clustering methods to try to find an optimal clustering of tinnitus patients.

Regarding the purpose of this thesis, as sleep-induced tinnitus modulation do not concern all tinnitus patients, TIAN and/or SIT patients appear as two good candidates of specific subphenotypes within the tinnitus population. Yet, one may question to what degree TIAN and/or SIT patients constitute also specific and distinct endotypes within the tinnitus population and/or specific and distinct subtypes within the tinnitus population.



## Article

# Comparing Clustering Methods Applied to Tinnitus within a Bootstrapped and Diagnostic-Driven Semi-Supervised Framework

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**Abstract:** The understanding of tinnitus has always been elusive and is largely prevented by its intrinsic heterogeneity. To address this issue, scientific research has aimed at defining stable and easily identifiable subphenotypes of tinnitus. This would allow better disentangling the multiple underlying pathophysiological mechanisms of tinnitus. In this study, three-dimensionality reduction techniques and two clustering methods were benchmarked on a database of 2772 tinnitus patients in order to obtain a reliable segmentation of subphenotypes. In this database, tinnitus patients' endotypes (i.e., parts of a population with a condition with distinct underlying mechanisms) are reported when diagnosed by an ENT expert in tinnitus management. This partial labeling of the dataset enabled the design of an original semi-supervised framework. The objective was to perform a benchmark of different clustering methods to get as close as possible to the initial ENT expert endotypes. To do so, two metrics were used: a primary one, the quality of the separation of the endotypes already identified in the database, as well as a secondary one, the stability of the obtained clusterings. The relevance of the results was finally reviewed by two ENT experts in tinnitus management. A 20-cluster clustering was selected as the best-performing, the most-clinically relevant, and the most-stable through bootstrapping. This clustering used a T-SNE method as the dimensionality reduction technique and a k-means algorithm as the clustering method. The characteristics of this clustering are presented in this article.

**Keywords:** tinnitus; semi-supervised clustering; subphenotype; bootstrap; benchmark; expert validation



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## Introduction

Tinnitus can be defined as “the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source” [1]. It is a debilitating symptom that affects 14% of the adult population, 2% experiencing a severe form of it [2]. Tinnitus can have disastrous effects on the quality of life of people suffering from it [3]. One of the main characteristics of this symptom is its intrinsic heterogeneity [4], a challenge that is currently being tackled by multiple coordinated efforts especially in the European research community, through the Tinnitus Database initiative [5], the European School on Interdisciplinary Tinnitus Research (ESIT) [6], and recently, the Unification of Treatments and Interventions for Tinnitus Patients (UNITI) project [7].

It has been suggested that tinnitus heterogeneity is partially responsible for the lack of significant treatment outcomes in various clinical trials for tinnitus [5,8–10]. Furthermore, several sources advocate for stopping seeing tinnitus as a symptom that would admit a one-size-fits-all solution [11–13]. Moreover, it has been suggested that tinnitus interventions might prove to be more specifically effective for particular subtypes of tinnitus [14]. A



tinnitus subtype refers here to a part of the tinnitus population with a condition that can be used to guide treatment decisions [15,16].

Likewise, there are convergent opinions on the fact that the observed tinnitus heterogeneity derives from the heterogeneity of underlying mechanisms, potentially cumulative [17–19]. In fact, research to identify the underlying pathophysiological mechanisms has led to the identification of several distinct etiologies accounting only for a part of the tinnitus population [20]. Such endotypes (parts of a population with a condition with distinct underlying mechanisms [15,21,22]) are close to having reached consensus. Those endotypes can be diagnosed through specific medical examinations: otosclerosis [23], vestibular schwannoma [24], pulsatile tinnitus [25]. As a consequence, the quest to obtain a tinnitus endotype segmentation appears as a partially solved puzzle [20]. It is interesting to note that, for some cases, the link between phenotypes and the potential associated pathophysiological mechanism is a matter of intense debate. For example, although it seems that Menière’s disease and hydrops (which can now be objectively diagnosed [26]) are linked, the relation between the two entities is not totally bijective and is still being discussed [27]. Various methods have been attempted to identify a global tinnitus segmentation: defining tinnitus subgroups on the response to a tinnitus treatment [28,29], exploring in a data-driven approach the potential inherent structure of tinnitus symptom profiles (i.e., sub-phenotypes) [30–32], highlighting the existence of a particular subtype in a hypothesis-driven fashion [33]. Such attempts often use algorithmic methods designated as clustering to try to infer such segmentations [15,34]. Tinnitus clustering was performed either on the basis of questionnaire information [30,34], medical imaging [35,36], or audiological explorations [31,37], and more rarely, tinnitus clustering has been performed on the basis of free text contents on social networks through a natural language processing method [38,39].

An important methodological limitation to such studies is the limited supervision or the absence of supervision used by those clustering methods to compare their outputs to one another. This makes it difficult to concretely define what makes a clustering closer to an ideal segmentation. At best, some studies have used clusters’ silhouette as the clustering quality criteria [30,40]. In addition, few of those studies have large sample sizes, this being another limitation [41,42].

More fundamentally, this raises the question of the definition of the ideal segmentation. Such clusterings create subphenotype segmentations that would convey limited practical clinical value in and of themselves unless they aimed to obtain as similar as possible either the optimal subtype segmentation or the optimal endotype segmentation. Here, subphenotype refers to a segmentation based on the distinction between sets of observable characteristics [15,22]. In fact, Genitsaridi legitimately presented in her thesis that nothing proves that the three conceptual segmentations (in subphenotypes, subtypes, and endotypes) are identifiable to one another. To illustrate that, it can be plausible that one treatment can work for two different endotypes or that two different endotypes express the same phenotypes or even that, according to individuals, a unique endotype presents itself with varying phenotypes (as for example the subphenotype of tinnitus with otosclerosis is probably not the same before and after surgical intervention). Table 1, quoted as an excerpt of [43], enables anchoring this important semantic distinction.

In this study, the main objective was to establish a tinnitus subphenotype clustering that would get as close as possible to the ideal tinnitus endotypes’ segmentation. To achieve this goal, the fact that the tinnitus endotype segmentation is already a partially resolved problem, as some etiologies are already known (Menière disease, otosclerosis, etc.), was exploited. This was performed within an original semi-supervised framework to drive the evaluation of clusterings’ quality. Thus, setting the resolution of this problem within this partially labeled framework enabled a quantitative comparison and, thus, a proper benchmark of different algorithmic methods.

**Table 1.** Subgrouping rules’ semantic distinctions; approved excerpt from Genitsaridi, 2021.

Term	Definition
Subgroup	A part of a population (generic term)
Subphenotype	A part of a population with a distinct set of observable characteristics (based on Lötvall et al., 2011)
Subtype	A part of a population with a condition that can be used to guide treatment decisions (based on Saria and Goldenberg, 2015)
Endotype	A part of a population with a condition with distinct underlying mechanisms (based on Anderson, 2008; Lötvall et al., 2011)

## Materials and Methods

### *Population and Data Acquisition*

The investigated database initially comprised 3703 entries of a case history questionnaire recorded by tinnitus patients over the last 20 years of practice by V.L., ENT specialist at the Lille University Hospital, France. Entries were paper-filled then computer-recorded and carefully anonymized before being compiled for analysis in a comma separated value (csv) format file. Patients gave their informed consent that their collective entries could be aggregated, anonymized, and then, used for clinical research purposes.

Features of the database included demographic variables (age, sex, etc.), characteristics of the tinnitus (side, frequency, loudness, etc.), subjective visual analog scales measuring the impact of tinnitus on patients' quality of life (on anxiety, sleep disturbance, etc.), information on patients' lifestyle (sleep duration, practice of sports, etc.), as well as, whenever possible, the diagnosis of V.L. Tables 2 and 3 summarize the main features characteristics over the preprocessed database.

**Table 2.** Sample characteristics: quantitative features of the preprocessed database.

Sample Characteristics for Quantitative Features (N = 2772)					
	Mean	Std	Min	Max	Missing values (%)
Age (in years)	51.3	14.74	18	95	1.41
Tinnitus Handicap Inventory (THI)	50.98	23.83	0	100	4.4
Tinnitus duration (in months)	67.79	93.12	0	852	9.92
What percentage of time is tinnitus present (in %)?	66.34	28.19	0	100	16.31
VAS scale Tinnitus annoyance (0 to 10)	6.89	2.17	0	10	4.98
VAS scale Anxiety (0 to 10)	4.89	3.25	0	10	5.81
VAS scale Sleep quality (0 to 10)	5.25	3.35	0	10	6.28
VAS scale Hyperacusis (0 to 10)	5.05	3.41	0	10	5.77
VAS scale Vertigo (0 to 10)	2.36	2.94	0	10	5.77
VAS scale Headache (0 to 10)	2.16	3.23	0	10	0,29
VAS scale Jaw pain (0 to 10)	1.9	2.79	0	10	6.78
VAS scale Cervical pain (0 to 10)	2.63	3.39	0	10	0.4
Khalfa questionnaire score (hyperacusis)	19.72	9.73	0	42	11
HAD questionnaire on anxiety	9.18	4.24	0	21	12.59
HAD questionnaire on depression	6.47	4.6	0	21	12.73
Insomnia Sleep Index (ISI) score	12.39	6.62	0	28	8.44
Epworth scale score	7.62	4.7	0	24	7.65
Sleep onset latency (in min)	35.72	27.23	0	121	11.62

Abbreviations : HAD : Hospital Anxiety and Depression scale, VAS : Visual Analog Scale



**Table 3.** Sample characteristics: categorical features of the preprocessed database.

<b>Sample Characteristics for Categorical Features (N =2772)</b>				
<b>Occurrences count</b>	<b>Yes / Choice 1</b>	<b>Sometimes / Choice 2</b>	<b>No / Choice 3</b>	<b>Missing values (%)</b>
Gender (Choice 1 : Female ; Choice 2 : Male )	1491	1226		1.95
Tinnitus apparition ( Choice 1 : brutal, Choice 2 : progressive)	1665	1099		0.3
Tinnitus side (Choice 1 : left, Choice 2 : bilateral, Choice 3 : right)	1015	910	760	3.14
Tinnitus lateralisation (1 : bilateral, 2 : partially lateral, 3 : lateral)	910	743	1032	3.14
Tinnitus intensity (1 : Low, 2 : Medium, 3 : Elevated)	1282	990	500	0.3
Was tinnitus caused by an acoustic trauma ? (Yes, No)	460		2304	0.3
Is the tinnitus pulsatile ? (Yes, No)	231		2533	0.3
Is the tinnitus a narrow band noise ? (Yes, No)	283		2481	0.3
Do you have somato-sensory modulations ? (Yes, No)	446		2318	0.3
Do you have jaw somato-sensory modulations ? (Yes, No)	317		2447	0.3
Do you have neck somato-sensory modulations ? (Yes, No)	256		2508	0.3
Do you have often headaches (Yes, No)	826		1938	0.3
Do you have often cervical pain/rigidity? (Yes, No)	1198		1566	0.3
Do you have trouble falling asleep ? (Yes, Sometimes, No)	972	505	1134	5.81
Do you have nocturnal awakenings ? (Yes, Sometimes, No)	425	530	1644	6.24
Are you feeling tired when awake ? (Yes, Sometimes, No)	653	574	1360	6.67
Do you often snore ? (Yes, No)	1152		1438	6.57
Do you have sleep apnea syndrome ? (Yes, Probably, No)	217	238	2102	7.76
Normal hearing ? (Yes, No)	337		2427	0.3
Sensorineural hearing loss (Yes, No)	1563		656	19.95
Transmissionnal hearing loss (Yes, No)	197		2022	19.95
Notch Hearing Loss (Yes, No)	251		1968	19.95
High Frequencies hearing loss (Yes, No)	146		2073	19.95
Cophosis (Yes, No)	38		2181	19.95

This database offers the advantage of gathering a variety of tinnitus-related descriptors, as well as, when possible, the medical diagnosis given by an expert medical doctor. The latter offers the opportunity to test diagnostic-driven semi-supervised approaches of clustering.

Only a minority subset of the dataset was labeled with a diagnosis by the expert doctor. Some endotypes were less represented than others, reflecting their unequal prevalence in clinical practice. The different endotypes considered in this study and their prevalence in the dataset are presented in Table 4.

**Table 4.** Endotypes' prevalence in the database.

<b>Endotypes Prevalence in the Dataset (N=2772)</b>		
<b>Endotype</b>	<b>Occurrences</b>	<b>Percentage of the sample</b>
Pulsatile tinnitus	231	8.33%
Otosclerosis	38	1.37%
Menière's disease	35	1.26%
Neurinoma	24	0.87%
Petrous bone fracture	14	0.51%
Eustachian tube dysfunction	7	0.25%
<b>Total</b>	<b>349</b>	<b>12.59%</b>

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## *Preprocessing*

Several preprocessing steps were needed to make the raw data exploitable. Such steps are described hereafter. Preprocessing steps were conducted with the objective to limit the introduction of additional bias in the dataset.

### *Missing Value Imputation*

Case history questionnaire collection was paper-based before being computer-recorded. Such a procedure induced, at both steps, missing values in the raw dataset. Missing values' imputation is a classic problem in data analysis and machine learning [44,45]. Mainly, two methods have been proposed to remediate this issue: removing or replacing the missing values. The main objective of missing value management is to limit as much as possible the introduction of additional bias in the dataset while keeping a maximum of patients and features available for analysis. To meet these two objectives, the following method was implemented:

- First, each patient that had more than 40 percent of missing values in the initial 107 features was deleted to ensure overall data consistency. Through this procedure, out of the 3703 initial patients, 2772 were retained (74.9% of the initial 3703 patients sample).
- Then, for each feature, if the number of patients for which the feature was missing was higher than 25 percent, the feature was excluded from the analysis. Through this procedure, out of the 107 features considered, 44 were retained (41% features retained).
- Filling the remaining missing values using the MissForest algorithm, specially designed to fill missing values with an iterative imputation method based on a random forest [46].

At the end of this process, the final dataset no longer contained any missing values and consisted of 2772 patients and 44 features.

### Bootstrap Procedure

With the aim to perform an objective comparison of performances between combinations of dimensionality reduction methods and clustering algorithms, stability assessment of the clusterings was performed. This stability assessment was realized through a bootstrap procedure. The dataset was split into a training set and a test set three times, with a resampling with replacement procedure. Such partitionings all contain the entirety of the dataset, split randomly in different ways according to the procedure described hereafter.

In classical cross-validation practice, the design of such partitionings results in a higher percentage of data attributed to the training set and a lower proportion to the test set. In the case of the present study, the t-distributed stochastic neighbor embedding (t-SNE) method was included in the benchmark. This method relies on the high-dimensional topological structure and local density of the data. Due to this fact, having significantly different numbers of samples in the training sets and test sets would result in an increased probability of divergence in the high-dimensional spatial distribution of samples and, as a consequence, an increased divergence in the projection spaces. It was, hence, necessary for this method to have a 50-50 split of the dataset. Hence, we could not perform a classic cross-validation procedure to be able to compare all combinations of methods tested in the benchmark in the same conditions. This is why it was decided instead to bootstrap three 50-50 partitionings between the training and test sets for all combinations of methods.

As the evaluation of clustering performances is based on the diagnoses of an ENT tinnitus expert, it was important that each endotype was equally represented in each partitioning of the data between the training and test subdatasets. Hence, a random assignment procedure was applied to each endotype and the unlabeled data group to equally divide them between the three bootstrapped training and test subdatasets. Following the presented results are the average of the performances between the three partitionings of the dataset.

### *Dimensionality Reduction Methods*

Even after excluding features with missing values, the remaining number of variables is important and justifies the use of dimensionality reduction methods to achieve the best performances of the clustering algorithms.

There are methods that try to reduce the number of features ahead of the clustering method while trying to preserve as much information as possible from the initial dataset. In this study, three different dimensionality reduction methods were used and compared: PCA [47], factor analysis of mixed data (FAMD) [48], and finally, t-distributed stochastic neighbor embedding (t-SNE) [49].

The number of dimensions was tested repeatedly for a defined range of values and treated as a hyperparameter, thus validating a posteriori the quality of the dimensionality reduction method.

Each of the three methods is hereafter described in further detail.

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### Principal Components Analysis

PCA is a classical dimensionality reduction technique that is typically used to summarize large datasets with a small number of descriptors while retaining the maximum amount of information. PCA does not aim at selecting the best characteristics while dropping others; instead, it constructs some new characteristics named principal components, based on the original features of the dataset. More formally, PCA is a linear dimensionality reduction technique that creates a set of pairwise orthogonal axes that maximize the variance in the data. Thus, this method helps remove redundancy in the new reduced feature space.

### Factor Analysis of Mixed Data

PCA was designed for quantitative and non-categorical data analysis. However, our dataset is composed of a mix of categorical and non-categorical variables. FAMD was chosen for our benchmark of dimensionality techniques as it is similar to PCA, but takes into account the mixed aspect of the data. The implementation used is reachable in the Python library Prince (<https://github.com/MaxHalford/prince>, accessed on 23 November 2022).

### t-Distributed Stochastic Neighbor Embedding

The last two methods allow an analysis of the global structure of the data, but do not provide an insight into the local topological structure of the data points. Given the objective to create an accurate clustering of endotypes for tinnitus, the local grouping of data points may be of particular importance. Thus, a third dimensionality reduction technique was considered.

The dimensionality reduction algorithm called t-distributed stochastic neighbor embedding (t-SNE) is an unsupervised learning algorithm. Developed by Laurens vander Maaten and Geoffrey Hinton [50], it enables the analysis of data described in high-dimensional spaces (via a large number of descriptors) to be mapped into a reduced dimensional space. This algorithm is widely used because it facilitates the visualization of data with many descriptors. Through this method, data points that are close in the original high-dimensional space have a higher probability of remaining close to one another in the two- or three-dimensional space of projection. Conversely, data points that are distant in the original space have a low probability of having close representations in the space of projection.

There is a hyperparameter that has a strong impact on the output of the t-SNE algorithm: the perplexity. It characterizes the balance of importance between the local neighborhood structure versus the global neighborhood structure of the data. A large perplexity will lead the algorithm to put the emphasis on the global neighborhood structure of the data. Oppositely, a small perplexity will bring out the local structures of the original data. In this study, the t-SNE method was tested for a wide range of perplexity values (from 5 to 200).

### *Clustering the Dataset*

In this study, a clustering step was applied after the dimensionality reduction. Thus, the best clustering will be selected, and the adequate parameters to reduce the dimensionality will be inferred from it.

Two different clustering algorithms were compared: the k-means clustering algorithm and density-based spatial clustering of applications with noise (DBSCAN) clustering algorithm [51].

### k-Means Clustering

k-means is a clustering algorithm that aims at partitioning a dataset of observations into k clusters: each data point is attributed to the cluster with the nearest mean. It is a classic method of clustering that has already been tried in several former studies for tinnitus subphenotyping [34,52]. The three main assets of this method are its easiness of interpretation, simplicity of implementation, and speed of convergence. Due to the nature of this study, the number of clusters was not predefined. Yet, it is necessary to specify to the algorithm the number k of clusters to find for it to be able to run; a range from 2 to 20 was hence implemented for the grid search (as shown in Table 5). The distance measure on numeric attributes was the square Euclidean distance.

**Table 5.** Range of hyperparameters.

Hyperparameters and Associated Grid Search Ranges			
Hyperparameter	Associated algorithm (s)	Range of exploration	Steps of exploration
Number of components	PCA, FAMD	[ 2, 20 ]	1
Number of components	t-SNE	[2, 6]	1
Perplexity	t-SNE	[5, 200]	5 by 5 to 40 then to 25 by 25 from 50 to 200
Number of clusters	K-means, DBSCAN *	[ 2, 20 ]	1
Epsilon	DBSCAN	[ 0 , 10 ]	0,1
Minsample	DBSCAN	[ 2, 15 ]	1

\* For DBSCAN, the number of cluster cannot be directly assigned, hence only the solutions in the range from 2 to 20 clusters were selected.

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### Density-Based Spatial Clustering of Applications with Noise

DBSCAN is a non-parametric clustering algorithm that takes a given set of points in an initial space, then groups together points that are densely packed together (points with many nearby neighbors), and marks as outliers points that are isolated in low-density regions (whose nearest neighbors are too far away).

It was selected for its different characteristics from k-means: it is a density method and is able to find arbitrarily shaped clusters, while k-means produces Voronoi-cell-shaped clusters. DBSCAN has been used once to try to perform tinnitus subphenotyping [53].

DBSCAN exploration is driven by two hyperparameters: The first is *minsamples*, the minimal number of samples (or total weight) in a neighborhood for a point to be considered as a core point. This includes the point itself. Second is *eps* (standing for epsilon): the maximum distance between two samples for one to be considered as being in the neighborhood of the other. The ranges of exploration of these hyperparameters for the grid search are shown in Table 5.

### *Quantified Evaluation of the Quality of the Clusterings*

The following procedure was applied for the benchmark. For each type of clustering and dimensionality reduction technique tested, the best hyperparameters for clustering were identified through grid search exploration, presented in Table 5. Six combinations of dimensionality reduction techniques and clustering methods were, hence, tested and compared according to the different mathematical methods presented hereafter.

Then, a shortlist of the best clusterings was obtained according to these mathematical criteria and was then presented and analyzed by two tinnitus ENT experts to check their clinical relevance. Out of this comparison, a single clustering was selected and is presented hereafter.

To check the quality of the clusterings, three separate quantified evaluation criteria were used.

### Silhouette Score

The “silhouette measure of cohesion and separation” is a measure for the overall goodness-of-fit of the cluster structure, which is described in [54,55]. More precisely, the silhouette value is a measure of how similar an object is to its own cluster (cohesion) compared to other clusters (separation). The silhouette ranges from -1 to +1, with a high value indicating that the object is well matched to its own cluster and poorly matched to neighboring clusters. If most objects have a high value, then the clustering configuration is considered appropriate. If many points have a low or negative value, then the clustering configuration may have too many or too few clusters. Due to its construction, this score will advantage the clustering algorithm that will tend to form spherical-like clusters, such as k-means, over less regularly shaped clustering methods, such as DBSCAN. Moreover, its interpretation is less obvious in the framework of the dimensionality reduction t-SNE algorithm used in this study. Hence, this score will only be shown because it is a classical way to evaluate clustering and was used in a former study on tinnitus clustering [30], but will not be eventually determinant for the choice of the final clustering.

### Stability Assessment

For each combination of the dimensionality reduction techniques and clustering algorithms, it is necessary to ensure the stability of the clusterings obtained. To achieve that, a bootstrap procedure was designed.

It is common for artificial structures to emerge that do not correspond to the real separation of the data. In the case of the present study, an output would be deemed stable through bootstrapping if the structure of the clusterings obtained through the application of the same method with the same parameters on the training and test sets of the data are similar. The similarity between two clusterings, which can be identified for two data partitions, can be reliably measured by the adjusted mutual information (AMI) [56]. This measure was, hence, selected for this study.

To measure the agreement of two data partitions (i.e., clusterings)  $U$  and  $V$ , the AMI takes a value of 1 when the two partitions are identical and 0 when the AMI between two partitions equals the value expected due to chance alone. Its calculation is implemented by the following formula:

$$AMI(U, V) = \frac{MI(U, V) - E\{MI(U, V)\}}{\max\{H(U), H(V)\} - E\{MI(U, V)\}} \quad (1)$$

The bootstrap procedure was the following: Given a partitioning  $i$  of the data (between 1 and 3), the clustering method is fit on the (already projected in reduced dimension) training and the test sets. The prediction method of the two obtained models is then applied to the training and the test set. The output of this procedure is four clusterings: two clusterings on the training set (the one fit on the training set and the one fit on the test set) and two clusterings on the test set (the one fit on the training set and the one fit on the test set).

The AMI was applied between the two pairs of clusterings stemming from the same data (i.e., respectively between the two clusterings of the training set and between the two clusterings of the test set). The average of two scores' AMI was then taken as the final score.

This method was applied for the k-means clustering, yet it was not possible to apply it for the DBSCAN method, as it is a transductive method; hence, in this procedure, the fitting method cannot be disentangled from the prediction method. In this case, a proxy of cross-validation was performed by calculating the difference of the number of clusters between the training and test clusterings' outputs of the DBSCAN applied with the same hyperparameters.

Here, an eligibility threshold of at least 0.7 for the averaged AMI score and a difference of 0 between the number of clusters emerging from the training and test sets were applied to filter out the best solutions of the benchmark.

### Clustering Similarity to the Endotype Labeling Clustering Enabled by the Partial Medical Diagnosis of the Patients

As a key goal of this study was to take advantage of the fact that the endotype segmentation is a partially resolved problem, the quality of the obtained clusterings was evaluated through this partial knowledge. The dataset considered contains, whenever possible, a diagnosis of the endotype of the patient provided by an ENT specialist (V.L.).

The optimal clustering of the whole dataset would be a clustering that would be at least able to separate each of the known endotypes and assign it to a separate cluster. In order to be able to quantify how close a clustering is to an optimal clustering of reference, a metric is needed. Such an evaluation criterion is given by the V-measure, an entropy-based cluster evaluation measure, presented by Rosenberg and Hirschberg [57].

The V-measure between a clustering considered as the reference and a clustering obtained as the output of an experimental algorithmic procedure is defined as the weighted harmonic mean of two other metrics called homogeneity ( $h$ ) and completeness ( $c$ ) and is given by the following formula:

$$V \text{ measure} = \frac{2}{\beta + 1} \frac{h * c}{\beta * h + c} \quad (2)$$

where  $\beta$  is a hyperparameter  $\in [0, \infty]$ , quantifying the relative importance of homogeneity and completeness. The V-measure score is bounded between 0 and 1, where a score of 1 corresponds to a perfectly complete and homogeneous matching between clusterings. If  $\beta = 1$ , the emphasis is on homogeneity. Otherwise, completeness is highlighted. One can note the analogy between this metric and the F-score used in classification and being composed of the precision and recall. A clustering result is homogeneous when all of the clusters it formed contain only data points that are members of a single class. A clustering result satisfies completeness if all the data points that are members of a given class are elements of the same cluster.

In this study, we wanted to isolate to the best of our ability the known endotype clusters. After careful examination of the results produced by various  $\beta$  values,  $\beta = 0.1$  was chosen as the better proxy.

The whole process is summarized in Figure 1. The range of exploration for hyperparameters used for the grid search is presented in Table 5.

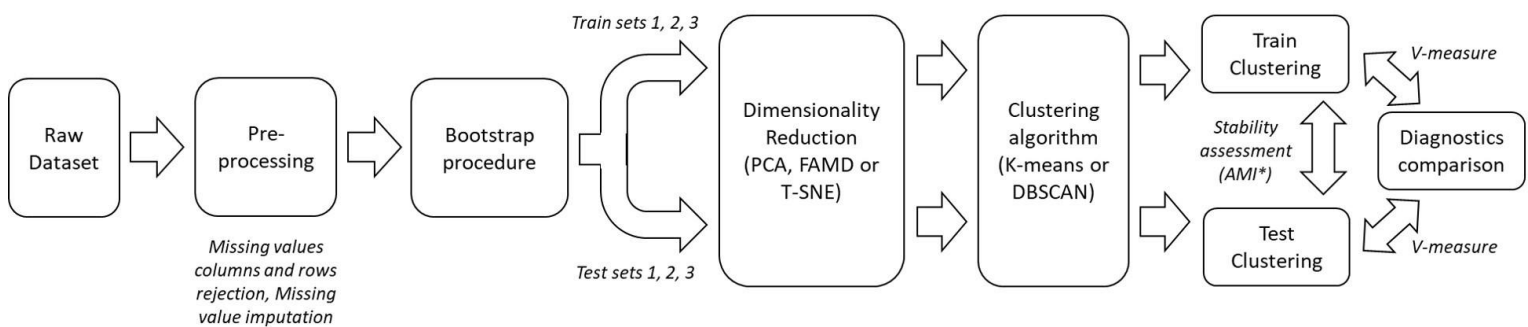


Figure 1. Overview of the processing pipeline

### Qualitative Evaluation of the Obtained Clusterings

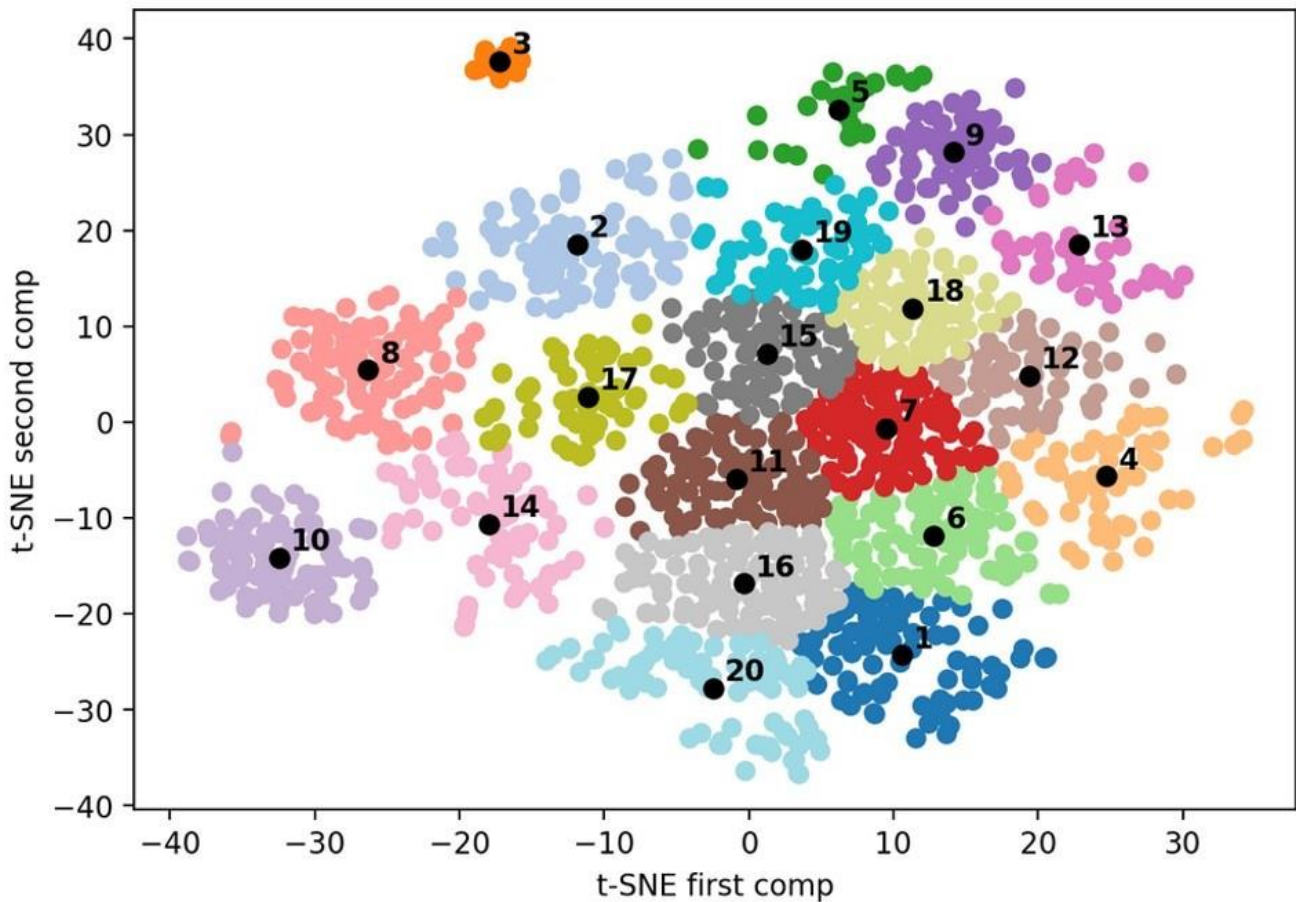
The grid search exploration of all hyperparameters for all combinations of the method of the benchmark and their ranking using the evaluation criteria led to a subset of best-performing clusterings. To be able to present the overall best-achieved clustering obtained by this study, a last step of qualitative evaluation was achieved by ENT tinnitus experts A.L. and V.L.



The subset of the three overall best-performing clusterings obtained at the end of the quantitative evaluation procedure was selected and presented for the quantitative evaluation of the appointed experts.

Each clustering was presented with the following information: the combination of hyperparameters and methods leading to this clustering, an illustration of the clustering in the reduced dimensionality projection of the dataset when possible (as in Figure 2 of the article), a table presenting the specific characteristics of each cluster.

The procedure of the qualitative evaluation of the clusterings was performed by each expert independently. The evaluation consisted of assigning a score between 0 and 5 for each cluster of each clustering. A score of 0 means that the cluster appears incoherent and does not relate to anything encountered in their clinical practice, and a score of 5 means that the cluster fits perfectly a well-known and potentially documented specific subphenotype of patients often encountered in clinical practice. Then, a general appreciation of each clustering was freely given to each clustering.



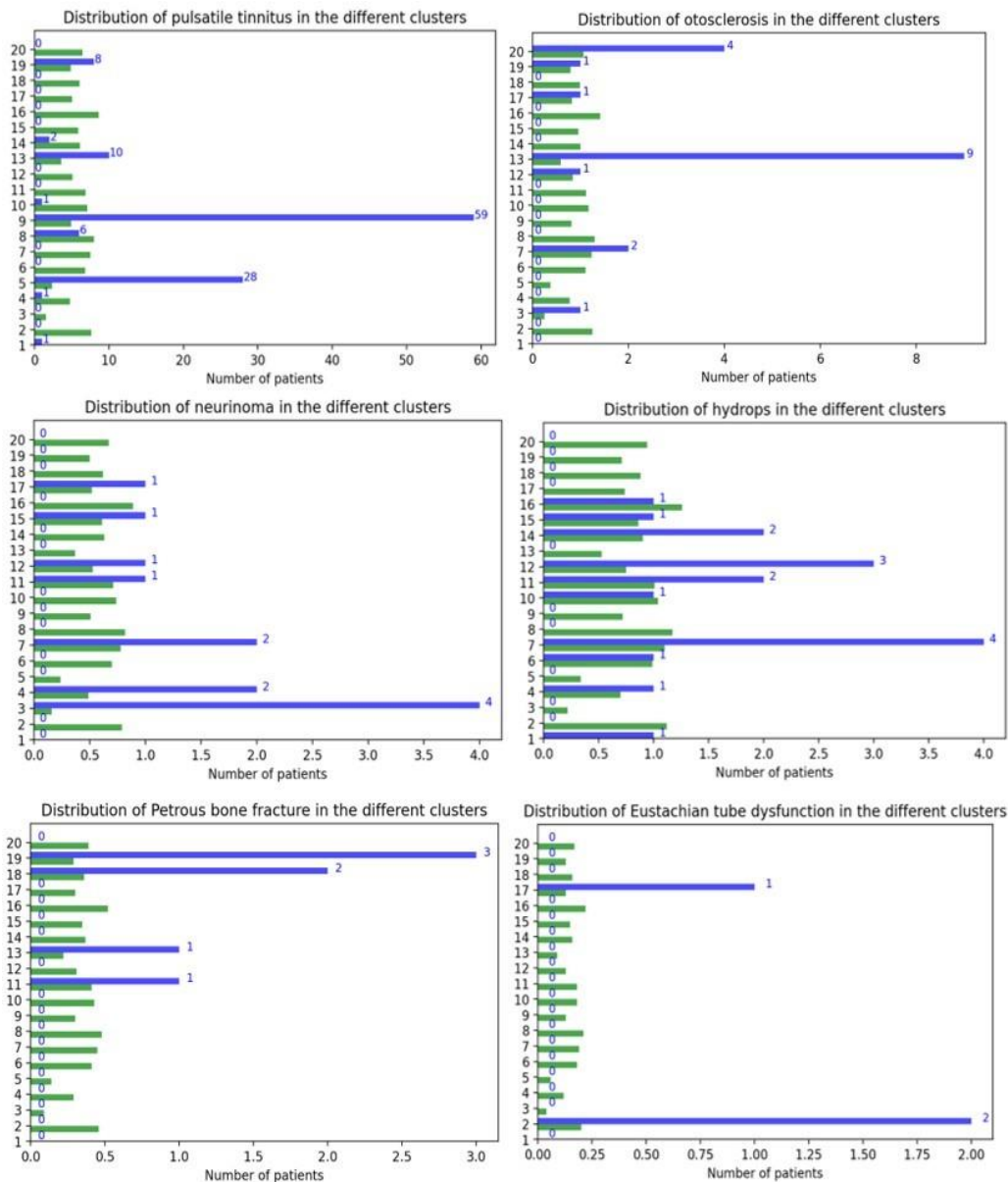
**Figure 2.** Selected clustering representation of the two-dimensional t-SNE projection. The black points represent each of the clusters' centers (i.e., their centroids). The numbers are the labels of each cluster. Table 6 refers to these cluster numbers to characterize each of the clusters.

The final score for each clustering was obtained by averaging the scores for all clusters and for the two experts. The final best clustering obtained by this procedure is presented in the Results Section, by Figures 2 and 3 and Table 7.

**Table 6.** Performance benchmark.

Algorithms Best Performances Comparison				
Dimensionality reduction method	Clustering algorithm	V-Measure (Beta = 0.1)	Stability assessment (AMI *)	Silhouette score
Principal Component Analysis	K-means	0.142	0.716	0.321
Principal Component Analysis	DBSCAN	0.035	0 clusters difference	-0.17
Factor Analysis of Mixed Data	K-means	0.146	0.707	0.324
Factor Analysis of Mixed Data	DBSCAN	0.049	0 clusters difference	-0.15
t-distributed stochastic neighbor embedding	K-means	0.381	0.728	0.351
t-distributed stochastic neighbor embedding	DBSCAN	0.346	0 clusters difference	0.008

\* AMI: adjusted mutual information, calculated between k-means clustering, not possible for DBSCAN cluster-ings comparison.



**Figure 3.** Endotypes' repartition. The blue bars represent the number of samples of a specific endotype present in the cluster of the number it faces. The green bars represent the number of samples of the same specific endotype that this cluster would contain if the patients of this endotype were randomly assigned to the clusters. For example, on the top left, Cluster 9 contains 59 patients presenting a pulsatile tinnitus, although if the assignment of pulsatile tinnitus patients per cluster was random, we should have expected to have between five and six pulsatile patients in this cluster.

## Results

### Results Overview

Table 6 presents the results of the best-achieved performances for each combination of methods of the benchmark explored in this study, for the evaluation metrics presented in the methods.

The best performances on all three evaluation criteria were achieved simultaneously by the combination of the t-SNE dimensionality reduction technique and the k-means clustering algorithm. These performances were evaluated on the averaged performances on the three partitionings of the dataset obtained by the stratified random subsampling procedure. A set of three best-performing clusterings was constituted at the end of this procedure and was then presented for the quantitative evaluation of the two ENT tinnitus experts.

The three best clusterings were obtained from the combination of the t-SNE dimensionality reduction technique and the k-means clustering algorithm. The sets of hyperparameters of these three clusterings were: Clustering 1: perplexity = 40, number of components for t-SNE: 2, number of clusters of the k-means: 20; Clustering 2: perplexity = 75, number of

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components for t-SNE: 2, number of clusters of the k-means: 20; Clustering 3: perplexity = 5, number of components for t-SNE: 2, number of clusters of the k-means: 18. The three clusterings presented to the ENT tinnitus experts were the ones of the partitionings having the best V-measure score for the given set of hyperparameters.

The overall averaged qualitative scores between the ENT Tinnitus experts' evaluations gave the following scores:

Clustering 1: 4.18/5, Clustering 2: 4.53/5, Clustering 3: 4.22/5. The best-performing clustering at the end of this procedure was Clustering 2 with hyper-parameters" perplexity = 75, number of components for t-SNE: 2, number of clusters of the k-means: 20. Both ENT tinnitus experts ranked this clustering as the most-clinically relevant.

As this clustering is projected in a two-dimensional space by the t-SNE method, it was possible to present it in Figure 2. The details of the characteristics of each cluster of this clustering are presented in Table 7 (at the end). The endotypes' repartition associated with this clustering is presented in Figure 3.

## Discussion

In this study, the main objective was to establish a tinnitus subphenotype clustering (i.e., a clustering of parts of a population with a distinct set of observable characteristics [22,43] that would get as close as possible to the ideal tinnitus endotype segmentation (i.e., a segmentation between parts of a population with a condition with distinct underlying mechanisms [21,43]). To achieve this goal, a bootstrapped semi-supervised and diagnostic-driven benchmark of combinations of algorithmic methods was performed to obtain the best-possible clusterings of a given dataset of tinnitus patients. The final choice presented in the results was selected qualitatively by ENT tinnitus experts among almost equally performing clusterings on the basis of its most-accurate clinical relevance. The best clusterings were performed by a combination of t-SNE dimensionality reduction and k-means clustering and successfully separated the known endotypes of tinnitus within different clusters. The important number of clusters (18 to 20) of the final subset of best-performing clusterings highlights the clinically observed and reported highly heterogeneous nature of tinnitus [4]. The obtained subphenotypes yielded interesting bases for further explorations of the underlying pathophysiological mechanisms of tinnitus on specific tinnitus homogeneous subpopulations of patients. This could facilitate the discovery of new endotypes of tinnitus.

### *Final Clustering Description*

As the finally selected clustering was projected in a two-dimensional space by the t-SNE dimensionality reduction step, it can easily be displayed and analyzed. It is important to specify that the presented clustering was applied on the training set of the third partitioning of the data. This is the reason why only half of the whole sample of patients is included in it.

The general spatial organization of this clustering, as well as the two others that were evaluated is composed of a big core (here, the grouping of Clusters 1, 4, 6, 7, 11, 12, 15, 16, 18, 19, and 20) and gravitating satellites (Satellite Clusters 2, 3, 5, 8, 9, 10, 13, 14, and 17).

Only the finally selected clustering is presented in this study, yet it is important to note that some regularities were observed in all three clusterings presented for the evaluation by the ENT Tinnitus experts:

- The cophosis cluster (Cluster 3) was always dense and isolated in all clusterings. These patients have most probably a unilateral cophosis, and it makes sense that it contained neurinoma patients (probably post neuro-radiological procedure).
- The high frequencies of hearing loss and tinnitus cluster (Cluster 10), the pulsatile group composed of Clusters 5 and 9, and the somatic group composed of Clusters 8 and 14 were always satellites of the clusterings. The pulsatile and somatosensory groups were sometimes partitioned in two as in this clustering and sometimes unified within only one cluster.
- The main core group of patients had always a gradient structure where, at one extremity, the impact of tinnitus and associated symptoms is very important at one end (as in Clusters 12, 15, 18, and 19) and the impact is either mild or absent at the other end (patients not impaired as in Clusters 1, 16, and 20). These "poles" have an influence on the general spatial organization: the otosclerosis Satellite Cluster 13 where the patients are symptomatic and annoyed was close to Clusters 12 and 18, and similarly, non-disturbed somatic tinnitus patients Cluster 14 was close to Clusters 16 and 20. It is worth mentioning that the gradient of impact on the quality of life of tinnitus was almost aligned and coincident with the gradient of associated quality of sleep measured by ISI, VAS sleep quality, sleep latency, nocturnal awakenings, etc. In fact, sleep was disturbed in Clusters 7, 12, 15, 18, and 19 in opposition to Clusters 1, 14, 16, and 20 (except that, in Cluster 20, patients have OSA, but do not seem to be disturbed by it).
- This clustering seemed to highlight and isolate clusters centered on sudden hearing loss (Cluster 11) and head trauma (Cluster 19) and to show an association between hyperacusis and headaches (Clusters 15 and 17). It was also interesting to observe that one of the pulsatile tinnitus clusters had the feature "side right" presenting an important effect size. In fact, it is reported in the literature that, very often, the tinnitus is localized on the right side, due to the important prevalence of venous origin pulsatile tinnitus in the population [58]. Likewise, it is no surprise that, for both



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pulsatile tinnitus groups, effect sizes highlighted a over-prevalence of women in these groups, as well as lateralized tinnitus.

### *Merits*

#### Changing Framework from Non-Supervised to Semi-Supervised Enabling Benchmark on Performance

This study was the first in the field of tinnitus to leverage the partial existing knowl-edge of tinnitus heterogeneity to drive the clustering procedure. Although this procedure can probably be largely improved in the future (see the Limits Section and the Suggestions for Future Research Section), it opens the path to a new framework of analysis on the issue of tackling tinnitus heterogeneity.

The main perspective that this new framework brings for future research is a (partial) ground base for evaluating the performance of tinnitus patient segmentation (and in the case of the present study, tinnitus clustering). This basis enables quantitatively evaluating and, thus, comparing the performances between different competing algorithmic methods or a combination of methods to solve the task at hand. For the first time, a benchmark of performances between several combinations of methods was made possible to evaluate which combination best reproduces the partially known diagnostic segmentation. It should be noted that the best-performing clustering obtained in the present study achieved a

0.386 score on the main criterion, the V-measure score. Such a score is comparable to the best performances achieved for spondyloarthritis clustering by a recent study with a similar database size of 3438 patients. The best clustering of this study obtained a V-measure score of 0.588 [59].

#### Stability Assessment

This study is also the first to have performed an equivalent to a cross-validation procedure (here, a bootstrap procedure) aiming at ensuring the quantified stability of its clusterings, following the suggestion of [15]. Here, three partitionings of the dataset into training and test subdatasets were conducted following a resampling with replacement procedure. The evaluation of stability involved the use of the adjusted mutual information score between clusterings, as described in the stability assessment section.

Applying such a procedure is a well-known safeguard against over-fitting of the model and ensures its replicability to some extent.

It is also important to mention that, in the present study, adjusted mutual information scores between the best-performing clusterings were surprisingly quite elevated ( $>0.7$ ), suggesting a quite stable structure of the dataset.

#### Performing Clustering on a Large and Rich Patient Questionnaire Sample

Such semi-supervised paradigm adoption would hardly have been possible without the importance of the unified dataset analyzed in this study. It is also important to stress that the 44 features reported per sample in this database covered a wide spectrum of tinnitus patient characteristics from hearing, hyperacusis, to somato-sensory modulations and to associated sleep disturbance and depression. Such a specter covers the majority of items suggested to be addressed by the review on tinnitus clustering published by [15].

#### Reproducing in the Benchmark Already Tested Dimensionality Reduction Methods and Clustering Methods and Proposing Original Combinations

In the present study, the methods (PCA, k-means, and DBSCAN) used by [52,53] were included in the benchmark and applied on the same dataset. Likewise, the silhouette score evaluation method presented in [30] was reproduced and presented, although it was not the main criterion for discriminating the performances of the clusterings.

New original methods have also been proposed and included in the benchmark of this study: One was the factor analysis for mixed data framework that appeared as a promising improvement to the classic PCA approach. It actually performed slightly better than PCA when combined with either k-means or DBSCAN. Likewise, t-SNE appeared as a relevant dimensionality reduction technique to be applied on such mixed data and performed best in combination with the k-means clustering method.

### *Limits*

#### Missing Values

A first limit of this study was the non-negligible presence of missing data in the initial dataset, which required excluding some features, as well as a non-negligible amount of patients (929 rows) and the use of missing value imputation. Although an adaptive and stable method was used for missing value imputation (MissForest [46]), even more accurate results could have been obtained with a complete and larger dataset.

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### Limited Number of Diagnostics

The main aim of the study was to create a clustering that would find and separate the known endotypes of tinnitus. Yet, due to the retrospective nature of this work performed on an already acquired dataset, several limitations are to be considered on this matter in the present study. First, although this labeling was performed by a skilled ENT specialist and on the basis of objective diagnostic measurement, it cannot be excluded that some diagnoses were wrongly attributed to some patients. Even more, some patients were probably not diagnosed, although they were part of a known endotype. The diagnosis partitioning that served as a reference in this study is hence limited in its validity.

Secondly, the prevalence of some endotypes is naturally rare in the tinnitus population. This dataset was obtained over several years of clinical practice taking care of any patient that sought the help of this practitioner. Consequently, there has been no specific selection procedure applied that would have led to a more advantageous representation of known endotypes in the dataset. As a consequence, the total percentage of labeled data in the dataset was quite low (12.59%), and the prevalence of some endotypes was extremely low (seven patients for Eustachian tube dysfunction).

Lastly, a question that remains open is the boundary between what can be considered as a “known endotype” and a “comorbidity”. It could be argued that “ototoxicity”, a good potential candidate, should not be included in such work as several different drugs could lead to such an attribution of the label without affecting similarly the auditory system. Yet, the question is posed when it comes to more prevalent subgroups such as presbycusis, acoustic trauma, somato-sensory tinnitus, or sudden hearing loss to a lesser extent: Should such conditions be considered as endotypes of tinnitus? More refined criteria to delimit between what should be considered eligible labels or comorbidity should be proposed in the future.

On the other hand, some etiologies chosen in the present study could be considered as heterogeneous. For example, pulsatile tinnitus patients all received the same diagnostic label, although it could be argued that one should have separated patients affected by semicircular canal dehiscence, carotid aneurysm, neurovascular conflict, etc. This example highlights the question of the level of granularity one should give to the definition of a tinnitus etiology, a question that goes beyond the scope of the present work. Here, the decision to take pulsatile tinnitus as a unique diagnostic label was a pragmatic choice acknowledging the limited number of labels available to map such pulsatile tinnitus sub-etiologies. The limited size of the database in and of itself also conditioned the maximum number of clusters that could be allowed for the grid search. Moreover, only a weak constraint from the V-measure was placed on the algorithms on the number of clusters that could include pulsatile tinnitus. As a consequence, the best clustering presented in the results exhibited two different clusters with pulsatile tinnitus patients.

### Mono-Label Clustering

In this study, a methodological choice was to attribute each patient to one endotype and one endotype only. It was hence a mono-label clustering. Yet, it could be easily argued that this methodological choice over-simplifies the sometimes complex and intricate nature of clinical presentations of some patients. For example, as the ENT tinnitus experts commented on the results of the final clustering, it was reassuring to observe that some “pulsatile tinnitus” patients were attributed to the cluster where otosclerosis was predominant (Cluster 13). Indeed, in some cases, otosclerosis can produce a tinnitus presenting with a pulsatile sound.

### Biases of the Questionnaire

There is no ideal questionnaire to make an optimal anamnesis of tinnitus. However, some good directions were given regarding the important components such questionnaire should at least contain so that the chances to perform a good clustering are maximized [15]. Here, due to the retrospective nature of this study concerning the database acquisition, the questionnaire used, although reasonably complete, did not include all the items suggested by this review.

Another more subtle bias in the questionnaire is the heterogeneity in the level of scrutiny given to some dimensions of the symptomatology compared to others. In the case of the questionnaire used for this study, only one feature in the dataset was associated with vertigo (VAS scale on vertigo), whereas eight features were devoted to the impact of tinnitus on sleep (ISI, Epworth, VAS scale on sleep disturbance, nocturnal awakenings, sleep latency, quality of the sleep onset, snoring, sleep apnea). This bias was most probably introduced by the fact that V.L. has studied sleep medicine in addition to his ENT specialization. Such over-representation of sleep features in the dataset, compared to others, induced biases in the dataset that may not have been solved by the redundancy limitations induced by the dimensionality reduction techniques.

It could also of course be argued that the focus given on tinnitus interactions with sleep in the present study brings additional value to this study. Indeed, until now, the description of the nature of those interactions had been limited [60].

### Limited Range of the Hyperparameters for the Grid Search

In the present study, the grid search parameters were set to explore a range of values that may have constrained the exploration to a space yielding suboptimal performances. A wider range for grid search was explored in testing the dataset before the decision was made on these ranges. From these explorations, it seems that widening the ranges for the dimensionality reduction hyperparameters’ PCA, FAMD, or t-SNE components, as well as for perplexity for t-SNE

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did not seem to produce better performances. It was also remarkable to note that the best performances on the V-measure were always obtained on the lowest possible numbers of components (mostly 2, sometimes 3).

Notably, it is unsure whether the ranges explored for minimum sample and epsilon hyperparameters for DBSCAN were optimal. Above all, the range of exploration for the k-means number of clusters was selected as a trade-off and not as the optimal for performance. In fact, simulations of the V-measure's best performances showed it to be an increasing function of the maximum number of clusters. This function, for the different combinations of algorithms, had an asymptotic convergence. The asymptotic value, as well as the speed of convergence depended on the combination of algorithms, as well as the value of the parameter  $\beta$  of the V-measure. For the different simulations performed, it was observed that the combination t-SNE + k-means, which elicited the best results for this study, was also the combination of algorithms that converged the most rapidly to the asymptotic value and had the most-elevated asymptotic value.

The maximal value of 20 for the range of exploration of the number of clusters was the result of a trade-off: this number was enough to reach 75% of the asymptotic value for this method, while breaking the samples into groups of around 70 samples on average. It made it possible to characterize the symptomatic specificities of each cluster. Likewise, it brought a fine granularity for the evaluation of clusterings for the ENT tinnitus experts and separated the endotypes without dividing each endotype too many times into different groups. What was surprising was that, while simulating the clusterings for a greater number of clusters (for example taking a maximal number of clusters yielding at least 95% of the asymptotic value of the V-measure), the obtained clustering appeared to divide the endotypes too much. This suggests that the V-measure might not be totally optimal in achieving the desired goal. It is important to point out that increasing the value of  $\beta$  instead (to favor less the optimization on homogeneity) resulted in another problem: the results regrouped different (and clinically incompatible) endotypes in the same clusters.

#### Limited Stability Assessment for the DBSCAN Output

In the present study, a rigorous bootstrap procedure was applied to assess the stability of the k-means clustering method's output. Yet, such a method could not be applied for the DBSCAN algorithm. In fact, due to the transductive nature of DBSCAN (i.e., it cannot predict the labels of new data), the fit and predict methods of DBSCAN cannot be disentangled, so it was not possible to make a prediction of the labels of a subset of samples with a model fit on the other sample subset. Counting the difference of the clusters in the outputs proposed by the DBSCAN was used as a replacement for the stability assessment: indeed, the number of clusters of the output clustering is a free parameter of DBSCAN. Yet, it can be questioned whether such replacement constitutes the best-possible stability assessment for a transductive method.

#### *Suggestions for Future Research*

##### Widen Hyperparameter Search on Larger Databases

As stated in the Limits Section, our grid search ranges were limited, especially for the maximal number of clusters, which was chosen as a trade-off considering the sample size of the database.

On the other hand, it seems intuitive to induce that if six different endotypes of tinnitus are already present in 12.59% of the dataset as in the present study, it could be expected that the total number of clusters of an ideal clustering should be above 20. Future research should hence work to apply such techniques on wider datasets to enable widening the range of hyperparameters.

Similarly, the set of features of our database was limited and did not cover all the important dimensions advised in [15]. Future research should constitute their databases prospectively and, hence, actively shape the questionnaires so as to cover globally the anamnesis of a tinnitus patient. Focus should also be put on not over-weighting the exploration of some dimensions compared to others (as illustrated in the limits for vertigo and sleep in our case).

##### Change Framework to Longitudinal Data

A supplementary important suggestion for future research would be to switch from an initial dataset composed of a unique point in time (and thus, a unique completion of a given questionnaire) per patient to a longitudinal dataset in which each patient should answer a given set of questionnaires at some strategic points in time. In fact, the clustering chosen to be presented in this study tried to capture the time dimension by the feature "tinnitus duration". Yet, such a metric poorly captures the level of intrusiveness of a patient, which can evolve at different speeds according to the psychological and behavioral adaptation to the tinnitus and to the efficiency of therapeutic interventions. Likewise, some clusters tend to reflect such a difference of temporality, with clusters that evoke a state of initial crisis and others where one could hypothesize that patients are habituated to their condition (i.e., where the tinnitus annoyance is significantly lower).

It would naturally require more resources to lead such a study over a longer time frame to enable mapping the trajectories of patient symptoms. However, such initiatives could be led by digital mobile platforms such as TrackYourTinnitus [61] or Siopi [62]. Furthermore, it would require reorganizing the framework of analysis of such a characterization of each patient so as to achieve a clustering of different trajectories of patients, rather than a clustering of questionnaire entries.

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### Going Further in the Semi-Supervised Framework

In the present study, the semi-supervision of the algorithm only intervened in the evaluation of the clusterings obtained at the end of a systematic unsupervised process set in motion on a constrained grid search exploration space. This is the reason why the description of the procedure is only referred to as a semi-supervised *framework*. Yet, future research should investigate how to include semi-supervision directly into the pipeline of clustering. It could be at the level of the dimensionality reduction or at the level of the clustering algorithms [63,64].

### Going from Mono-Label to Multi-Label Clustering and beyond

As suggested among the limits of the present study, the methodological choice of applying a mono-label clustering might not be well fit to describe the clinical reality of patient symptomatology. When defining endotypes more restrictively, it becomes possible for a patient to be part of several endotypes: for example, a patient presenting presbycusis with somato-sensory tinnitus due to a jaw instability would hence be assigned to two endotypes, as these two reasons in and of themselves can lead to the emergence of tinnitus. It would hence appear useful for future research to adapt the clustering framework to perform a multi-label clustering.

To go even further, it can be questioned whether segmentation, due to its discrete and non-continuous nature, is the best methodological tool to address tinnitus heterogeneity. Another possibility to address the heterogeneity problem would be to tackle it with a more continuous and local approach by only looking locally for the best neighbors to a given patient. Such an approach has been attempted by Siopi as its mutual-help community could involve metric learning methods (supervised or weakly supervised) such as metric learning with application for clustering with side information (MMC) [65], large margin nearest neighbor metric learning (LMNN) [66], or other deep metric learning methods.

### Apply the Semi-Supervised Clustering to Other Labels

It seems important to point out that a semi-supervised framework for tinnitus clustering can also be applied taking as a reference something different from endotype labels. For example, taking individual treatment responses as the labels could also be very interesting to try to define subtypes of tinnitus.

### Explore Other Dimensionality Reduction Techniques and Clustering Techniques

Here, methods that had been tested in past studies were replicated and two new original dimensionality reduction techniques were introduced. Yet, a great amount of other dimensionality reduction techniques and clustering methods could be tested in the future so as to outperform the results obtained in the present study. Interesting candidates would be HDBSCAN [67] for which, in some references, its transductive nature could be overcome by cross-validation ([https://hdbscan.readthedocs.io/en/latest/prediction\\_tutorial.html](https://hdbscan.readthedocs.io/en/latest/prediction_tutorial.html), accessed on 23 November 2022). This method has the advantage of not tending to form Voronoi-cell-shaped clusters that tend to have similar numbers of samples per cluster (like DBSCAN). Such methods appear to be more adapted in the case of subgrouping samples in groups that can have diverging prevalence in the population.

Additionally, a very good semi-supervised candidate could be the heterogeneity through discriminative analysis (HYDRA) method [68], which has proven to be quite efficient at subtyping schizophrenia [69,70]. However, this method would be best fit for application to neuroimaging datasets, rather than questionnaire datasets.

## Conclusions

The present study aimed at presenting a new semi-supervised framework to bring guidance when facing the issue of heterogeneity in the population of tinnitus patients. It is the first to achieve such a clustering while enabling quantified comparisons between the performance of different algorithmic combinations. Through this process and through a bootstrap procedure for stability assessment, a 20-cluster solution was selected and presented. With this solution, most clusters were confirmed by ENT tinnitus experts to convey strong clinical relevance. Such clusters define homogeneous subphenotypes of patients. Those are relevant to be studied independently to look for objective signatures of different potential underlying pathophysiological mechanisms.

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**Conflicts of Interest:** R.G., A.H. and L.K. are employees of Siopi, who's mission is to create a mutual-help community to help tinnitus patients. One of the attributed missions of Siopi is to shed light on the intrinsic heterogeneity of tinnitus. R.G. and L.K. are shareholders of Siopi.

## Abbreviations

The following abbreviations are used in this manuscript:

THI: Tinnitus Handicap Inventory

VAS: Visual analog scale

HAD: Hospital Anxiety and Depression scale

ISI: Insomnia Sleep Index

ENT: Ear, nose, and throat

PCA: Principal component analysis

FAMD: Factor analysis of mixed data

t-SNE: t-distributed stochastic neighbor embedding

DBSCAN: Density-based spatial clustering of applications with noise

AMI: Adjusted mutual information

OSA: Obstructive sleep apnea

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Table 7, Individual clusters characteristics of the finally selcted clustering

Cluster number	Cluster general description	Number of patients	Positive differentiation		Negative differentiation	
			Feature	Effect size	Feature	Effect size
1	Acoustic trauma without annoyance	83	Initial acoustic trauma Progressive apparition Tinnitus duration (in months) Men	0.96 0.8 0.71 0.69	ISI VAS Sleep quality Trouble falling asleep THI Tired when awake HAD anxiety VAS Anxiety Nocturnal awakenings HAD depression Brutal onset VAS Tinnitus annoyance	-1.3 -1.2 -1.1 -1.1 -1.0 -0.98 -0.96 -0.86 -0.84 -0.71 -0.7
2	Notch hearing losses	91	Notch Hearing Loss VAS Anxiety Trouble falling asleep THI Tired when awake HAD anxiety ISI VAS Sleep quality Sleep onset latency	4.6 0.56 0.53 0.49 0.43 0.41 0.35 0.33 0.33	Sensorineural hearing loss Age (in years) Tinnitus pulsatile Necksomato-sensory modulations	-1.5 -0.73 -0.32 -0.31
3	Cophosis group	18	Cophosis Hyperacusis Khalifa VAS Tinnitus annoyance VAS Vertigo Tinnitus lateralised THI Age (in years) VAS Hyperacusis Tinnitus duration (in months) Nocturnal awakenings % time tinnitus present	>10 0.65 0.64 0.63 0.62 0.58 0.39 0.39 0.34 0.33 0.32	Sensorineural hearing loss Initial acoustic trauma Normal hearing Jaw somato-sensory modulations VAS Headache Notch Hearing Loss Tinnitus pulsatile	-1.6 -0.45 -0.38 -0.36 -0.33 -0.32 -0.31
4	Loud narrow band tinnitus in OSA elderly	57	Narrow band noise OSA High tinnitus intensity Age (in years) VAS Tinnitus annoyance Sensorineural hearing loss Snoring VAS Cervical pain Cervical pain/rigidity % time tinnitus present	2.7 0.62 0.54 0.52 0.47 0.45 0.44 0.42 0.36 0.33	Headaches Notch Hearing Loss VAS Headache	-0.34 -0.33 -0.32
5	Right pulsatile tinnitus	28	Tinnitus pulsatile Normal hearing Tinnitus side right Tinnitus lateralised Notch Hearing Loss	3.8 1.4 0.8 0.56 0.31	Sensorineural hearing loss Snoring Age (in years) VAS Cervical pain Men Cervical pain/rigidity HAD depression Initial acoustic trauma Tinnitus duration (in months) VAS Anxiety THI VAS Tinnitus annoyance	-1.2 -0.62 -0.62 -0.62 -0.54 -0.53 -0.49 -0.46 -0.39 -0.37 -0.34 -0.33
6	Acoustic trauma with hearing loss	81	Initial acoustic trauma Sensorineural hearing loss Men Age (in years) Tinnitus duration (in months) Progressive apparition	1.4 0.65 0.49 0.43 0.41 0.35	Brutal onset VAS Headache VAS Anxiety Headaches HAD anxiety Tinnitus lateralised VAS Sleep quality Sleep onset latency Somato-sensory modulations Normal hearing VAS Jaw pain	-0.59 -0.58 -0.55 -0.52 -0.5 -0.42 -0.42 -0.42 -0.4 -0.4
7	Tinnitus and insomnia	90	Sensorineural hearing loss ISI VAS Sleep quality Tired when awake Nocturnal awakenings Trouble falling asleep	0.63 0.51 0.51 0.42 0.38 0.37	VAS Headache Headaches Somato-sensory modulations Normal hearing Jaw somato-sensory modulations Snoring Necksomato-sensory modulations Notch Hearing Loss Narrow band noise Tinnitus pulsatile High Frequencies hearing loss	-0.58 -0.54 -0.46 -0.4 -0.38 -0.38 -0.35 -0.34 -0.32 -0.32 -0.31



8	Neck Somatosensory tinnitus	95	Neck somato-sensory modulations Somato-sensory modulations Jaw somato-sensory modulations VAS Cervical pain Cervical pain/rigidity HAD anxiety VAS Jaw pain THI VAS Vertigo ISI VAS Anxiety	5.3 3.2 1.8 0.93 0.74 0.7 0.64 0.6 0.57 0.56 0.55		
9	Pulsatile tinnitus	59	Tinnitus pulsatile Trouble falling asleep Tinnitus lateralised Sensorineural hearing loss Sleep onset latency Age (in years)	4.8 0.68 0.6 0.54 0.39 0.31	High tinnitus intensity Men Initial acoustic trauma Somato-sensory modulations Cervical pain/rigidity Normal hearing Tinnitus duration (in months) Jaw somato-sensory modulations	-0.53 -0.52 -0.47 -0.35 -0.34 -0.34 -0.32 -0.31
10	High frequency hearing loss with tinnitus	85	High Frequencies hearing loss Normal hearing Tired when awake	8.5 2.3 0.33	Sensorineural hearing loss % time tinnitus present Age (in years) Snoring OSA	-1.8 -0.43 -0.39 -0.32 -0.31
11	Sudden hearing loss	82	Brutal onset Sensorineural hearing loss Tinnitus lateralised Headaches	0.94 0.68 0.55 0.39	Progressive onset ISI Somato-sensory modulations VAS Jaw pain Normal hearing Sleep onset latency Jaw somato-sensory modulations HAD anxiety Tired when awake Neck somato-sensory modulations Notch Hearing Loss	-0.8 -0.53 -0.46 -0.45 -0.4 -0.37 -0.37 -0.36 -0.36 -0.35 -0.34
12	Elderly people with bothersome tinnitus and OSA	61	OSA HAD depression Snoring THI % time tinnitus present Hyperacusis Khalifa VAS Tinnitus annoyance Sensorineural hearing loss Epworth Age (in years) VAS Anxiety	1.8 0.73 0.73 0.73 0.69 0.63 0.62 0.62 0.6 0.59 0.59	Somato-sensory modulations Normal hearing Jaw somato-sensory modulations Brutal onset Notch Hearing Loss Tinnitus pulsatile	-0.41 -0.39 -0.37 -0.34 -0.33 -0.32
13	Otosclerosis oriented group	43	Transmissional hearing loss Progressive onset Tinnitus pulsatile Tinnitus side right Tired when awake VAS Sleep quality ISI VAS Vertigo	4.7 0.59 0.56 0.47 0.39 0.35 0.34 0.32	OSA Brutal onset Initial acoustic trauma Somato-sensory modulations Jaw somato-sensory modulations Notch Hearing Loss Normal hearing	-0.43 -0.42 -0.4 -0.38 -0.36 -0.33 -0.32
14	Somatosensory tinnitus without annoyance	73	Somato-sensory modulations Jaw somato-sensory modulations Neck somato-sensory modulations Men	2.8 2.7 1.1 0.58	THI ISI VAS Sleep quality VAS Anxiety VAS Tinnitus annoyance HAD anxiety Trouble falling asleep Hyperacusis Khalifa HAD depression % time tinnitus present VAS Hyperacusis	-0.79 -0.75 -0.67 -0.64 -0.62 -0.61 -0.6 -0.55 -0.54 -0.51 -0.46
15	Tinnitus and headaches	70	Headaches VAS Headache ISI THI Sensorineural hearing loss VAS Sleep quality VAS Tinnitus annoyance % time tinnitus present VAS Hyperacusis Trouble falling asleep Hyperacusis Khalifa	1.2 0.9 0.63 0.62 0.6 0.6 0.55 0.54 0.43 0.42 0.42	Cervical pain/rigidity VAS Cervical pain Somato-sensory modulations Normal hearing Jaw somato-sensory modulations Neck somato-sensory modulations Notch Hearing Loss Tinnitus pulsatile High Frequencies hearing loss	-0.54 -0.53 -0.46 -0.4 -0.37 -0.35 -0.33 -0.32 -0.3 -0.3

16	Habituated patients	103	Sensorineural hearing loss	0.44	VAS Sleep quality ISI Tired when awake THI VAS Anxiety Nocturnal awakenings VAS Tinnitus annoyance Hyperacusis Khalfa HAD anxiety Trouble falling asleep VAS Hyperacusis	-1.2 -1.1 -1.0 -0.92 -0.88 -0.87 -0.86 -0.83 -0.78 -0.74 -0.72
17	Young people with normal hearing with bothersome tinnitus and hyperacusis	60	Normal hearing VAS Headache HAD anxiety THI VAS Jaw pain VAS Hyperacusis Hyperacusis Khalfa VAS Anxiety	2.0 0.46 0.44 0.43 0.42 0.36 0.33 0.33	Age (in years) Sensorineural hearing loss Snoring Tinnitus lateralised Initial acoustic trauma Notch Hearing Loss Tinnitus pulsatile	-1.3 -1.2 -0.48 -0.42 -0.37 -0.33 -0.32
18	Tinnitus patients with depression	71	HAD depression THI Sleep onset latency HAD anxiety VAS Anxiety ISI VAS Sleep quality VAS Tinnitus annoyance VAS Cervical pain % time tinnitus present Trouble falling asleep	1.6 1.3 1.2 1.2 1.1 1.1 1.1 0.95 0.94 0.83 0.81	Somato-sensory modulations Normal hearing Jaw somato-sensory modulations Neck somato-sensory modulations Epworth Notch Hearing Loss Tinnitus pulsatile Narrow band noise High Frequencies hearing loss	-0.46 -0.4 -0.37 -0.35 -0.33 -0.33 -0.32 -0.3 -0.3
19	Head trauma tinnitus (Majority of petrous bone fractures)	58	VAS Headache VAS Jaw pain Headaches VAS Vertigo HAD anxiety HAD depression THI ISI VAS Sleep quality VAS Anxiety VAS Cervical pain	2.0 1.4 1.3 1.1 1.1 1.1 1.0 1.0 0.98 0.96 0.92	Progressive onset Men Somato-sensory modulations OSA Neck somato-sensory modulations	-0.52 -0.47 -0.35 -0.34 -0.34
20	Tinnitus with OSA seemingly affecting middle ear conduction, not bothersome	77	Transmissional hearing loss Narrow band noise OSA Snoring	1.0 0.86 0.56 0.39	THI VAS Sleep quality ISI VAS Anxiety Hyperacusis Khalfa Tired when awake VAS Hyperacusis VAS Tinnitus annoyance Trouble falling asleep HAD depression HAD anxiety	-1.1 -1.1 -1.1 -1.0 -1.0 -1.0 -0.99 -0.84 -0.81 -0.76 -0.71

THI : Tinnitus Handicap Inventory, ISI : Insomnia Severity Index, HAD : Hospital Anxiety and Depression scale score, OSA : Obstructive sleep apnea, VAS : Visual Analog Scale, Hyperacusis Khalfa : Khalfa questionnaire score on hyperacusis

# Chapter 4

## Epidemiology of nap-induced tinnitus modulations

## 4. Epidemiology of nap-induced tinnitus modulations

In the last chapter we explored tinnitus heterogeneity and we tried to perform an endotype/diagnostic-driven semi-supervised segmentation of the tinnitus population into homogeneous subphenotype of tinnitus patients. Similar to the results of (van den Berge et al., 2017), our analyses did not lead to the isolation of the TIAN population within a distinct subphenotype of tinnitus patients. One may hence question if there such TIAN patients have characteristic symptomatologic profiles compared to the rest of the tinnitus population. To explore this question, in the present study we investigated the symptomatologic characteristics of patients reporting NITM (increase or decrease following naps), through a cross-sectional analysis of two databases gathering a total of 9742 patients. The two databases we analyzed were based on questionnaires which both included a question on tinnitus modulation by naps, along multiple questions on tinnitus associated symptomatologic characteristics. One questionnaire was a general screening assessment within the clinical environment of Regensburg's university tinnitus clinic, the other was centered around somatosensory attributes of tinnitus and was administered as a large-scale survey on Tinnitus Hub platform, an online tinnitus patient community.

Article – original research

# Nap-induced modulations of tinnitus – a cross-sectional database analysis

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**Abstract:** It is clinically well known that in some individuals tinnitus is positively or negatively influenced by naps. Here we aimed at systematically investigating this phenomenon, by assessing its frequency and by exploring associated clinical or demographic characteristics.

Data from two different databases with a total of 9,742 people with tinnitus were investigated. Through the Tinnitus Hub "Investigating physical links to tinnitus" survey database, 6,115 participants with tinnitus were sampled for a comprehensive survey regarding tinnitus characteristics. Using the TRI database, 3,627 outpatients who presented to a German tertiary tinnitus clinic during the period between 2010 and 2023 and had completed validated tinnitus questionnaires were included. After separate analysis of the databases, these results were then compared with each other.

In the Tinnitus Hub survey database, a total of 31.1% reported an influence on tinnitus by taking a nap, with much more frequent worsening after a nap than improvement (23.0% a little or a lot worse, 8.1% a little or a lot better). In the TRI database, a total of 26.9% reported an influence on tinnitus by taking a nap (17.7% worse, 9.2% better).

The influence of napping on tinnitus was associated in both databases with other clinical features, such as the dependence of tinnitus on night quality, stress and somatosensory maneuvers.

The present study confirms the clinical observation that more tinnitus sufferers report worsening after a nap than tinnitus sufferers reporting an improvement. It was consistently shown that tinnitus sufferers reporting nap-induced modulation of tinnitus also report more frequently an influence of night sleep on their tinnitus. Co-occurrence of influence of stress on tinnitus and influence of naps on tinnitus could suggest a specific influence of serotonergic drive on central auditory pathways. Whether the observed association between tinnitus worsening after naps and somatosensory modulation of tinnitus might be mediated by the occurrence of sleep associated symptoms such as bruxism, snoring or sleep apnea events during naps should be investigated in future studies. Further clinical and polysomnographic research is warranted to better understand the interaction between sleep and tinnitus.

**Keywords:** tinnitus; tinnitus disorder; distress; depression; nap; sleep; somatosensory modulations

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## 1. Introduction

Tinnitus is defined as the perception of a sound in the absence of an external acoustic source [1,2]. The prevalence is high at about 10-15%, with about 1-2% of the general population also having severe tinnitus [3–8]. Tinnitus shows a high clinical heterogeneity, e.g., regarding loudness, pitch, sound quality, laterality and continuity [2]. While some tinnitus patients have constant tinnitus, some have variable tinnitus, e.g., intermittent or fluctuating in intensity [9]. Tinnitus patients often report that some factors can modulate their tinnitus, causing either an improvement or a worsening.

In this context, the clinical phenomenon that a daytime nap can have an effect on tinnitus is well known. In clinical settings, this phenomenon is queried in the frequently used Tinnitus Sample Case History Questionnaire (TSCHQ) of the Tinnitus Research Initiative (TRI) with question 22 (influence by nap: worsens/improves/no effect) [10], as well as in the ESIT-SQ questionnaire of the European School of Interdisciplinary Tinnitus research (ESIT) as a potential modulatory factor of tinnitus (question B18 on factors decreasing tinnitus and question B19 on factors increasing tinnitus) [11]. It is remarkable that individually different effects are possible and also that a measure intuitively assessed as relaxing can have negative effects on tinnitus. To date, this phenomenon has only been rudimentarily investigated scientifically [12–14] and sometimes compared to the rare par due to the fact in both cases, patients describe abnormally loud sounds upon awakening [15,16]. Several past reviews suggested that nap modulations of tinnitus were a specific subcase of somatosensory modulation of tinnitus and

reported anecdotally that this phenomenon seemed to be amplified in the sitting position [15–17]. A recent study investigated night polysomnographic characteristics of tinnitus patients reporting increases of tinnitus after naps. It compared them to the characteristics of a matched control group of tinnitus patients not presenting such increases. Patients with nap-induced tinnitus increase seemed to have less deep sleep (N3) and less paradoxical sleep (Rapid-eye movement / REM) than controls [18].

Yet a symptomatologic characterization of the population of tinnitus patients reporting an effect of naps on their tinnitus remains elusive. To fill this gap, samples from two ecologically relevant large databases (from the TRI database [19] and from the online forum Tinnitus Talk <https://www.tinnitustalk.com/> [20]) were used to clinically characterize groups of patients who experience an improvement, those who perceive a worsening and those who deny any influence of naps on their tinnitus perception. This approach aims (1) at a better understanding of the influence of sleep on tinnitus and (2) at exploring whether nap-induced modulation might represent a clinically useful criterion for tinnitus subtyping.

## 2. Materials and Methods

### 2.1. Data collection

#### 2.1.1. TRI database

The TRI database consists of a sample of 3627 questionnaire records from patients who visited the tertiary tinnitus clinic between 2010 and 2023 [19]. All data were collected at intake assessments during the first visit at the clinic. This decision was made to mitigate the potential biases of clinical interventions and/or multiple visits to the clinic on the target variable, in the present case, nap-induced tinnitus modulations. Ethical approval for the collection of this database was obtained from the Ethics Committee of the University of Regensburg, protocol number 08/046, and all patients provided their written consent after oral information to have their data pseudonymised, stored, analyzed, and published for scientific purposes.

#### 2.1.2. Tinnitus Hub "Investigating physical links to tinnitus" survey database

The Tinnitus Hub survey database consisted of a sample of 6115 records from participants collected through a Web-based survey in February 2017. The initial goal of this survey was to assess the presence of physical symptoms in a convenience sample of participants with tinnitus. It was launched on the online forum, Tinnitus Talk, managed by Tinnitus Hub.

As presented in [20], the motivation of the survey topic emerged from participants' interactions on the online forum and is a good example of citizen science [21]. Questions were designed in consultation with tinnitus researchers and a small pool of the forum's community and trial e questions were clear and unambiguous and that no technical issues were present. The final questionnaire consisted of 21 questions that asked for different physical symptoms that come as comorbidities with tinnitus and for a set of tinnitus characteristics. Among these comorbidities, the participants were asked whether or not naps modulated their tinnitus.

The survey was advertised on the Tinnitus Talk website and launched as an open survey, on the online forum, Tinnitus Talk. No incentives were offered to participants. An internet protocol check was used to identify and block potential duplicate entries from the same user. All participants gave informed consent for their anonymized data to be used for scientific purposes. No personal information was collected during the process. Ethical approval was obtained from the Ethical committee of the Antwerp University Hospital for the use of this survey for research purposes (Reference number : 19-43-485).

### 2.2. Databases variables

In the present study we analyzed two databases reaching different subpopulations of tinnitus patients, to reduce selection bias and to obtain more robust results [22]. The questions about nap-induced tinnitus modulation were quite similar in the two databases: "Does taking a possible answers "worsens my tinnitus", "reduces question was "How do the following affect your worse", "A little worse", "No difference", "A common and presented hereafter. Also, some features were only present in the TRI or the Tinnitus Hub databases, they will also be presented hereafter.

### 2.2.1. Common variables to the two databases

Common variables in the two databases in addition to nap modulations were :

- Gender and age of participants;
- Tinnitus duration;
- Whether tinnitus consisted in a pulsatile sound, a tonal sound or another type of sound;
- Events related to tinnitus onset;
- Rating scales of tinnitus loudness and annoyance;
- Percentage of time aware of the tinnitus percept;
- Influence of stress, sleep (different formulations) and noise (possibility to mask it, worsening) on tinnitus;
- Presence of somatosensory modulations of tinnitus
- Self-reported hearing loss grade;
- Reported comorbidities in addition to tinnitus: headache, neck pain/stiffness (different formulations), temporomandibular pain (different formulations).

### 2.2.2. TRI database specific variables

Variables unique to the the TRI database included :

- Handedness of participants
- Laterality of the tinnitus percept;
- Whether tinnitus appeared progressively or abruptly;
- Whether or not other direct family members had tinnitus;
- Standardized questionnaire scores such as the Tinnitus Handicap Inventory (THI) and the Tinnitus Questionnaire (TQ);
- More granularity on tinnitus grading scales "Severity" questionnaire;
- Impact of tinnitus on the general quality of life measured by the World Health Organization Quality Of Life (WHOQOL-bref) questionnaire on different dimensions;
- Percentage of time participants felt angry and/or frustrated by their symptoms
- Other reported comorbidities in addition to tinnitus such as, e.g., vertigo or, hyperacusis
- How many treatments patients had already tried to alleviate their tinnitus;
- Whether or not patients are using hearing aids and/or receive psychiatric treatment because of their tinnitus

### 2.2.2. Tinnitus Hub survey database specific variables

Variables unique to the Tinnitus Hub survey database included :

- More granularity on the variability of tinnitus loudness and annoyance over time;
- Whether patients experienced fleeting tinnitus events and on which frequency;
- Events that can trigger ear fullness
- Whether or not patients tend to clench or grind their teeth
- Tinnitus modulations related to jaw movements;
- More granularity on the way the jaw or the temporomandibular joint is aching;
- Influence of anxiety and sport practice on the tinnitus percept

## 2.3. Data processing

Data processing consisted first in labeling all "know" when this choice was possible, it was coded as "no". Categorical variables encoded as strings in response to multiple choice questions were treated as separate columns and each of the created columns received a value. Another processing step for the TRI database consisted in excluding all records that were not a first visit from a patient (i.e., all follow-up visits records). Moreover, only scores and not individual question answers from standardized



questionnaires THI, TQ, Tinnitus Functional Index (TFI), Major Depression Index (MDI), WHOQOL-bref were included as variables. As TFI and MDI scores were only available in less than half of the patients, they were not included in the analysis.

There was a difference in the possible answers to the question of nap-induced modulations of tinnitus between the two databases. In fact, in the TRI database, there were "has no effect" whereas in the Tinnitus Hub survey database, "A lot worse", "No difference", "A little better", "A little worse" option were excluded from the analysis).

The difference in granularity of the answers is reflected in the Figure 1 and 2 of the Results section. Yet, in order to be able to perform the same group comparisons on the two databases, in the Tinnitus Hub survey database the answers "A lot worse" and "A little worse" were merged in a column "Worse" and "A little better" were merged in a column "Better". As the possible answers for stress, anxiety, good sleep, bad sleep and light, moderate and intense workout influence on tinnitus in the Tinnitus Hub survey database were saved with the same possible answers choices, the same processing (merging "A lot worse" and "A little worse" these variables as well.

#### 2.4. Statistical analysis:

The two databases were analyzed separately. The analysis consisted in comparing in each database the differences between the three groups : "Tinnitus Worsened", "Tinnitus Improved" by naps (TI).

There were four types of answers to questionnaire items : scales (for example, tinnitus annoyance rating scale), gradations (for example for the degree of self reported hearing loss), categorical unique choices (only one choice of answer could be selected among a set of possible answers, as for example for tinnitus laterality) and finally categorical multi-choices (the participant could select as many answers as he wished among a selection of possible answers, as for example the sound characterization of the tinnitus percept). Ratings and gradations were analyzed similarly and referred to in the following sections as scales.

##### 2.4.1. Variable testing

For scale type of answers, the comparison between the three groups was performed with the non-parametric Kruskal Wallis test. An effect size was associated with this Kruskal Wallis test, an implementation of this effect size can be found in the R.statix 0.6.0 package at the following link :

[https://www.rdocumentation.org/packages/rstatix/versions/0.6.0/topics/kruskal\\_effsize](https://www.rdocumentation.org/packages/rstatix/versions/0.6.0/topics/kruskal_effsize) . For categorical unique choices type of answers, a Chi-Squared test was performed between all possible answers. For categorical multi-choices, each possible answer was assigned as an independent boolean variable and was tested separately between "Yes" and "No" with the same effect size.

##### 2.4.2. Post-hoc tests

For questions with a scale type answer, Dunn's non-parametric test [23] was used for pairwise post-hoc comparisons. As no specific effect size formula could be found, the effect size for each pairwise test. For categorical types of answers, pairwise chi-squared tests were performed and Cramér's V was used as effect size for each pairwise comparison.

##### 2.4.3. Control for multiple comparisons

Holm adjustment for multiple comparisons [24] was applied on all variables before post-hoc testing for each database independently. Pairwise post-hoc tests were only performed if the controlled p-values of the tested variable were below 0.05. A second Holm adjustment for multiple comparisons procedure was then applied on the obtained post-hoc p-values of all post-hoc tests for each database independently.

##### 2.4. Software choices



Data processing and statistical analyses was performed in R (version 4.0.3, R Core Team, Vienna, Austria, 2020) and in Python (Anaconda 2022.10, Austin, Texas, USA and PyCharm 2020.3.2, JetBrains, Prague, Czech Republic). Data processing in R was performed with the packages tidyverse [25] and tidymodels with its default settings [26]. Data processing and statistical analyses were performed in python with the Pandas library [27] the scipy.stats library [28], the statsmodel library [29] as well as the Scikit post hoc library [30].

The code used to perform this analysis is accessible on the GitHub open-source repository at this URL :

[https://github.com/RobinGuillard/TinniNap\\_DB\\_study](https://github.com/RobinGuillard/TinniNap_DB_study)

The TRI data presented in this study are available on reasonable request from the corresponding author.

The Tinnitus Hub survey database is available on reasonable request to Tinnitus Hub and S.M.

### 3. Results

#### 3.1. Nap influence on tinnitus in the two databases

In the Tinnitus Hub survey database, 31.1% reported an influence on tinnitus by taking a nap (23.0% a little or a lot worse, 8.1% a little or a lot better), in the TRI database 26.9% (17.7% worse, 9.2% better) (Figure 1 and 2). There are no significant differences between the distributions of participants' modulation of tinnitus through naps in the two databases ( $p = 0.99$ ).

The TW group was found to be much more numerous than the TI group (TW : 1404 VS TI : 507 more than double in the Tinnitus Hub survey database, TW : 642 VS TI : 334 not far from the double in the TRI database).

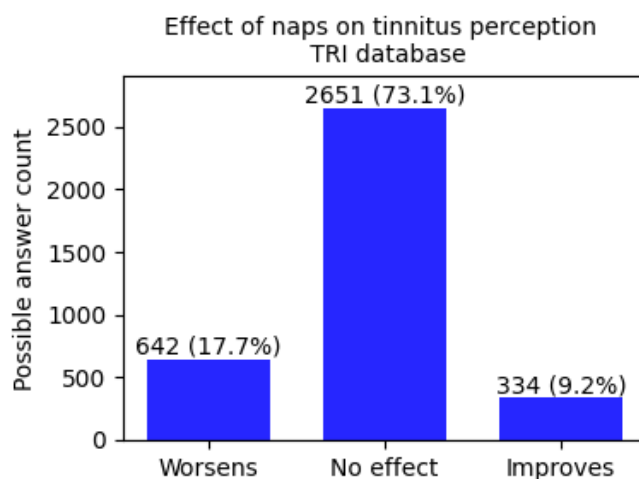


Figure 1 : Repartition of the sample between groups on the base of the effect of naps on tinnitus percept for the Tinnitus Hub survey database

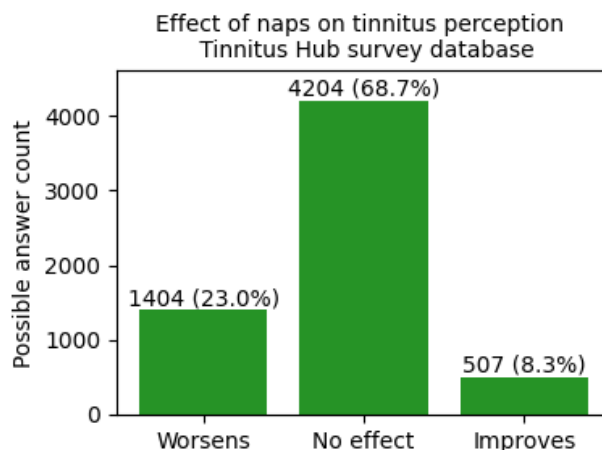


Figure 2 : Repartition of the sample between groups on the base of the effect of naps on tinnitus perception for the TRI Database

The main socio-demographic data and tinnitus characteristics with distribution differences of the two databases can be found in Table 1. This comparison shows that on the majority of common criteria in both databases significant differences exist. The most striking difference can be observed for self-reported stress being the initial cause of tinnitus onset : a medium effect size difference of 0.35 was observed between the TRI database (50,6% yes, 49,4% no), and the Tinnitus Hub survey database (17% yes, 83% no). To a lesser extent, small effect size differences between databases samples were identified for age (higher in TRI Database), tinnitus loudness (higher in TRI Database), and annoyance (higher in TRI Database) scales, gender (more males in TRI Database), acoustic trauma as the initial cause of tinnitus onset (higher in Tinnitus-Hub Database), hearing impairment (higher in Tinnitus-Hub Database), somatosensory modulations (higher in Tinnitus-Hub Database) and modulation of tinnitus by sounds worsening (higher in TRI Database) and suppressing (higher in Tinnitus-Hub Database).

**Table 1.** Socio-demographic and tinnitus characteristics in each database and comparison of such characteristics. *SD*: Standard Deviation, \*: significant *p*-value

	TRI database (N= 3627)	Tinnitus Hub database (N= 6115)	Statistic	P-Value	Effect size
<b>Age</b>			H = 13465652*	p < 0.001	0.215 (Small)
Mean (SD)	59.8 (13.85)	54.1 (13.81)			
Median [Min Max]	61.0 [2.0, 103.0]	57.0 [6, 96]			
Missing	1 (0.0%)	0 (0.0%)			
<b>Tinnitus duration</b>			H = 9859789	0.506	0.008 (Negligible )
Mean (SD)	100.7 (111.82)	101.8 (110.16)			
Median [Min Max]	52.5 [0.5, 726.0]	53.0 [0.0, 371.0]			
Missing	373 (10.3%)	4 (0.1%)			
<b>Loudness</b>			H = 12739120*	p < 0.001	0.205 (Small)
Mean (SD)	6.4 (2.19)	5.6 (2.33)			
Median [Min Max]	7.0 [0.0, 10.0]	6.0 [0.0, 10.0]			
Missing	156 (4.3%)	24 (0.4%)			
<b>Annoyance</b>			H = 13115675*	p < 0.001	0.239 (Small)
Mean (SD)	6.8 (2.43)	5.5 (3.04)			
Median [Min Max]	7.0 [0.0, 10.0]	5.0 [0.0, 10.0]			
Missing	152 (4.2%)	22 (0.4%)			
<b>Awareness</b>			H = 11861923*	p < 0.001	0.081 (Negligible )
Mean (SD)	77.6 (80.46)	68.5 (27.66)			
Median [Min Max]	80.0 [0.0, 999.0]	75.0 [0, 100]			

Epidemiology of nap-induced tinnitus modulations

Missing	38 (1.0%)	0 (0.0%)		
<b>Gender</b>			Chi2 = 186.8* p < 0.001	0.139 (Small)
Male	2392 (65.9%)	3154 (51.7%)		
Female	1235 (34.1%)	2942 (48.3%)		
Missing	0 (0.0%)	19 (0.3%)		
<b>Initial cause head or neck trauma</b>			Chi2 = 20.1* p < 0.001	0.047 (Negligible)
No	2850 (93.3%)	5535 (90.5%)		
Yes	204 (6.7%)	580 (9.5%)		
Missing	573 (15.8%)	0 (0.0%)		
<b>Initial cause stress</b>			Chi2 = 1136.3* p < 0.001	0.352 (Medium)
No	1508 (49.4%)	5076 (83.0%)		
Yes	1546 (50.6%)	1039 (17.0%)		
Missing	573 (15.8%)	0 (0.0%)		
<b>Initial cause acoustic trauma</b>			Chi2 = 312.2* p < 0.001	0.185 (Small)
No	2950 (96.6%)	5131 (83.9%)		
Yes	104 (3.4%)	984 (16.1%)		
Missing	573 (15.8%)	0 (0.0%)		
<b>Hearing impairment</b>			Chi2 = 426.0* p < 0.001	0.210 (Small)
No	1401 (39.3%)	1219 (19.9%)		
Yes	2166 (60.7%)	4896 (80.1%)		
Missing	60 (1.7%)	0 (0.0%)		
<b>Neck pain</b>			Chi2 = 20.2* p < 0.001	0.046 (Negligible)
No	1482 (41.8%)	2847 (46.6%)		
Yes	2062 (58.2%)	3268 (53.4%)		
Missing	83 (2.3%)	0 (0.0%)		
<b>Somatosensory modulations</b>			Chi2 = 340.1* p < 0.001	0.187 (Small)
No	2258 (63.2%)	2678 (43.8%)		
Yes	1313 (36.8%)	3437 (56.2%)		
Missing	56 (1.5%)	0 (0.0%)		
<b>Temporo-mandibular joint pain</b>			Chi2 = 13.5* p < 0.001	0.037 (Negligible)
No	2639 (73.9%)	4724 (77.3%)		
Yes	931 (26.1%)	1391 (22.7%)		
Missing	57 (1.6%)	0 (0.0%)		
<b>Headache</b>			Chi2 = 1.4 0.245	0.012 (Negligible)
No	2154 (60.8%)	3790 (62.0%)		

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Yes	1391 (39.2%)	2325 (38.0%)	
Missing	82 (2.3%)	0 (0.0%)	
<b>Pulsatile tinnitus</b>			Chi2 = 65.5* p < 0.001 (Negligible) 0.082
No	3252 (89.7%)	5121 (83.7%)	
Yes	375 (10.3%)	994 (16.3%)	
Missing	0 (0.0%)	0 (0.0%)	
<b>Pulsatile tinnitus not following heartbeat</b>			Chi2 = 11.0* p < 0.001 (Negligible) 0.034
No	3288 (90.7%)	5661 (92.6%)	
Yes	339 (9.3%)	454 (7.4%)	
Missing	0 (0.0%)	0 (0.0%)	
<b>Some sounds worsen tinnitus</b>			Chi2 = 349.7* p < 0.001 (Small) 0.197
No	916 (31.2%)	3185 (52.1%)	
Yes	2023 (68.8%)	2930 (47.9%)	
Missing	688 (19.0%)	0 (0.0%)	
<b>Some sounds suppress tinnitus</b>			Chi2 = 334.4* p < 0.001 (Small) 0.191
No	723 (23.7%)	580 (9.5%)	
Yes	2334 (76.3%)	5535 (90.5%)	
Missing	570 (15.7%)	0 (0.0%)	
<b>Stress modulates tinnitus</b>			Chi2 = 58.3* p < 0.001 (Negligible) 0.055
Improves	37 (1.0%)	27 (0.4%)	
No change	976 (27.7%)	2112 (34.5%)	
Worsens	2513 (71.3%)	3976 (65.0%)	
Missing	101 (2.8%)	0 (0.0%)	
<b>Naps modulates tinnitus</b>			Chi2 = 38.3* p < 0.001 (Negligible) 0.044
Improves	334 (9.2%)	507 (8.3%)	
No change	2651 (73.1%)	4204 (68.7%)	
Worsens	642 (17.7%)	1404 (23.0%)	
Missing	0 (0.0%)	0 (0.0%)	

### 3.2. Group comparisons

Group comparison in the TRI database and the Tinnitus Hub Survey Database are respectively presented in tables 2 and 3. Only variables eliciting significant differences after Holm correction were reported.

#### 3.2.1. Congruent findings

In both databases, the largest effect sizes for group comparison were obtained for the variables concerning sleep. In the TRI database, the relationship between sleep and tinnitus during the day was stronger in TI and TW than in NE, with an overall medium effect size. Likewise, similar results were found in the Tinnitus Hub survey database, where the

influence of a good night sleep elicited important differences between the 3 groups, with again the NE group standing out, as well as the influence of poor sleep.

Then, in both databases, modulation by stress and by somatosensory maneuvers seemed to elicit consistent small effect size comparison differences.

Finally to a lesser extent, in both databases, congruent significant differences between groups were found on gender, age, tinnitus annoyance, initial cause of onset linked to a stressful situation and influence of sound on tinnitus : worsening of tinnitus with sounds in some situations, and possibility to mask tinnitus with specific type of sounds.

On the other hand, in both databases, several common features were consistently found not to differentiate between groups : acoustic trauma and presbycusis as initial causes of tinnitus onset, neck and temporomandibular pain prevalences, headache prevalence, tonal or pulsatile forms of tinnitus prevalences.

### 3.2.2. Differences between databases

The only notable incongruence between database group comparisons was found on tinnitus duration comparison.

Group comparison was significant for the Tinnitus longest tinnitus duration. However, in the TRI database, group comparison was not significant and the group reporting worsening of tinnitus following naps was found. Additionally, on several variables, only one database yielded significant differences in group comparison. In fact, a significant difference on tinnitus loudness was found only in the TRI database, although the trend tended to point in the same direction in the Tinnitus Hub survey database.

Moreover, a significant difference in the percentage of time aware of the tinnitus percept, head or neck injury as initial causes of onset of tinnitus and hearing loss were only found in the Tinnitus Hub survey database although, again, the trend pointed in the same direction in the TRI database.

### 3.2.3. Findings in variables unique to TRI database

Among the variables only explored using the TRI database, group comparison was found significant on the side of the tinnitus (with less lateralization for TW compared to TI and NE, above all in the left ear), although results were found not significant for the degree of lateralization. Group comparison also found differences on whether tinnitus was intermittent or continuous (with more intermittent tinnitus in TI and TW compared to NE group), whether it fluctuated from day to day (more variations for TI and TW groups compared to NE group), THI and TQ questionnaire scores (more tinnitus distress in TW group compared to NE group), hyperacusis (more hyperacusis for TI group compared to TW and NE group), physical discomfort when exposed to noise (more discomfort for TI and TW groups compared to NE group), number of treatments tested by participants (more tinnitus treatments tested for TW group compared to NE group), the proportion of participants who tried using hearing aids (more patients of TW group tested hearing aids compared to NE group).

### 3.2.4. Findings in variables unique to Tinnitus Hub survey database

Among the variables only explored by the Tinnitus Hub survey database, group comparison was found significant on ototoxic treatment as the initial cause of onset of tinnitus (with a higher proportion of TW patients reporting it than in the NE group), multiple events in which participants reported ear fullness : after physical activity (with a higher proportion of TW patients reporting it than in the NE group), after a bad sleep (with a small effect size, a higher proportion of TW and TI patients reporting it than in the NE group), after working at a desk (with a higher proportion of TI patients reporting it than in the NE group), after periods of stress (with a small effect size, a higher proportion of TW and TI patients reporting it than in the NE group); the frequency of occurrence of fleeting tinnitus (with a higher proportion of TW and TI patients reporting it than in the NE group); mixture of tones (with a higher proportion of TW patients reporting it than in the NE group) and electric type of noise (with a higher proportion of TW patients reporting it than in the NE group) as tinnitus type of sounds (not tested in the TRI database); influence of anxiety on tinnitus (with a small effect size, a higher proportion of TW and TI patients reporting a worsening of tinnitus with anxiety compared to the NE group); and influence of physical activity for all intensities from light exercise to intense workout (in all cases, more NE group responders reported physical activity had no effect on their tinnitus than in TW and TI).

**Table 2.** Group comparison in the TRI database. Only variables eliciting significant differences after Holm correction were reported. *SD* : Standard Deviation, *TW* : Tinnitus worsens after naps, *NE* : No effect of naps on

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*tinnitus*, *TI* : Tinnitus improves after naps, *THI* : Tinnitus Handicap Inventory, *TQ* : Tinnitus Questionnaire, \* :  $p < 0.05$  before Holm correction, \*\* :  $p < 0.05$  after Holm correction.

	Worsens N= 642	No effect N= 2651	Improves N= 334	Statistic	p - value	Effect size	Post-hoc p-value	Post-hoc effect size
<b>Age (years)</b>				H = 13.2**	0.04	0.003 (Negligible)		
Mean (SD)	61.8 (14.67)	59.4 (13.45)	59.7 (14.6)				TW VS NE	0.012 0.175 (Negligible)
Median [Min Max]	61.5 [21.0, 102.0]	60.0 [18.0, 103.0]	60.0 [21.0, 100.0]				TI VS NE	1.0 0.024 (Negligible)
Missing	0 (0.0%)	2 (0.1%)	0 (0.0%)				TW VS TI	0.52 0.141 (Negligible)
<b>Average loudness</b>				H = 13.5**	0.035	0.003 (Negligible)		
Mean (SD)	66.6 (22.57)	64.4 (22.63)	61.1 (23.43)				TW VS NE	0.52 0.098 (Negligible)
Median [Min Max]	70.0 [0.0, 100.0]	70.0 [0.0, 100.0]	60.0 [0.0, 100.0]				TI VS NE	0.305 0.145 (Negligible)
Missing	27 (4.2%)	85 (3.2%)	7 (2.1%)				TW VS TI	0.01 0.24 (Small)
<b>THI score</b>				H = 53.8**	p < 0.001	0.015 (Small)		
Mean (SD)	53.6 (22.29)	46.8 (23.33)	52.2 (21.75)				TW VS NE	p < 0.001 0.297 (Small)
Median [Min Max]	54.0 [0.0, 100.0]	46.0 [0.0, 100.0]	50.0 [4.0, 100.0]				TI VS NE	0.002 0.236 (Small)
Missing	13 (2.0%)	41 (1.5%)	6 (1.8%)				TW VS TI	1.0 0.064 (Negligible)
<b>TQ score</b>				H = 23.8**	p < 0.001	0.008 (Negligible)		
Mean (SD)	43.9 (17.19)	39.7 (17.91)	41.5 (16.76)				TW VS NE	p < 0.001 0.233 (Small)
Median [Min Max]	44.0 [4.0, 84.0]	39.0 [1.0, 84.0]	41.0 [4.0, 79.0]				TI VS NE	1.0 0.099 (Negligible)
Missing	130 (20.2%)	612 (23.1%)	75 (22.5%)				TW VS TI	1.0 0.14 (Negligible)
<b>How much of a problem is your tinnitus at present? (0 : no problem, 5 : a very big problem)</b>				H = 18.4**	0.004	0.005 (Negligible)		
Mean (SD)	2.6 (0.9)	2.4 (0.89)	2.4 (0.85)				TW VS NE	0.001 0.193 (Negligible)
Median [Min Max]	3.0 [0.0, 4.0]	2.0 [0.0, 4.0]	2.0 [0.0, 4.0]				TI VS NE	1.0 0.014 (Negligible)
Missing	53 (8.3%)	187 (7.1%)	35 (10.5%)				TW VS TI	0.098 0.209 (Small)
<b>How STRONG or LOUD is your tinnitus at present? (0 to 10 scale)</b>				H = 15.2**	0.017	0.004 (Negligible)		
Mean (SD)	6.7 (2.15)	6.4 (2.19)	6.1 (2.23)				TW VS NE	0.353 0.108 (Negligible)
Median [Min Max]	7.0 [0.0, 10.0]	7.0 [0.0, 10.0]	6.0 [0.0, 10.0]				TI VS NE	0.235 0.154 (Negligible)
Missing	34 (5.3%)	98 (3.7%)	24 (7.2%)				TW VS TI	0.005 0.263 (Small)
<b>How UNCOMFORTABLE is your tinnitus at present,</b>				H = 27.9**	p < 0.001	0.007 (Negligible)		

**if everything around you is quiet? (0 to 10 scale)**

Mean (SD)	7.2 (2.23)	7.1 (2.33)	6.4 (2.47)	TW VS NE	1.0	0.059 (Negligible)
Median [Min Max]	8.0 [0.0, 10.0]	8.0 [0.0, 10.0]	7.0 [1.0, 10.0]	TI VS NE	p < 0.001	0.303 (Small)
Missing	33 (5.1%)	104 (3.9%)	25 (7.5%)	TW VS TI	p < 0.001	0.367 (Small)

**How easy is it for you to IGNORE your tinnitus at present? (0 to 10 scale)**

Mean (SD)	7.1 (2.51)	6.9 (2.69)	6.4 (2.71)	H = 14.1**	0.026	0.003 (Negligible)
Median [Min Max]	8.0 [0.0, 10.0]	7.0 [0.0, 10.0]	7.0 [0.0, 10.0]	TW VS NE	1.0	0.082 (Negligible)
Missing	30 (4.7%)	98 (3.7%)	24 (7.2%)	TI VS NE	0.044	0.185 (Negligible)
				TW VS TI	0.008	0.277 (Small)

**Degree of hyperacusis (0 : None, 4 : Very important)**

Mean (SD)	2.3 (1.15)	2.2 (1.21)	2.5 (1.2)	H = 25.5**	p < 0.001	0.007 (Negligible)
Median [Min Max]	2.0 [0.0, 4.0]	2.0 [0.0, 4.0]	2.0 [0.0, 4.0]	TW VS NE	1.0	0.088 (Negligible)
Missing	6 (0.9%)	16 (0.6%)	1 (0.3%)	TI VS NE	p < 0.001	0.291 (Small)
				TW VS TI	0.066	0.211 (Small)

**Tinnitus side**

Right ear	67 (10.5%)	340 (12.9%)	52 (15.6%)	Chi2 = 47.6**	p < 0.001	0.033 (Negligible)
Left ear	77 (12.1%)	449 (17.0%)	61 (18.3%)	TW VS NE	p < 0.001	0.044 (Small)
Both ears, worse in left	167 (26.2%)	553 (21.0%)	67 (20.1%)	TI VS NE	1.0	0.014 (Negligible)
Both ears, worse in right	126 (19.7%)	428 (16.2%)	56 (16.8%)	TW VS TI	0.086	0.03 (Negligible)
Both ears, equally	109 (17.1%)	618 (23.4%)	65 (19.5%)			
Inside the head	91 (14.3%)	250 (9.5%)	32 (9.6%)			
Elsewhere	1 (0.2%)	1 (0.0%)	0 (0.0%)			
Missing	4 (0.6%)	12 (0.5%)	1 (0.3%)			

**Tinnitus cause : psychological (stress, anxiety, depression)**

Yes	257 (46.9%)	1143 (51.5%)	108 (37.5%)	Chi2 = 21.7**	p < 0.001	0.055 (Negligible)
No	291 (53.1%)	1075 (48.5%)	180 (62.5%)	TW VS NE	1.0	0.031 (Negligible)
Missing	94 (14.6%)	433 (16.3%)	46 (13.8%)	TI VS NE	p < 0.001	0.073 (Negligible)
				TW VS TI	0.305	0.042 (Negligible)

**Tinnitus varies from day to day**

Yes	489 (77.1%)	1485 (56.8%)	264 (80.0%)	Chi2 = 136.9**	p < 0.001	0.137 (Small)
No	145 (22.9%)	1128 (43.2%)	66 (20.0%)	TW VS NE	p < 0.001	0.155 (Small)
Missing	8 (1.2%)	38 (1.4%)	4 (1.2%)	TI VS NE	p < 0.001	0.133 (Small)
				TW VS TI	1.0	0.016 (Negligible)

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<b>Tinnitus intermittent or continuous ?</b>				Chi2 = 38.9**	p < 0.073 0.001 (Small)	
Intermittent	112 (17.8%)	307 (11.7%)	74 (22.4%)			TW VS NE 0.002 0.067 (Negligible)
Continuous	517 (82.2%)	2317 (88.3%)	256 (77.6%)			TI VS NE p < 0.001 0.09 (Negligible)
Missing	13 (2.0%)	27 (1.0%)	4 (1.2%)			TW VS TI 1.0 0.027 (Negligible)
<b>Influence of stress over tinnitus</b>				Chi2 = 84.2**	p < 0.076 0.001 (Small)	
Worsens	477 (77.2%)	1742 (67.5%)	294 (89.6%)			TW VS NE p < 0.001 0.057 (Negligible)
Improves	8 (1.3%)	29 (1.1%)	0 (0.0%)			TI VS NE p < 0.001 0.097 (Small)
No effect	133 (21.5%)	809 (31.4%)	34 (10.4%)			TW VS TI p < 0.001 0.057 (Negligible)
Missing	24 (3.7%)	71 (2.7%)	6 (1.8%)			
<b>Sleep at night and tinnitus during the day</b>				Chi2 = 399.0**	p < 0.235 0.001 (Medium)	
Linked	261 (71.5%)	338 (22.8%)	127 (68.6%)			TW VS NE p < 0.001 0.295 (Small)
Not linked	104 (28.5%)	1145 (77.2%)	58 (31.4%)			TI VS NE p < 0.001 0.216 (Small)
Missing	277 (43.1%)	1168 (44.1%)	149 (44.6%)			TW VS TI 1.0 0.01 (Negligible)
<b>Some sounds can worsen tinnitus</b>				Chi2 = 34.4**	p < 0.069 0.001 (Negligible)	
Yes	374 (73.5%)	1407 (66.0%)	242 (81.2%)			TW VS NE 0.048 0.053 (Negligible)
No	135 (26.5%)	725 (34.0%)	56 (18.8%)			TI VS NE p < 0.001 0.086 (Negligible)
Missing	133 (20.7%)	519 (19.6%)	36 (10.8%)			TW VS TI 0.385 0.04 (Negligible)
<b>Some sounds can suppress tinnitus</b>				Chi2 = 15.5**	0.015 0.046 (Negligible)	
Yes	431 (78.9%)	1665 (74.7%)	238 (84.4%)			TW VS NE 0.859 0.033 (Negligible)
No	115 (21.1%)	564 (25.3%)	44 (15.6%)			TI VS NE 0.016 0.058 (Negligible)
Missing	96 (15.0%)	422 (15.9%)	52 (15.6%)			TW VS TI 1.0 0.03 (Negligible)
<b>Some sounds can cause physical discomfort</b>				Chi2 = 14.3**	0.025 0.044 (Negligible)	
Yes	359 (62.7%)	1357 (58.9%)	208 (69.8%)			TW VS NE 1.0 0.026 (Negligible)
No	214 (37.3%)	946 (41.1%)	90 (30.2%)			TI VS NE 0.014 0.059 (Negligible)
Missing	69 (10.7%)	348 (13.1%)	36 (10.8%)			TW VS TI 0.859 0.034 (Negligible)
<b>Somatosensory : Jaw or head movements can modulate tinnitus</b>				Chi2 = 98.6**	p < 0.117 0.001 (Small)	
Yes	325 (51.5%)	835 (32.0%)	153 (46.6%)			TW VS NE p < 0.001 0.152 (Small)
No	306 (48.5%)	1777 (68.0%)	175 (53.4%)			TI VS NE p < 0.001 0.087 (Negligible)
Missing	11 (1.7%)	39 (1.5%)	6 (1.8%)			TW VS TI 1.0 0.023 (Negligible)



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Number of treatment tested				Chi2 = 36.0**	0.003	0.032 (Negligible)		
0 (none)	76 (12.0%)	392 (15.0%)	63 (19.0%)				TW VS NE	0.002 0.039 (Negligible)
One	83 (13.1%)	441 (16.9%)	48 (14.5%)				TI VS NE	1.0 0.021 (Negligible)
2 to 4	175 (27.7%)	776 (29.7%)	92 (27.8%)				TW VS TI	0.175 0.03 (Negligible)
5 and more	148 (23.4%)	453 (17.3%)	67 (20.2%)					
several	42 (6.6%)	102 (3.9%)	8 (2.4%)					
many	108 (17.1%)	453 (17.3%)	53 (16.0%)					
Missing	10 (1.6%)	34 (1.3%)	3 (0.9%)					
Hearing aid user				Chi2 = 24.9**	0.013	0.034 (Negligible)		
right	15 (2.4%)	42 (1.6%)	13 (4.0%)				TW VS NE	0.036 0.039 (Negligible)
left	20 (3.2%)	68 (2.6%)	11 (3.4%)				TI VS NE	0.417 0.03 (Negligible)
both	98 (15.6%)	274 (10.5%)	33 (10.3%)				TW VS TI	1.0 0.025 (Negligible)
none	495 (78.8%)	2220 (85.3%)	264 (82.2%)					
Missing	14 (2.2%)	47 (1.8%)	13 (3.9%)					

**Table 3.** Group comparison in the Tinnitus Hub survey database. Only variables eliciting significant differences after Holm correction were reported. *SD* : Standard Deviation, *TW* : Tinnitus worsens after naps, *NE* : No effect of naps on tinnitus, *TI* : Tinnitus improves after naps, \* :  $p < 0.05$  before Holm correction, \*\* :  $p < 0.05$  after Holm correction.

	Worsens N= 1404	No effect N= 4204	Improves N= 507	Statistic	P-value	Effect size	Post-hoc test	Post-hoc effect size
<b>Age (years)</b>				H = 17.6**	0.009	0.003 (Negligible)		
Mean (SD)	54.0 (14.08)	54.4 (13.6)	51.7 (14.54)				TW VS NE	1.0 0.03 (Negligible)
Median [Min Max]	57.0 [14, 93]	57.0 [6, 96]	54.0 [15, 94]				TI VS NE	0.002 0.197 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)				TW VS TI	0.039 0.161 (Negligible)
<b>Tinnitus duration (months)</b>				H = 16.2**	0.016	0.002 (Negligible)		
Mean (SD)	93.8 (100.93)	106.0 (113.33)	89.0 (105.63)				TW VS NE	1.0 0.11 (Negligible)
Median [Min Max]	52.0 [1.0, 371.0]	59.0 [0.0, 371.0]	42.0 [1.0, 371.0]				TI VS NE	0.007 0.151 (Negligible)
Missing	2 (0.1%)	2 (0.0%)	0 (0.0%)				TW VS TI	0.796 0.047 (Negligible)

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<b>Average annoyance</b>				H = 30.5**	p < 0.005 0.001 (Negligible)		
Mean (SD)	5.9 (2.99)	5.4 (3.06)	5.6 (2.94)			TW VS NE	p < 0.001 0.169 (Negligible)
Median [Min Max]	6.0 [0.0, 10.0]	5.0 [0.0, 10.0]	5.0 [0.0, 10.0]			TI VS NE	1.0 0.054 (Negligible)
Missing	8 (0.6%)	12 (0.3%)	2 (0.4%)			TW VS TI	1.0 0.118 (Negligible)
<b>Annoyance on bad days</b>				H = 24.5**	p < 0.004 0.001 (Negligible)		
Mean (SD)	7.0 (3.2)	6.5 (3.2)	6.6 (3.19)			TW VS NE	p < 0.001 0.138 (Negligible)
Median [Min Max]	8.0 [0.0, 10.0]	7.0 [0.0, 10.0]	7.0 [0.0, 10.0]			TI VS NE	1.0 0.035 (Negligible)
Missing	21 (1.5%)	69 (1.6%)	4 (0.8%)			TW VS TI	0.914 0.103 (Negligible)
<b>% of time aware of tinnitus</b>				H = 26.6**	p < 0.004 0.001 (Negligible)		
Mean (SD)	71.9 (26.17)	67.7 (28.15)	65.9 (26.81)			TW VS NE	p < 0.001 0.15 (Negligible)
Median [Min Max]	76.0 [0, 100]	75.0 [0, 100]	70.0 [0, 100]			TI VS NE	1.0 0.065 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)			TW VS TI	p < 0.001 0.226 (Small)
<b>Frequency of fleeting tinnitus (0 : never, 5 : daily)</b>				H = 60.0**	p < 0.009 0.001 (Negligible)		
Mean (SD)	2.9 (1.82)	2.5 (1.91)	2.8 (1.89)			TW VS NE	p < 0.001 0.228 (Small)
Median [Min Max]	4.0 [0, 5]	3.0 [0, 5]	3.0 [0, 5]			TI VS NE	0.022 0.161 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)			TW VS TI	1.0 0.067 (Negligible)
<b>Gender</b>				Chi2 = 59.6**	p < 0.001 0.07 (Small)		
Male	832 (59.7%)	2031 (48.6%)	291 (57.9%)			TW VS NE	p < 0.001 0.092 (Negligible)
Female	562 (40.3%)	2151 (51.4%)	212 (42.1%)			TI VS NE	0.005 0.05 (Negligible)
Missing	10 (0.7%)	22 (0.5%)	4 (0.8%)			TW VS TI	1.0 0.008 (Negligible)
<b>Tinnitus sound : A mixture of tones</b>				Chi2 = 21.7**	0.001 0.042 (Negligible)		
No	904 (64.4%)	2977 (70.8%)	338 (66.7%)			TW VS NE	p < 0.001 0.057 (Negligible)
Yes	500 (35.6%)	1227 (29.2%)	169 (33.3%)			TI VS NE	1.0 0.024 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)			TW VS TI	1.0 0.011 (Negligible)
<b>Tinnitus sound : electric/interference</b>				Chi2 = 17.3**	0.01 0.038 (Negligible)		
No	1041 (74.1%)	3337 (79.4%)	402 (79.3%)			TW VS NE	0.003 0.052 (Negligible)
Yes	363 (25.9%)	867 (20.6%)	105 (20.7%)			TI VS NE	1.0 0.0 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)			TW VS TI	0.932 0.029 (Negligible)
<b>Tinnitus cause : head or neck injury</b>				Chi2 = 26.0**	p < 0.001 0.046 (Negligible)		

Epidemiology of nap-induced tinnitus modulations

No	1228 (87.5%)	3859 (91.8%)	448 (88.4%)			TW VS NE	p < 0.001	0.061 (Negligible)
Yes	176 (12.5%)	345 (8.2%)	59 (11.6%)			TI VS NE	0.525	0.032 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)			TW VS TI	1.0	0.006 (Negligible)
<b>Tinnitus cause : psychological (stress, anxiety, depression)</b>				Chi2 = 60.1**	p < 0.001			0.07 (Small)
No	1101 (78.4%)	3593 (85.5%)	382 (75.3%)			TW VS NE	p < 0.001	0.079 (Negligible)
Yes	303 (21.6%)	611 (14.5%)	125 (24.7%)			TI VS NE	p < 0.001	0.075 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)			TW VS TI	1.0	0.017 (Negligible)
<b>Tinnitus cause : ototoxicity</b>				Chi2 = 18.1**	0.007			0.038 (Negligible)
No	1212 (86.3%)	3799 (90.4%)	451 (89.0%)			TW VS NE	0.001	0.054 (Negligible)
Yes	192 (13.7%)	405 (9.6%)	56 (11.0%)			TI VS NE	1.0	0.012 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)			TW VS TI	1.0	0.018 (Negligible)
<b>Tinnitus cause : unknown</b>				Chi2 = 18.8**	0.005			0.039 (Negligible)
No	72 (5.1%)	122 (2.9%)	26 (5.1%)			TW VS NE	0.006	0.049 (Negligible)
Yes	1332 (94.9%)	4082 (97.1%)	481 (94.9%)			TI VS NE	0.455	0.033 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)			TW VS TI	1.0	0.0 (Negligible)
<b>Fluctuations of tinnitus</b>				Chi2 = 257.3**	p < 0.001			0.084 (Small)
No fluctuations	268 (19.1%)	1512 (36.0%)	80 (15.8%)			TW VS NE	p < 0.001	0.092 (Small)
Grows louder as day progresses	703 (50.1%)	1782 (42.4%)	218 (43.0%)			TI VS NE	p < 0.001	0.084 (Small)
Grows quieter as day progresses	122 (8.7%)	193 (4.6%)	36 (7.1%)			TW VS TI	p < 0.001	0.039 (Negligible)
Changes within the day or over days without any pattern	311 (22.2%)	717 (17.1%)	173 (34.1%)					
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					
<b>Influence of stress over tinnitus</b>				Chi2 = 292.6**	p < 0.001			0.109 (Small)
Worsens	1128 (80.3%)	2439 (58.0%)	409 (80.7%)			TW VS NE	p < 0.001	0.136 (Small)
No effect	271 (19.3%)	1746 (41.5%)	95 (18.7%)			TI VS NE	p < 0.001	0.09 (Small)
Improves	5 (0.4%)	19 (0.5%)	3 (0.6%)			TW VS TI	1.0	0.007 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					
<b>Influence of anxiety over tinnitus</b>				Chi2 = 317.5**	p < 0.001			0.114 (Small)
Worsens	1090 (77.6%)	2272 (54.0%)	394 (77.7%)			TW VS NE	p < 0.001	0.141 (Small)
No effect	309 (22.0%)	1910 (45.4%)	107 (21.1%)			TI VS NE	p < 0.001	0.095 (Small)

Epidemiology of nap-induced tinnitus modulations

Improves	5 (0.4%)	22 (0.5%)	6 (1.2%)			TW VS TI	1.0	0.019 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					
<b>Influence of a good night sleep over tinnitus</b>				Chi2 = 1373.5**	p < 0.001			0.237 (Medium)
Worsens	476 (33.9%)	272 (6.5%)	24 (4.7%)			TW VS NE	p < 0.001	0.257 (Medium)
No effect	430 (30.6%)	2665 (63.4%)	67 (13.2%)			TI VS NE	p < 0.001	0.21 (Medium)
Improves	498 (35.5%)	1267 (30.1%)	416 (82.1%)			TW VS TI	p < 0.001	0.165 (Small)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					
<b>Influence of poor sleep over tinnitus</b>				Chi2 = 694.5**	p < 0.001			0.169 (Medium)
Worsens	1134 (80.8%)	1844 (43.9%)	379 (74.8%)			TW VS NE	p < 0.001	0.22 (Medium)
No effect	250 (17.8%)	2320 (55.2%)	118 (23.3%)			TI VS NE	p < 0.001	0.123 (Small)
Improves	20 (1.4%)	40 (1.0%)	10 (2.0%)			TW VS TI	0.706	0.026 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					
<b>Some sounds can worsen tinnitus</b>				Chi2 = 20.0**	0.003			0.04 (Negligible)
No	663 (47.2%)	2268 (53.9%)	254 (50.1%)			TW VS NE	p < 0.001	0.055 (Negligible)
Yes	741 (52.8%)	1936 (46.1%)	253 (49.9%)			TI VS NE	1.0	0.02 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)			TW VS TI	1.0	0.014 (Negligible)
<b>Some sounds can reduce tinnitus</b>				Chi2 = 36.6**	p < 0.001			0.055 (Negligible)
No	426 (30.3%)	1002 (23.8%)	167 (32.9%)			TW VS NE	p < 0.001	0.062 (Negligible)
Yes	978 (69.7%)	3202 (76.2%)	340 (67.1%)			TI VS NE	p < 0.001	0.057 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)			TW VS TI	1.0	0.013 (Negligible)
<b>Tinnitus sound masking</b>				Chi2 = 128.7**	p < 0.001			0.046 (Small)
No masking	101 (7.2%)	410 (9.8%)	69 (13.6%)			TW VS NE	p < 0.001	0.058 (Small)
Only a small selection of specific sounds	162 (11.5%)	357 (8.5%)	63 (12.4%)			TI VS NE	p < 0.001	0.033 (Negligible)
Shower / water noises	287 (20.4%)	485 (11.5%)	68 (13.4%)			TW VS TI	p < 0.001	0.033 (Negligible)
TV, Music or general background noise	334 (23.8%)	1291 (30.7%)	135 (26.6%)					
White noise or special masking noises	197 (14.0%)	555 (13.2%)	80 (15.8%)					
Masked by nearly all sounds	323 (23.0%)	1106 (26.3%)	92 (18.1%)					
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					
<b>Influence of intense workout over tinnitus</b>				Chi2 = 252.2**	p < 0.001			0.102 (Small)
Worsens	424 (30.2%)	645 (15.3%)	126 (24.9%)			TW VS NE	p < 0.001	0.121 (Small)
No effect	847	3282	295			TI VS	p < 0.001	0.096 (Small)

Epidemiology of nap-induced tinnitus modulations

	(60.3%)	(78.1%)	(58.2%)				NE	
Improves	133 (9.5%)	277 (6.6%)	86 (17.0%)				TW VS TI	p < 0.001 0.043 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					
<b>Influence of moderate workout over tinnitus</b>				Chi2 = 326.7**	p < 0.001	0.116 (Small)		
Worsens	423 (30.1%)	584 (13.9%)	117 (23.1%)				TW VS NE	p < 0.001 0.135 (Small)
No effect	801 (57.1%)	3219 (76.6%)	267 (52.7%)				TI VS NE	p < 0.001 0.11 (Small)
Improves	180 (12.8%)	401 (9.5%)	123 (24.3%)				TW VS TI	p < 0.001 0.056 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					
<b>Influence of light exercise over tinnitus</b>				Chi2 = 320.8**	p < 0.001	0.115 (Small)		
Worsens	231 (16.5%)	284 (6.8%)	59 (11.6%)				TW VS NE	p < 0.001 0.113 (Small)
No effect	937 (66.7%)	3424 (81.4%)	278 (54.8%)				TI VS NE	p < 0.001 0.13 (Small)
Improves	236 (16.8%)	496 (11.8%)	170 (33.5%)				TW VS TI	p < 0.001 0.072 (Small)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					
<b>Somatosensory change : pressing the jaw on the side</b>				Chi2 = 48.3**	p < 0.001	0.063 (Negligible)		
No	1121 (79.8%)	3670 (87.3%)	422 (83.2%)				TW VS NE	p < 0.001 0.087 (Negligible)
Yes	283 (20.2%)	534 (12.7%)	85 (16.8%)				TI VS NE	0.564 0.032 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)				TW VS TI	1.0 0.02 (Negligible)
<b>Somatosensory change : pushing jaw backwards</b>				Chi2 = 24.2**	p < 0.001	0.044 (Negligible)		
No	1151 (82.0%)	3667 (87.2%)	439 (86.6%)				TW VS NE	p < 0.001 0.062 (Negligible)
Yes	253 (18.0%)	537 (12.8%)	68 (13.4%)				TI VS NE	1.0 0.004 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)				TW VS TI	0.837 0.03 (Negligible)
<b>Somatosensory change : Pushing the jaw outwards rapidly</b>				Chi2 = 37.8**	p < 0.001	0.056 (Negligible)		
No	1022 (72.8%)	3385 (80.5%)	404 (79.7%)				TW VS NE	p < 0.001 0.078 (Negligible)
Yes	382 (27.2%)	819 (19.5%)	103 (20.3%)				TI VS NE	1.0 0.005 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)				TW VS TI	0.131 0.038 (Negligible)
<b>Somatosensory change : Pushing your hand against your forehead while resisting with the neck muscles</b>				Chi2 = 22.9**	p < 0.001	0.043 (Negligible)		
No	1094 (77.9%)	3513 (83.6%)	418 (82.4%)				TW VS NE	p < 0.001 0.061 (Negligible)
Yes	310	691	89				TI VS	1.0 0.007 (Negligible)

Epidemiology of nap-induced tinnitus modulations

	(22.1%)	(16.4%)	(17.6%)					NE	
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					TW VS TI	1.0 0.027 (Negligible)
<b>Somatosensory change : clenching teeth</b>				Chi2 = 32.1**	p < 0.051 0.001 (Negligible)				
No	1006 (71.7%)	3313 (78.8%)	377 (74.4%)					TW VS NE	p < 0.001 0.07 (Negligible)
Yes	398 (28.3%)	891 (21.2%)	130 (25.6%)					TI VS NE	0.932 0.029 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					TW VS TI	1.0 0.014 (Negligible)
<b>Somatosensory change : Tilting your head backwards</b>				Chi2 = 34.7**	p < 0.053 0.001 (Negligible)				
No	1132 (80.6%)	3656 (87.0%)	424 (83.6%)					TW VS NE	p < 0.001 0.074 (Negligible)
Yes	272 (19.4%)	548 (13.0%)	83 (16.4%)					TI VS NE	1.0 0.026 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					TW VS TI	1.0 0.018 (Negligible)
<b>Somatosensory change : no change with any of these actions</b>				Chi2 = 62.4**	p < 0.071 0.001 (Small)				
No	734 (52.3%)	1703 (40.5%)	241 (47.5%)					TW VS NE	p < 0.001 0.098 (Negligible)
Yes	670 (47.7%)	2501 (59.5%)	266 (52.5%)					TI VS NE	0.132 0.038 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					TW VS TI	1.0 0.023 (Negligible)
<b>Ear fullness : after activity mainly</b>				Chi2 = 28.4**	p < 0.048 0.001 (Negligible)				
No	1309 (93.2%)	4058 (96.5%)	480 (94.7%)					TW VS NE	p < 0.001 0.066 (Negligible)
Yes	95 (6.8%)	146 (3.5%)	27 (5.3%)					TI VS NE	1.0 0.025 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					TW VS TI	1.0 0.013 (Negligible)
<b>Ear fullness : after a bad sleep</b>				Chi2 = 72.7**	p < 0.077 0.001 (Small)				
No	1250 (89.0%)	3994 (95.0%)	452 (89.2%)					TW VS NE	p < 0.001 0.1 (Small)
Yes	154 (11.0%)	210 (5.0%)	55 (10.8%)					TI VS NE	p < 0.001 0.068 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					TW VS TI	1.0 0.0 (Negligible)
<b>Ear fullness : after working at a computer or desk</b>				Chi2 = 22.5**	p < 0.043 0.001 (Negligible)				
No	1355 (96.5%)	4101 (97.5%)	476 (93.9%)					TW VS NE	1.0 0.025 (Negligible)
Yes	49 (3.5%)	103 (2.5%)	31 (6.1%)					TI VS NE	p < 0.001 0.058 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)					TW VS TI	0.706 0.031 (Negligible)
<b>Ear fullness : after periods of stress / anxiety</b>				Chi2 = 85.3**	p < 0.084 0.001 (Small)				

## Epidemiology of nap-induced tinnitus modulations

No	1129 (80.4%)	3700 (88.0%)	386 (76.1%)		TW VS NE	p < 0.001	0.091 (Negligible)
Yes	275 (19.6%)	504 (12.0%)	121 (23.9%)		TI VS NE	p < 0.001	0.094 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)		TW VS TI	1.0	0.025 (Negligible)
<b>No ear fullness</b>				Chi2 = 42.3**	p < 0.001	0.059 (Negligible)	
No	907 (64.6%)	2386 (56.8%)	343 (67.7%)		TW VS NE	p < 0.001	0.066 (Negligible)
Yes	497 (35.4%)	1818 (43.2%)	164 (32.3%)		TI VS NE	p < 0.001	0.059 (Negligible)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)		TW VS TI	1.0	0.015 (Negligible)

## 4. Discussion

Both databases showed that the majority of participants did not experience any influence on tinnitus by a nap. The sample characteristics of both databases on this criterion were similar to the ones reported in [12] on another large tinnitus sample (TW: 16.4%, NE: 70.7%, TI: 12.9%) and in [31] on a smaller sample (TW: 23.5%, NE: 64.7%, TI: 11.8%). This could be indicative of a subphenotype with influence of nap on tinnitus, which is found in about 30% of the burdened people with tinnitus. It is noteworthy that in all three data sets, the proportion experiencing worsening of tinnitus from napping is higher than that experiencing improvement of tinnitus. In general rule, our results suggest that one out of five tinnitus sufferers reports increase of tinnitus after naps, while only one out of ten reports an improvement of tinnitus following a nap. It seems surprising that a potentially restorative measure such as a nap has the opposite effect on tinnitus in a certain proportion of people with tinnitus.

In general, it is known that a nap can have divergent effects on health and performance. Some studies show positive effects of napping such as improved alertness, physical and cognitive performance [32–34]. Others, however, show negative effects of napping such as an association with obesity, chronic diseases and overall mortality [35–37]. Particularly noteworthy in this context is a meta-analysis, the results of which suggest that a nap probably increases the risk of depression [38]. Although the results were quite heterogeneous, which was attributed, among other things, to the characteristics of the subject sample, but also to the nap pattern (e.g., duration, frequency, time), genetic aspects, inflammation and hyperactivity of the HPA axis were discussed as underlying mechanisms for the relationship between naps and the risk of depression. On the other hand, depressive symptoms occur frequently in tinnitus patients in clinical settings with a mean prevalence of 33% [39] and have a significant influence on the level of suffering [40,41], with the extent of depressive symptoms contributing significantly to tinnitus severity [42] and tinnitus severity increasing the likelihood of the presence of depressive symptoms [43]. Accordingly, for a certain proportion of tinnitus sufferers, naps could also increase tinnitus severity by increasing on the long run the risk of depression. It should be emphasized that in the present study the nap was not characterized in more detail in terms of duration, frequency or timing, although according to the available literature these aspects are probably important in terms of benefit or harm to health [44,45]. As such, it is also conceivable that the different effects in the study group are due to different characteristics of naps.

Sample characteristics comparison between databases revealed that they differed on the majority of common items. Such differences between samples collected in a clinical environment and samples collected on an online platform on tinnitus have already been reported in the past [29]. It is reassuring to note that the specificities found for the TW, NE and TI populations were vastly congruent between databases despite the general sample characteristics were found significantly different between the two databases (as shown in Table 1). Notably, such specificities were congruent on age, gender, somatosensory maneuvers, initial cause of onset linked to a stressful situation and influence of sound on tinnitus (worsening and suppressing). Having such congruent findings in two databases collected in two different contexts (online community and clinical environment) and with initial sample differences reflects high ecological validity and robustness of our findings.

In both databases, the largest effect sizes were shown in the group comparison for sleep variables. From this it can be deduced that in people whose tinnitus is modulated by a nap, night sleep is also often an influencing factor on tinnitus. Our data also show that a considerable proportion of tinnitus patients do not experience any influence of night sleep on

their tinnitus. While in the TRI database only an influence of night sleep on tinnitus was asked, in the Tinnitus Hub survey database a differentiation of the influence of good or poor night sleep was made, whereby significant group differences were found. Remarkably, in the group TW 33.9% stated to experience a worsening of tinnitus by good night sleep. In NE this was only 6.5% and in TI only 4.7%. In parallel, in TW, the group experiencing worsening of tinnitus due to poor sleep was the largest with 80.8% compared to 43.9% in group NE and 74.8% in group TI, respectively. This implies that tinnitus in group TW is particularly sensitive to change. It is possible that the response pattern of group TW also reflects the clinically known phenomenon for night sleep referred to by "morning roar". This means that tinnitus patients perceive the tinnitus in the morning after waking up as particularly loud and stressful, which is often attributed by the affected persons to the night sleep [46]. Nevertheless, 55.2% of the NE group stated that even poor sleep had no effect on the tinnitus, which could be an expression of a certain resilience to negative influences. Sleep disturbances have long been considered a symptom of tinnitus, with disturbed sleep being associated with higher tinnitus burden [47–53]. Additionally, some sleep disorders, such as sleep apnea, snoring and night terrors have been reported to be highly co-prevalent with tinnitus [54–57]. More modern concepts postulate a bidirectional relationship between sleep disturbances and higher tinnitus burden, analogous to other disorders such as PTSD or depression [58,59]. In this context, sleep satisfaction represents an important marker for tinnitus burden but also for global health [60]. Different studies show that sleep interventions can improve tinnitus and tinnitus interventions improve sleep [61–65]. However, to date, there is only little evidence on how sleep modulates tinnitus [18,66]. The available data suggest that sleep can also have a negative effect on tinnitus and, in principle, opposite effects such as good night sleep leading to worsening of tinnitus are possible. At the same time, the data suggest that only a subset of people with tinnitus experience modulation by sleep, which could be an expression of general resilience in the NE group or increased sensitivity to change by external influences in the others. Alternatively, specific mechanisms in sleep could have an influence on tinnitus analogous to conditions such as PTSD, in which specific mechanisms, such as REM sleep fragmentation, contribute significantly to the development and maintenance of the disorder [58]. For further clarification, polysomnographic examinations with correlation of tinnitus and sleep recordings over several days would be necessary, which is costly and would require great effort. Only a case report of such an attempt has been reported to date in the appendix of [18]. Reported findings are a correlation between Rapid Eye Movement (REM) sleep duration and overnight tinnitus modulation, as well as a correlation between snoring amount during the night and overnight tinnitus modulation.

In both databases, the influence of distress on tinnitus was more amplified in the TW and TI compared to NE. For many years, the co-activation of non-specific stress networks has been considered to play an important role in the development of tinnitus distress [67,68]. On the other hand, stress-induced mechanisms such as disrupted cortical networks, dysregulation in the autonomic nervous system, and changes in central serotonin and the HPA axis may play an important role in the development of sleep disorders [69–71]. Reactivity concepts in terms of vulnerability models have been developed for both sleep and stress [72,73]. This means the extent to which an individual reacts to stress exposure with stress reactions or disturbed sleep. An important link is hyperarousal, which plays a significant role in both tinnitus and insomnia [74]. Hyperarousal is related to increased activation of the sympathetic nervous system and accompanied by enhanced activity in limbic and autonomic areas of the brain [75]. Overall, it can be postulated that the influence of stress on the interplay between tinnitus and sleep is modulated via the individual sleep or stress reactivity outlined above, and the absence of influence of stress on tinnitus in a subgroup could be an expression of increased resilience.

The more frequent influence of stress on tinnitus in TW and TI groups could tend to suggest specific influence of serotonergic drive on central auditory circuits supporting tinnitus. In fact, serotonergic excitatory drive from the Dorsal Raphe Nucleus (DRN) has already been suggested as a potential modulator of tinnitus [67,76,77]. Some studies suggest that the increased prevalence of depression in the tinnitus population might be linked to alterations in the serotonergic system [77,78]. Since then, some studies analyzed serotonin characteristics in the tinnitus population, and found diverging results both for blood (hence peripheral) serotonin measurements [79–81] and central serotonin correlates [82–84]. Yet, these studies made their measurements on the whole tinnitus population without accounting for its intrinsic heterogeneity [85], hence what has not been revealed to hold true for the whole tinnitus population may be true for some of its subgroups, such as TW or TI. In fact, it is well-known that serotonergic activity fluctuates between wake and sleep and within sleep stages, notably with REM [86–89]. Notably, such modulations have also been reported to happen sometimes during naps [90]. An additional congruent interesting observation is that physical activity also modulates specifically more tinnitus in TI and TW populations. It has been reported in past studies that the serotonergic system is particularly involved during physical activity and fatigue following physical activity [91,92]. Such a possible modulation of tinnitus by the serotonergic system should be more closely investigated in future clinical



studies. Serotonin is already one of the biomarkers that has been repeatedly studied in relation to prognosis and severity of tinnitus. Nevertheless, the exact role of serotonin in tinnitus has not yet been clarified [93]. Another finding in both databases is the greater proportion of responders experiencing somatosensory modulations of their tinnitus in the TW group. Such observation suggests a potential link between these phenomena, as anecdotally suggested in past reviews [16–18]. A potential explanation of this association could be that increases in tinnitus following naps could actually be somatosensory increases of tinnitus following muscular events occurring during the nap, only perceived upon awakening. One could hypothesize that the TW population often experience bruxism events during naps, thus sending nociceptive signals from the trigeminal-innervated masticatory muscles to the spinal trigeminal nucleus, which would then in turn excite the cochlear nuclei, as described in [94]. It is important to note that such a scenario is yet to be confirmed as the TW group did not show higher jaw pain complaints compared to the other groups in the Tinnitus Hub survey database, and bruxism and jaw pain complaints have shown to be minimally correlated in the general population [95,96]. Another possibility would be that tinnitus sufferers from the TW population often experience sleep apnea and/or snoring events during their sleep. Such events most often involve the soft palate zone and most specifically the Tensor Veli Palatini muscle (TVP) [97], which is another muscle innervated by the trigeminal nerve. It has been reported that a proliferation of nociceptors in the soft palate occur in case of chronic sleep apnea and snoring occurrences [98], as well as an increase of density of the noradrenergic terminals in the trigeminal sensory nuclei in animals subjected to chronic intermittent hypoxia [99]. Such hypersensitivity could increase the risk of somatosensory modulations. Repeated activations of the TVP caused by apnea or snoring events during naps could then trigger a somatosensory modulation of tinnitus upon awakening. A correlation between overnight duration of snoring and overnight modulation of tinnitus has been reported in the 7-night polysomnography longitudinal case report in appendix of [18]. These hypotheses are worth further future investigation and should be tested by polysomnographic or polygraphic investigations.

A set of specific observations in the TI population may highlight a possible explanation to the improvements they report following naps. In fact, we observe that TI patients have a higher prevalence of hyperacusis symptoms than the TW and NE groups (in the TRI database), they also report more often pain and/or discomfort when exposed to sounds and their tinnitus worsens with sound exposition. From these observations, it could be hypothesized that by taking a nap in a calm and quiet environment it would appear logical that such patients report improvements in their symptoms. On the other hand, it is remarkable to observe that regarding the TW population, there are a lot of factors that seem to be able to increase tinnitus : stress, sleep, physical activity, sound exposition and somatosensory modulations. Such observation tends to highlight a global hypersensitivity of a subgroup of tinnitus patients to external stimuli.

#### Limitations:

It should be noted that for common items in both databases, wording of the questions and associated possible answers often varied between databases. Even if best possible matching was done to prevent discrepancies, part of divergences between the characteristics of the TW, NE and TI populations between databases may at least partly stem from these wording differences. However, the largely consistent results from the two databases in spite of differences in population characteristics and wording of questions underscores the robustness of our findings. Besides, by comparing the average scores of each group for all questionnaire items, an implicit assumption was made that there were no distinct subgroups of patients within the TI, TW and NE populations. Specific additional analyses should be conducted to study whether or not there is heterogeneity within the TI, TW and NE groups. Such analyses could take the form of a cluster analysis and may bring more insights on the question of whether TW and/or TI groups are composed of patients who developed tinnitus due to only one or several different pathophysiological mechanisms.

## 5. Conclusions

In this retrospective comparative study of two large samples with 9,742 participants, the influence of napping on tinnitus was systematically investigated for the first time. Consistent with previous data, only a minority reported that tinnitus could be influenced by naps, with significantly more in this group reporting a negative than a positive influence on tinnitus.

The influence of napping on tinnitus was associated in both databases with the modulation of tinnitus intensity by night sleep quality, by stress, by somatosensory maneuvers and physical activity. Group TI showed an association with sound sensitivity, hyperacusis and pain, suggesting that taking a nap combined with resting in a calm and quiet environment may improve symptoms. The TW group showed an association with general hypersensitivity to tinnitus, which may be modulated by multiple factors such as distress, sleep, physical activity, noise exposure or

somatosensory modulation. Possible underlying mechanisms of nap modulation on tinnitus were discussed but cannot be conclusively clarified.

Although the two groups were recruited very differently, very similar results were found regarding group distribution and the association of other influencing factors. Accordingly, the risk of a sample bias is minimized and the findings can be considered as robust.

Future studies should use polysomnography to investigate the phenomenon of nap modulation in tinnitus patients to better understand the underlying mechanisms and also the divergent effect. In this context, the potential role of the central serotonin system in modulation should also be investigated, as well as the complex interaction of somatosensory and nap modulation on tinnitus.

Likewise, further research may focus on the potential heterogeneity within each of these groups.

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki, and approved for the Tinnitus Hub survey database by the Ethics Committee of the Antwerp University Hospital, reference number : 19-43-485. It was approved for the TRI database by the Ethics Committee of the University of Regensburg, protocol number 08/046.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The code used to perform this analysis is accessible on the GitHub open-source repository at this URL : [https://github.com/RobinGuillard/TinniNap\\_DB\\_study](https://github.com/RobinGuillard/TinniNap_DB_study) The TRI data presented in this study are available on reasonable request from the corresponding author. The Tinnitus Hub survey database is available on reasonable request to Tinnitus Hub and S.M.

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# Chapter 5

## Polysomnographic explorations



## 5. Polysomnographic explorations of the SIT and TIAN populations

In the last chapter we explored the symptomatologic characteristics of the patients subjected to NITM. To go further in the investigation of the physiological correlates of such sleep-induced modulations of the tinnitus percept, we conducted two polysomnographic studies.

### 5.1 A comparative one-night polysomnographic assessment of SIT patients versus matched controls

In this study our goal was to explore the specific polysomnographic characteristics of SIT patients during night sleep. To this end, we designed a comparative study between a group of SIT patients and a group of matched controls (tinnitus patients without sleep-induced tinnitus modulations, matched on age, sex and self-reported degree of hearing loss). Each patient of each group went through one night of full polysomnographic assessment. Tinnitus loudness and intrusiveness were measured before and after the night to quantify overnight tinnitus modulation. Polysomnographic characteristics such as sleep architecture as well as the occurrence of sleep disorder events (bruxism events, sleep apnea events). An additional goal of this study was to assess potential correlations between each polysomnographic characteristic and overnight tinnitus modulation within each group.

We present as an appendix the case report of a SIT patient who underwent seven nights of longitudinal polysomnographic assessment. We also try to draw correlations between the longitudinal polysomnographic characteristics of this patient and the associated overnight tinnitus modulation.



## Article

# REM Sleep Impairment May Underlie Sleep-Driven Modulations of Tinnitus in Sleep Intermittent Tinnitus Subjects: A Controlled Study

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**Abstract:** (1) Background: Poor sleep and fragmented sleep are associated with several chronic conditions. Tinnitus is an auditory symptom that often negatively combines with poor sleep and has been associated with sleep impairment and sleep apnea. The relationship between tinnitus psychoacoustic characteristics and sleep is still poorly explored, notably for a particular subgroup of patients, for whom the perceived loudness of their tinnitus is highly modulated by sleep. (2) Methods: For this observational prospective study, 30 subjects with tinnitus were recruited, including 15 “sleep intermittent tinnitus” subjects, who had reported significant modulations of tinnitus loudness related to night sleep and naps, and a control group of 15 subjects displaying constant non-sleep-modulated tinnitus. The control group had matching age, gender, self-reported hearing loss grade and tinnitus impact on quality of life with the study group. All patients underwent a polysomnography (PSG) assessment for one complete night and then were asked to fill in a case report form, as well as a report of tinnitus loudness before and after the PSG. (3) Results: “Sleep Intermittent tinnitus” subjects had less Stage 3 sleep ( $p < 0.01$ ), less Rapid-Eye Movement (REM) Sleep ( $p < 0.05$ ) and more Stage 2 sleep ( $p < 0.05$ ) in proportion and duration than subjects from the control group. In addition, in the “sleep Intermittent tinnitus” sample, a correlation was found between REM sleep duration and tinnitus overnight modulation ( $p < 0.05$ ), as well as tinnitus impact on quality of life ( $p < 0.05$ ). These correlations were not present in the control group. (4) Conclusions: This study suggests that among the tinnitus population, patients displaying sleep-modulated tinnitus have deteriorated sleep quality. Furthermore, REM sleep characteristics may play a role in overnight tinnitus modulation. Potential pathophysiological explanations accounting for this observation are hypothesized and discussed.

**Keywords:** sleep intermittent tinnitus; sleep; REM; polysomnography; sleep apnea

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## 1. Introduction

Poor sleep has been associated with the onset or worsening of several chronic conditions [1–4]. Notably, insufficient sleep and poor sleep quality often seem to interact with the chronic condition creating an aggravating vicious circle, as described, for instance, in the case of type 2 diabetes [5], obesity and cardiovascular diseases [6]. Such a mutually reinforcing negative dynamic has also been described for poor sleep quality and tinnitus [7–10]. Tinnitus is defined as “the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source” [11]. This chronic condition is highly prevalent, affecting approximately 14% of the world population, 2% of which are affected in an intrusive and debilitating fashion [12].

Regarding sleep and tinnitus, several authors have shown an association between subjective insomnia and tinnitus [13–16]. In a specific review [17], Asnis et al. highlight

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that although insomnia is strongly co-prevalent with tinnitus, too few studies give details on which sleep characteristics (difficulty falling asleep, awakenings during the night and early morning awakening) are more typically associated with it [14,18–23]. A couple of these studies reported that all aspects of insomnia were present in tinnitus patients, most severely, the difficulty in falling asleep [18,19].

Several studies have also objectively analyzed the sleep of tinnitus patients through polysomnography (PSG) [24–30]. These studies converged on the fact that objective sleep is impacted in tinnitus patients [26]. Two of these studies found that Rapid-Eye Movement (REM) sleep in tinnitus patients was significantly reduced [25,27]. One study was performed on a selected tinnitus patient population that concomitantly suffered from Post-Traumatic Stress Disorder (PTSD). It concluded that REM sleep proportion and duration were inversely correlated with Tinnitus Functional Index (TFI) scores [30]. Another found that the electroencephalography (EEG) delta-band power of tinnitus patients was reduced compared to that of the control group [24]. A fifth found that sleep efficiency and total sleep time were significantly reduced for tinnitus patients, and the number of awakenings significantly increased [29]. In order to explain this multiform phenomenon, two publications theorized that sleep impairment and tinnitus could share a common mechanism based on the hyperarousal theory [10,31].

Additionally, several studies have tried to evaluate the co-prevalence of tinnitus with known sleep disorders, such as bruxism [32,33], sleep apnea [34,35], periodic limb movements during sleep [36], snoring [28] and night terrors [37]. These studies highlighted the strong co-prevalence between tinnitus, bruxism and sleep apnea.

A vast majority of these publications, whether focusing on sleep impairment or sleep disorders and tinnitus, analyzed these sleep characteristics in the tinnitus population without restrictively selecting a specifically homogeneous population, although it has been repeatedly suggested that tinnitus is a very heterogeneous symptom [38–41]. Keeping in mind that tinnitus is a highly heterogeneous condition, it is very unlikely that its interactions with sleep are consistent in all subgroups of tinnitus patients, as it is unlikely that a one-size-fits-all solution would be expected for such a highly heterogeneous symptom [42–44]. This is why studies aiming at understanding how sleep is impacted for some specific homogeneous tinnitus subpopulations may yield more decisive results.

Within the tinnitus population, there are two overlapping groups of patients for whom sleep plays a key role in their symptomatology. The first group describes significant and durable elevations of the tinnitus perceived loudness when awakening from naps [45,46]. This fact has been quite noticeable in clinical practice, as demonstrated by the fact that multiple studies have included this feature in their questionnaires [47–49]. A second, less numerous group of patients has been described in the scientific literature as “intermittent tinnitus” [50,51]; these patients display very significant modulations of tinnitus loudness after a night’s sleep. In this paper, this former group is referred to as sleep Intermittent tinnitus (SIT). They are specifically differentiated from patients exhibiting intermittent tinnitus, where the onset and offset of tinnitus are not linked to sleep occurrences. Such patients report that each day, upon awakening, the loudness of their tinnitus is assigned to a high or a low level, in a pseudo-cyclic pattern of 2 to 7 days or even a month in rare cases, and that this level of tinnitus loudness remains stable until the following sleep occurrence (night or nap), after which it may change again. In some cases, these patients report the complete disappearance of their tinnitus on certain days. This tinnitus subgroup also reports that if they have a nap on days when they have a low (or absent) tinnitus, there is a high probability that their tinnitus activates or increases in loudness upon awakening. Sleep fragmentation is also a common complaint in this subgroup of patients, which complains of frequent awakenings caused by their tinnitus onset.

In this second subgroup of SIT patients, sleep and its alteration seem to play a significant role in the modulation of tinnitus loudness, yet it has been poorly described and even less explored quantitatively. Therefore, the aim of our study is to assess the PSG sleep

characteristics of this SIT population, compare them with subjects having stable tinnitus and explore links between PSG characteristics and tinnitus sleep-induced modulations.

## 2. Materials and Methods

### 2.1. Participants

Two cohorts of, respectively, 15 SIT patients (mean  $\pm$  standard deviation age: 50.67 $\pm$  10.83, 10 men, 5 women) and 15 stable, permanent chronic tinnitus forming the control group of patients (48.67 $\pm$  13.26, 9 men, 6 women) and referred hereafter as Non-SIT group, were recruited to participate for a one-night polysomnography examination at Hôtel-Dieu hospital sleep department (VIFASOM) in Paris, France. Most of these patients were recruited by ENT doctor A. L. Some spontaneously enrolled in the study after a communication was made on social media platforms with the help of both the French patient tinnitus association France-Acouphènes and the mutual help digital community Siopi [52].

In both cohorts, patients had chronic tinnitus (over 6 months duration) and had either no tinnitus treatment or had a stable treatment for at least 3 months. Patients with Menière disease, acoustic schwannoma or pulsatile tinnitus were excluded from the study, as well as patients who reported epilepsy seizures and non-stabilized metabolic or cardiovascular conditions.

The SIT patients were all selected after thorough anamnesis with the investigators, the distinctive core trait of their tinnitus being that they all described strong modulations in relation to their sleep. Conversely, Non-SIT patients displayed stable non-fluctuating tinnitus without any modulation induced by night sleep or naps.

To the best of our ability, gender, age, and tinnitus intrusiveness measured by the THI and self-declared hearing loss grade were matched between groups. The etiological characteristics of each arm are presented in Table 1.

**Table 1.** Sample characteristics.

	SIT Group (n = 15)	Non-SIT Group (n =15)	p-Value	Effect Size
	Mean (Std)	Mean (Std)		
Gender ratio (W = 1; M = 0)	0.33 (0.47)	0.4 (0.49)	0.73	
Age (years)	50.67 (10.83)	48.67 (13.26)	0.71	
THI score (0 - 100)	54.4 (18.59)	47.87 (25.61)	0.38	
VAS score on tinnitus intensity (0, 10)	6.29 (1.67)	6.6 (1.54)	0.47	
VAS score on tinnitus annoyance (0, 10)	7.5 (1.64)	6.47 (2.31)	0.33	
Tinnitus pitch (High: 0, Medium: 0.5, Low: 1)	0.13 (0.34)	0.16 (0.35)	0.7	
Tinnitus lateralisation (Bilateral: 0, Partly lateral: 0.5, Unilateral: 1)	0.43 (0.32)	0.3 (0.4)	0.27	
Hearing loss grade (No: 0, Mild: 1, Medium: 2; Severe: 3)	0.73 (0.68)	0.87 (0.96)	0.95	
Have used or are using hearing aids (Yes: 1, No: 0)	0.47 (0.5)	0.53 (0.5)	0.74	
Tinnitus increases after naps (Strongly: 1, Mildly: 0.5, No: 0)	0.87 (0.29)	0.07 (0.17)	<0.01 **	3.499
Masked by noisy environment ? (Yes: 1, No: 0)	0.47 (0.5)	0.47 (0.5)	1.0	
Masked by white noise ? (Yes: 1, No: 0)	0.47 (0.5)	0.8 (0.4)	0.07	-0.712
Tinnitus raises with long noise exposure (Yes: 1, No: 0)	0.23 (0.36)	0.37 (0.43)	0.41	
Tinnitus raises with loud noise (Yes: 1, No: 0)	0.1 (0.2)	0.43 (0.44)	0.03 *	-0.938
Are daily noises uncomfortable ? (Yes: 1, No: 0)	0.53 (0.5)	0.6 (0.49)	0.74	
Is powerful noise exposure painful ? (Yes: 1, No: 0)	0.47 (0.5)	0.6 (0.49)	0.49	
Jaw stiffness in the morning (Frequency gradation)	0.47 (0.81)	0.53 (0.88)	0.94	
Jaw clenching during the day (Frequency gradation)	1.0 (1.32)	0.4 (0.8)	0.2	0.532
Facial pain or jaw pain (Frequency gradation)	0.73 (1.0)	0.4 (0.8)	0.29	

**Table 1.** *Cont.*

	SIT Group (n = 15)	Non-SIT Group (n = 15)	p-Value	Effect Size
	Mean (Std)	Mean (Std)		
Facial or jaw muscle fatigue (Frequency gradation)	0.6 (0.88)	0.13 (0.5)	0.08	0.631
Jaw popping (Frequency gradation)	0.67 (1.14)	0.67 (1.01)	0.88	
Headaches/migraine (Frequency gradation)	0.6 (0.95)	1.0 (1.15)	0.37	
Neck pain (Frequency gradation)	1.47 (1.54)	1.6 (1.08)	0.79	
Neck stiffness/hypomobility (Frequency gradation)	0.27 (0.77)	1.27 (1.24)	<0.01 **	-0.937
Ear fullness (Frequency gradation)	1.07 (1.06)	0.87 (1.2)	0.62	
Autophony (Frequency gradation)	0.13 (0.5)	0.4 (0.8)	0.31	
Otalgia (Frequency gradation)	0.6 (1.14)	0.73 (1.34)	0.94	
Sleep duration (<6 h: -1, 6-8 h: 0, >8 h: 1)	0.07 (0.57)	-0.07 (0.57)	0.55	
Self reported insomnia (Yes: 1, No: 0)	0.4 (0.49)	0.13 (0.34)	0.11	0.611
Hard to stay asleep (Yes: 1, No: 0)	0.6 (0.49)	0.6 (0.49)	1.0	
Hard to fall asleep (Yes: 1, No: 0)	0.27 (0.44)	0.47 (0.5)	0.27	
Snoring (Yes: 1, No: 0)	0.73 (0.44)	0.4 (0.49)	0.07	0.69

Std: standard deviation, Frequency gradation: (Always: 4, Often: 3, Sometimes: 2, Rarely: 1, Never: 0), \*:  $p < 0.05$ , \*\*:  $p < 0.01$ .

All patients gave their informed consent to participate in the present clinical trial, which received approval from the ethical committee on insomnia and artificial intelligence (CPP Idf2 2018 A01034-51).

One subject manifested the desire to go deeper in the exploration of his sleep and volunteered to perform six additional nights of polysomnographic measurements. The longitudinal exploration of this subject's sleep and associated tinnitus modulation is presented as a case report in Appendix A.

## 2.2. Clinical Assessment

### 2.2.1. Anamnesis Case Report Form

The participants of both arms completed an exhaustive Case Report Form (CRF). This CRF included questions about tinnitus modulations over time, its somatosensory modulations, history of comorbidities and associated pain symptoms (jaw, cervical area and headaches). It also contained screening questions on sleep disorders and how tinnitus was modulated according to night sleep and naps. Lastly, this CRF also included the Tinnitus Handicap Inventory (THI). The THI is a 25-item questionnaire yielding a score between 0 and 100 classically used in tinnitus clinical studies to assess the impact of tinnitus on quality of life [53]. The main clinical characteristics of both samples are presented in Table 1.

### 2.2.2. Overnight Tinnitus Variation Assessment

All participants filled out two short questionnaires on the night of their polysomnographic recording; one before going to bed and a second one shortly after awakening. These two questionnaires assessed tinnitus loudness and its associated intrusiveness using a visual analog scale (respectively, VAS-L and VAS-I), as well as the measures of the minimum masking levels (MML) of their tinnitus. MML was assessed with an MP3 device (Portable HD audio player, HIFI WALKER HX) and intra-auricular AGPTEK sleep headphones. The masking stimulation was a broadband white noise (20 Hz to 10 kHz). MML procedure started without any stimulation, and then the procedure progressively raised the masking stimulation intensity to the level that tinnitus was masked. The precise direction given to the participants was: "stop at the volume 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 in order to ensure the stability of the measurement.

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In addition to these questionnaires, the short morning survey included a sleep agenda. Patients were asked to estimate the time at which they fell asleep and later awoke, as well as the frequency and estimated time of any additional nocturnal events overnight.

### 2.2.3. Polysomnography Recording

Polysomnographic recordings were performed using two Nox A1 devices (Resmed, San Diego, CA, USA). The sampling rates of both devices were 200 Hz and 250 Hz. EEG channels were positioned as usual at scalp locations F3, F4, C3, C4, O1, O2, M1 and M2 according to the 10–20 system for electroencephalography (EEG) positioning [54]. Two EOG channels were positioned diagonally: one externally above one eye and the other externally under the other eye. As well as three EMG sensors, two placed on the right and left suprahyoid muscles and one on the chin as reference.

All EEG, EMG and EOG electrodes were gold cup electrodes filled with conductive paste (Weaver and Company—Ten20 Conductive Neurodiagnostic, Aurora, CO, USA). The skin was initially cleaned with alcoholic solution (Alcohol 70% vol.) and dried before applying the conductive paste and positioning the electrodes. Electrodes were held in place using adhesive conductive cream (Natus Genuine Grass EC2 electrode cream, Middleton, WI, USA) on the top and adhesive bands (Mölnlycke—Mefix—Self-adhesive fabric Gothenburg, Sweden).

Two ECG sensors were placed on left arm/right leg positions. Single-use humid electrodes were used as reference (on the forehead) and for ECG measurement (Medtronics—Kendall—hydrogel ECG electrodes H92SG, Watford, UK).

The Nox A1 units are equipped with additional sensors: accelerometers in the 3 dimensions, activity measurement, angular position of the device and dB audio measurement.

Sleep apnea was assessed by means of two plethysmography belts on the thorax and abdominal regions. Furthermore, oximetry and pulse were measured continuously by NONIN 3150 Bluetooth oximeter (Nonin: Plymouth, MN, USA) and nasal airflow was measured by a nasal cannula connected to the pressure sensor of the polysomnographic NOX A1 device.

## 2.3. Analyses

### 2.3.1. Polysomnography Scoring

Polysomnographic recordings were scored for sleep stages and sleep apnea following the ASSM recommendations by two experienced PSG technologists. For bruxism scoring, automatic scoring was first performed with the Tinnitus-n-sleep toolbox (<https://github.com/lkorcowski/Tinnitus-n-Sleep> accessed on 20 October 2022) and then reviewed manually. This toolbox automatically labels EMG jaw muscle signals for EMG bursts and scores bruxism events accordingly, following the recommendations given by Lavigne et al. [55,56]. This task was performed while rejecting artifacts provoked by body movements (measured by the accelerometer embedded on the NOX A1) and faulty electrode contact with the skin (measured by electrode impedance). It is important to acknowledge that, due to the COVID-19 pandemic, the use of a nasal cannula was not always possible. During this event, sleep apnea was not assessed, resulting in a restricted sample size for the analysis of this syndrome.

### 2.3.2. Statistical Analyses

Data were centralized on a common anonymized CSV (Comma Separated Value) file and analyzed using Python and Scipy library [57]. The Mann–Whitney U test and Cohen D effect size were used to compare samples between groups. Spearman correlation tests were performed for each group between these sleep characteristics that exhibited significant differences between groups and overnight variations of tinnitus measured by MML, VAS-L and VAS-I scales.



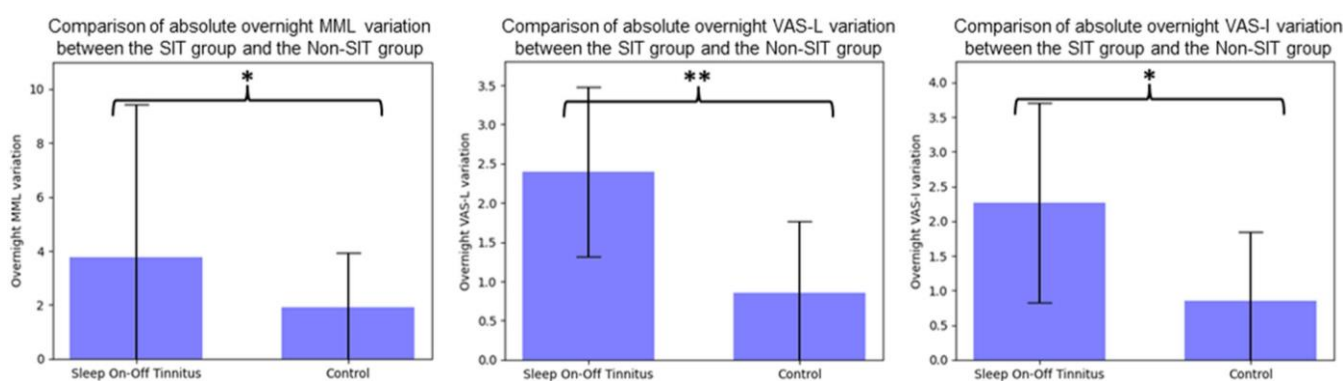
### 3. Results

#### 3.1. Etiological Group Comparison

Although the groups were matched by age, gender, self-declared hearing loss grade and tinnitus impact on their quality of life, as measured by the THI, differences were identified between groups on several CRF items, as presented in Table 1. The identified differences between groups were as follows:

- The proportion of patients experiencing an increase of tinnitus after naps were significantly higher in the SIT group than in the Non-SIT group ( $p < 0.01$ );
- The proportion of patients complaining of neck stiffness and/or lack of cervical mobility was significantly lower for the SIT group than for the Non-SIT group ( $p < 0.01$ );
- The proportion of patients experiencing rises of tinnitus after an exposition to loud noises was significantly lower in the SIT than in the Non-SIT group ( $p < 0.05$ ).

Moreover, according to our expectations, overnight absolute variations of tinnitus level, measured by MML and VAS-L and VAS-I scales, were all significantly higher in the SIT group compared to the matched sleep-stable tinnitus Non-SIT group ( $p < 0.05$  for MML and VAS-I,  $p < 0.01$  for VAS-L), as highlighted in Figure 1.



**Figure 1.** Comparison of absolute overnight tinnitus variation between groups, MML: Minimum Masking Level, VAS-L: Visual analog scale on tinnitus loudness, VAS-I: Visual analog scale on tinnitus intrusiveness. \*:  $p < 0.05$ , \*\*:  $p < 0.01$ .

During clinical interactions with SIT patients, at least one-third of them spontaneously reported a noteworthy phenomenon: whenever they woke up early in the morning with low or absent tinnitus, if by chance they went back to sleep even for a short period of time after this first awakening, then their tinnitus would almost systematically increase upon their second awakening. None of the patients in the Non-SIT group reported such a phenomenon.

#### 3.2. Sleep Characteristics Group Comparison

Among the Non-SIT group, one subject underwent the complete one-night polysomnography procedure yet slept less than three hours. Consequently, this subject's recording was excluded from the analysis. Due to the COVID-19 pandemic's sanitary prerogatives, airflow cannulas could not be used for five recordings (two of the SIT group and three of the Non-SIT group). Consequently, regarding the group comparison over the sleep apnea criterion, these recordings were excluded from analyses.

Polysomnographic sleep characteristics of the SIT group and the Non-SIT group are presented in Table 2. Significant differences in percentages of total sleep time of N2 stage (SIT:  $53.87 \pm 10.79$ , Non-SIT:  $44.74 \pm 6.5$ ,  $p < 0.05$ , Cohen D: 0.98), N3 stage (SIT:  $22.93 \pm 10.97$ , Non-SIT:  $28.52 \pm 5.88$ ,  $p < 0.01$ , Cohen D: 0.61) and REM stage (SIT:  $15.93 \pm 5.84$ , Non-SIT:  $21.08 \pm 4.66$ ,  $p < 0.05$ , Cohen D: 0.94) were identified between the SIT group and the Non-SIT group. Similarly, significant differences between sleep duration (in min) of the N3 stage (SIT:  $86.45 \pm 35.18$ , Non-SIT:  $114.89 \pm 22.8$ ,  $p < 0.01$ , Cohen D: 0.92) and REM stage (SIT:  $62.13 \pm 25.46$ , Non-SIT:  $87.18 \pm 26.5$ ,  $p < 0.05$ , Cohen D: 0.93) were identified between the SIT group and the Non-SIT group.

**Table 2.** Sleep characteristics comparison.

	SIT Group ( $n = 15$ )		Non-SIT Group ( $n = 14$ )		$p$ -Value	Effect Size		
	Mean (Std)	Mean (Std)	Mean (Std)	Mean (Std)				
Total sleep time (TST, in min)	385.63 (46.37)	408.35 (61.11)			0.23			
Wake time after sleep onset (WASO, in min)	59.31 (35.32)	68.79 (38.72)			0.6			
Sleep latency (min)	16.13 (18.71)	18.45 (16.83)			0.33			
REM sleep latency (min)	120.87 (44.89)	118.68 (54.67)			0.66			
Total Bruxism (number of episodes per hour)	13.05 (4.14)	15.85 (5.29)			0.14	-0.571		
Phasic Bruxism (number of episodes per hour)	1.72 (0.69)	1.88 (0.85)			0.61			
Tonic Bruxism (number of episodes per hour)	3.02 (1.81)	4.53 (2.17)			0.06	-0.733		
Mixed Bruxism (number of episodes per hour)	0.77 (0.44)	0.93 (0.39)			0.31			
Apnea Hypopnea Index (AHI) (*)	14.19 (10.58)	14.0 (10.1)			0.91			
Oxygen Desaturation Index (ODI)	12.77 (10.16)	13.37 (8.71)			0.79			
	<b>% TST</b>	<b>Duration (min)</b>	<b>% TST</b>	<b>Duration (min)</b>	<b>For % TST</b>	<b>Duration (min)</b>	<b>For % TST</b>	<b>Duration (min)</b>
N1 sleep (% , min)	7.2 (2.79)	27.55 (9.71)	5.68 (2.74)	22.05 (7.85)	0.13	0.1	0.53	0.6
N2 sleep (% , min)	53.87 (10.79)	209.04 (53.31)	44.74 (6.5)	184.34 (44.87)	<b>0.01 *</b>	0.2	0.98	
N3 sleep (% , min)	22.93 (10.97)	86.45 (35.18)	28.52 (5.88)	114.89 (22.8)	<b>&lt;0.01 **</b>	<b>&lt;0.01 **</b>	-0.61	-0.92
REM sleep (% , min)	15.93 (5.84)	62.13 (25.46)	21.08 (4.66)	87.18 (26.5)	<b>0.04 *</b>	<b>0.04 *</b>	-0.94	-0.93
Snoring (% , min)	20.23 (15.45)	74.75 (54.26)	19.08 (19.19)	72.46 (72.29)	0.66	0.65		
Supine position (% , min)	45.33 (33.81)	185.18 (149.91)	30.86 (24.89)	127.4 (105.41)	0.25	0.37		
Lateral position (% , min)	48.47 (31.79)	178.9 (114.28)	56.29 (27.42)	223.7 (108.22)	0.53	0.31		
Prone position (% , min)	4.46 (8.82)	18.61 (36.32)	10.43 (18.07)	45.95 (81.85)	0.16	0.15		

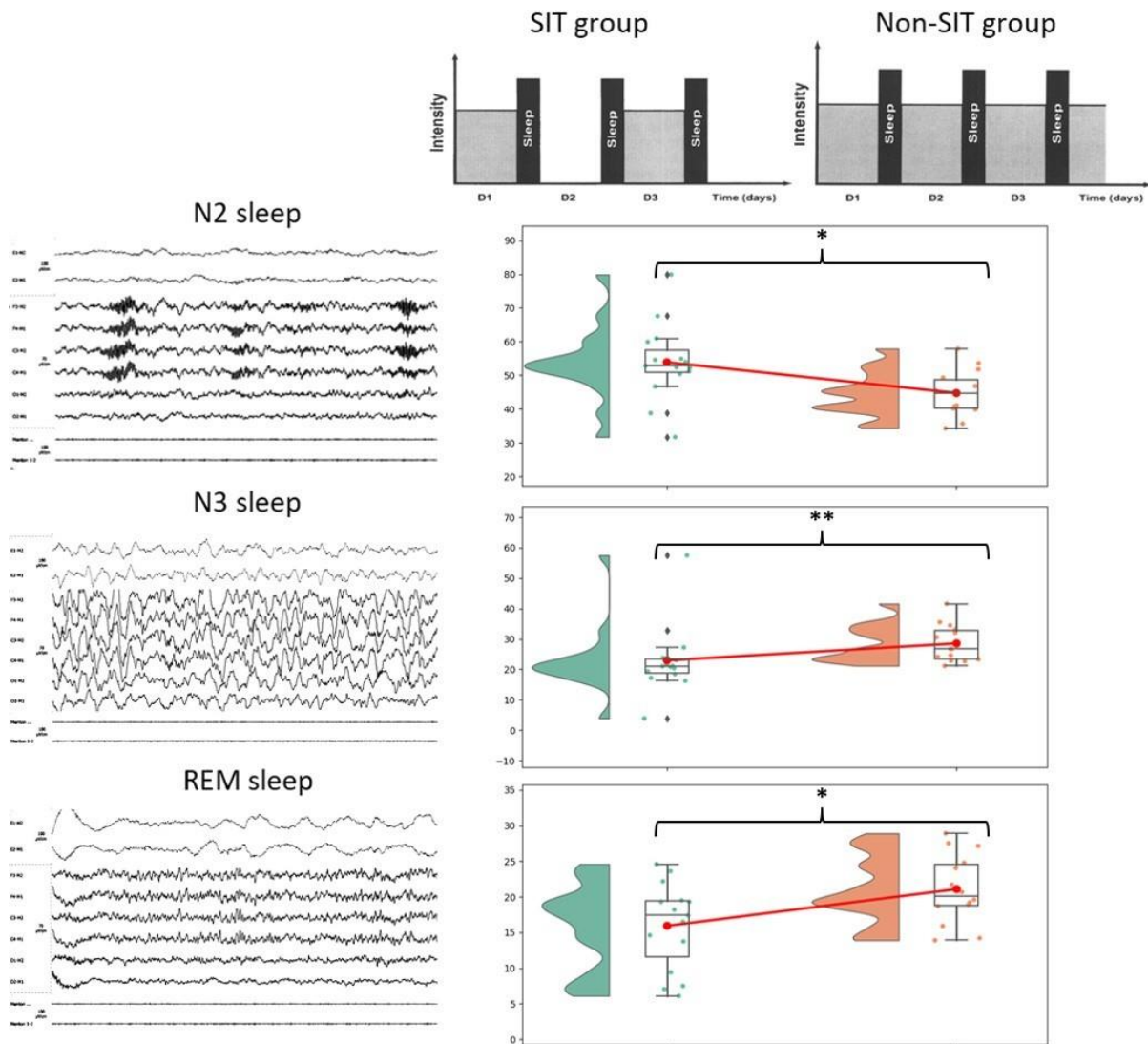
Std: standard deviation, REM: Rapid Eye Movement, TST: total sleep time. (\*): For AHI, SIT:  $n = 13$ , Non-SIT:  $n = 11$ . \*:  $p < 0.05$ , \*\*:  $p < 0.01$ .

An overall view of the group differences is displayed graphically in Figure 2.

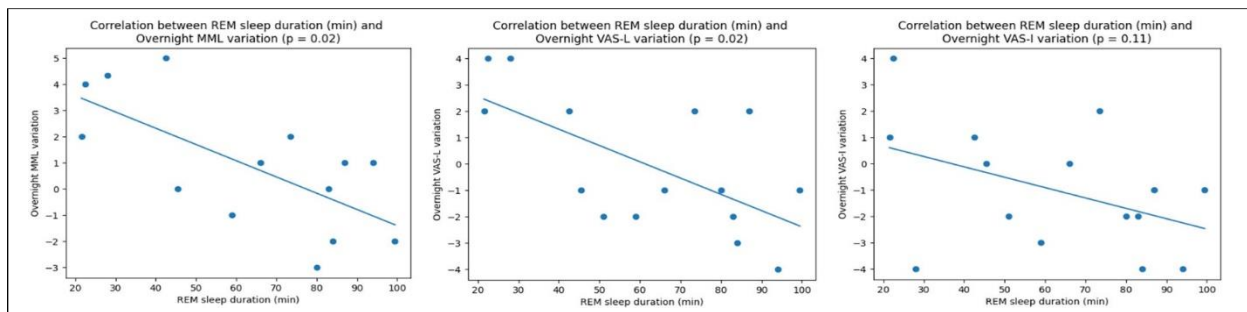
### 3.3. Correlations between Tinnitus Modulation and Sleep Characteristics

Correlation tests were performed between N2, N3 and REM sleep stages percentages of total sleep time and duration (in min) and overnight tinnitus variation measured by MML, VAS-L and VAS-I. Significant correlations were found only in the SIT group between REM sleep duration and overnight MML ( $p < 0.05$ ) and VAS-L ( $p < 0.05$ ) variation. These correlations are displayed in Figure 3. A similar significant correlation was found between REM stage percentage of total sleep time and overnight VAS-L variation ( $p < 0.05$ ) for the longitudinal case report presented as Appendix A. A significant correlation was also found between the THI scores and the REM sleep duration (in min) in the SIT group ( $p < 0.05$ ).





**Figure 2.** General overview of sleep characteristics main difference between SIT group and matched Non-SIT group. Tinnitus dynamic display figure adapted with permission from Ref. [50]. 2002, Cecile Nicolas-Puel. \*:  $p < 0.05$ , \*\*:  $p < 0.01$ .



**Figure 3.** Anticorrelations between REM sleep duration (in min) and overnight tinnitus variations measured by Minimum Masking Level (MML), Visual Analog Scales on Tinnitus Loudness (VAS-L) and Intrusiveness (VAS-I).

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#### 4. Discussion

This study aimed to understand the sleep characteristics of a specific subgroup of tinnitus patients presenting important sleep-driven modulations of their tinnitus percept, referred to as SIT patients. It has been repeatedly reported that tinnitus patients are often sleep deprived and/or suffer from impaired quality of sleep [13–15,17,29]. These studies have analyzed heterogeneous samples of the tinnitus population, neglecting de facto its reported intrinsic heterogeneity [44,58,59]. To the best of the authors' knowledge, the present study is the first to analyze the interactions between sleep and tinnitus in two homogeneous subgroups of tinnitus patients matched in gender, age, tinnitus intrusiveness and self-declared hearing loss grade.

In the present study, 15 SIT patients and 15 matched sleep-stable tinnitus Non-SIT patients participated in a one-night polysomnography assessment. Comparative analyses of the sleep characteristics of each group confirmed specificities in the sleep characteristics of SIT patients. The latter exhibited deteriorated sleep compared to Non-SIT patients as they presented more N2 stage (light sleep), less N3 stage (deep sleep) and less REM stage sleep. On the other hand, no significant differences were found between groups for sleep latency or wake time after sleep onset. This tends to highlight that the differences between groups do not seem linked to an underlying difference in sleep quantity but instead to sleep quality. Moreover, as no significative differences were identified between groups for sleep apnea (measured by Apnea-Hypopnea Index and Oxygen Desaturation Index), this comorbidity does not seem to account for the SIT specificities. Additionally, it is important to mention that, although not significant, a difference between groups on sleep bruxism was noted with a medium Cohen-D effect size. However, this difference highlighted that SIT patients actually had fewer sleep bruxism episodes per hour as compared to Non-SIT patients. One possible explanation could be that SIT patients experience more intense temporo-mandibular joint (TMJ) and/or facial pain than Non-SIT patients. In fact, in their study, Rompré et al. showed that such pain is associated with lower frequencies of orofacial activities [60]. In the present study, this hypothesis seems to be strengthened by the fact that etiological items group comparison shows that SIT group experienced slightly more facial and/or TMJ pain compared to the Non-SIT group (yet not significant) and more TMJ muscle fatigue ( $p = 0.08$ , medium effect size of 0.63). Future research at a larger scale should test this hypothesis further.

##### 4.1. REM Sleep Seems to Be Specifically Implicated in SIT Sleep-Driven Modulations

Before starting this prospective study, A.L. and R.G. collected polysomnography reports over the years of several SIT patients who spontaneously performed such assessments to try to understand why their tinnitus was influenced by their sleep. These preliminary aggregations of sleep reports (not published) pointed to an impairment of REM sleep.

The present study confirmed that this specific tinnitus subgroup had less REM sleep proportion and duration ( $p < 0.05$ ) than matched Non-SIT patients. It is important to mention that, according to Ohayon et al. [61], for a healthy sample of the population of mean age 50 years old, the proportion of REM sleep over total sleep time should be around 20%. Yet, the SIT sample of the present study had 15.9% of REM sleep, which appears sensibly lower. In comparison, the Non-SIT group averaged a normal 21% of REM sleep.

It is also important to mention that two former publications on polysomnographic analyses on tinnitus patients [25,27] found congruent findings that REM sleep appeared quantitatively deteriorated in the tinnitus population compared to healthy Non-SIT patients, although these authors did not specifically select SIT patients nor reported their representative proportion in their samples.

Another interesting finding is the correlation observed between the duration of REM sleep during the polysomnographic assessment and the variation of tinnitus overnight, measured by MML and VAS-L in the SIT group. Likewise, the same significative correlation was found across seven nights on the same subject in the longitudinal case report presented in Appendix A. It is interesting to note that such a correlation was found for measurements

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accounting for psychoacoustics characteristics of the tinnitus percept only and not for the VAS-I, which accounts for intrusiveness and hence the psychological reaction to the percept.

However, the additional fact that a significative correlation was found between THI scores of SIT patients and their REM sleep duration is puzzling and harder to interpret. In fact, by its definition, people affected by SIT have very different experiences depending on the days (both perceptually and emotionally), and yet the THI asks general questions that address tinnitus “on the average of time”. Hence, this questionnaire is probably not fit to account for the tinnitus inter-day variability of this specific tinnitus subgroup. One could hypothesize that SIT patients answer the THI questionnaire picturing themselves on days when their tinnitus is present and bothers them. If we take this hypothesis for granted, the observed correlation could then suggest that the more REM sleep deteriorates in SIT patients, the more tinnitus impacts the quality of life of these patients on loud tinnitus days.

The observed correlation between THI scores and REM duration in the SIT group is quite similar to the recently reported significant correlation between Tinnitus Functional Index (TFI) scores and REM sleep duration and proportional in-total sleep time in Post-Traumatic Stress Disorder (PTSD) patients experiencing tinnitus [30]. This correlation is all the more interesting, considering the parallels that can be drawn between PTSD and tinnitus. The co-prevalence and association between tinnitus and PTSD are notorious [30,62–64]. Additionally, it is noteworthy that most tinnitus patients maintain a precise memory of the moment when they first experienced their tinnitus, which could be thus assimilated to a traumatic and stressful event. This could explain why treatments such as Eye Movement Desensitization and Reprocessing (EMDR) therapy have repeatedly been suggested as a potentially good approach to help tinnitus patients [65,66]. Two reviews on EMDR can be found here: [67,68]. Although the PTSD relation to REM sleep’s polysomnographic characterization yields conflicting results, recent findings in human sleep and, above all, rodent sleep identified that REM sleep could somehow be maladaptive in PTSD cases, with abnormal levels of noradrenaline during sleep and early after awakening, resulting in abnormally elevated locus coeruleus firing during REM sleep [69]. It is currently postulated that locus coeruleus firing during REM sleep impedes the loosening of the emotional schema associated with the traumatic memory [70]. Whether or not SIT patients have similar pathophysiological responses as PTSD patients remains an open question for future research. Indeed, the CRF in the present study has not explored the psychological characteristics of the sample. It could also be interesting to test EMDR procedures on this specific population to see if it proves to be specifically effective.

The correlation between the impairment of REM sleep and SIT modulation poses the question of any causal relationship.

Indeed, some studies have suggested that REM sleep could be impaired for healthy individuals exposed to continuous noise during their sleep [71–73]. In the SIT population, the onset of tinnitus during the night could damage REM sleep similarly to such continuous noise.

Conversely, the present results could suggest that REM sleep impairment could cause the modulation of tinnitus. Such a hypothesis is undermined by two other observations. In fact, the SIT group reports significantly more frequent tinnitus nap modulations than the Non-SIT group. Still, REM sleep is uncommon during naps, except during morning naps [74,75] or at the end of long afternoon naps of more than 45 min duration [76]. However, SIT patients report rises in their tinnitus even after *short*-duration naps and *anytime* in the day. Another important point is that after night, SIT patients displayed important *rises or decreases* in their tinnitus, whereas after naps or after morning sleep prolongations, they only reported *rises*. Somehow, there seems to be a dissymmetry in the way sleep interacts with tinnitus during nights and during naps, and this suggests a potential circadian role. Such clinical observations from aggregated case reports need to be confirmed with rigorous prospective measurements. Yet, if proven right, it could thus be deduced that tinnitus sleep intermittent modulations can happen without the occurrence of REM sleep during naps.

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Additionally, an underlying root pathophysiological mechanism could be the origin of both the modulation of tinnitus and the impairment of REM sleep, explaining this correlation. Such a phenomenon would also occur during naps and provoke, in these cases, only rises of the tinnitus percept. Such putative pathophysiological mechanisms could be facial muscle atonia modulations (neck and or jaw potentially linked to sleep position), sleep apnea or sleep bruxism and also, more interestingly, REM sleep middle-ear muscle activity (MEMA) of the Tensor tympani and/or Tensor Veli Palatini reported by [77–80].

#### 4.2. Merits

To the best of the authors' knowledge, the present study has the merit of being the first to take into account tinnitus heterogeneity for the exploration of polysomnographic characteristics of the tinnitus population. It is also the first to have objectivized, through polysomnography assessments, the sleep characteristics of tinnitus patients reporting important sleep-driven modulation of their tinnitus, referred to here as SIT patients. Another merit compared to past studies of the domain is that the present study precisely reported the etiological characteristics of each recruited group while also presenting not only their polysomnographic characteristics but also their sleep apnea and bruxism assessments.

#### 4.3. Limits

The first limitation of this study is its small sample size. It proved difficult to recruit SIT patients in the time span of the study, above all, as the study was monocentric. It seems the target subgroup of tinnitus patients only represents a small minority of tinnitus patients. This first limitation induced another one: due to the small sample sizes in this study, statistical rigorousness and conservative corrections (as, for instance, Bonferroni correction) could not be applied to account for the multiple tests performed in the analyses. Hence, only limited credit can be given to the conclusion of the present study and its statistical methodology. Future research should definitely try to independently reproduce the present work in order to try to confirm its results.

The fact that polysomnography was only assessed during one night without a preliminary habituation night, nor actigraphy nor sleep diaries was another limitation to this study, although the E-CRF provided some declarative first elements on sleep duration, insomnia and snoring status. As a potential consequence, one Non-SIT group subject slept less than three hours and his/her night had to be excluded.

Moreover, SIT patients describe diverging variations of their tinnitus across nights, only one of them being sampled in this study. Although an important variance of overnight tinnitus percept variation was captured in this study, it appears valuable in such circumstances to perform longitudinal measurements of each patient. The longitudinal measurement of one patient, presented in the case report in Appendix A, is a first step in this direction. Future research should try to generalize these longitudinal observations to the totality of their cohorts.

Another methodological limitation lies in the measurement of overnight tinnitus variations. In fact, by measuring only MML, VAS-L and VAS-I at only two-time points, once before and once after the polysomnographic recording, one cannot know if the observed variation was important or insignificant according to the subject's daily experience of tinnitus variations. It would bring additional value to track each subject the variation of their tinnitus percept over several days to have insight into their individual tinnitus variance and dynamic. Such individual longitudinal normalization would provide more validity to group correlations and effect size computations between objective physiological assessments and such overnight tinnitus variation measurements.

Likewise, in this study, groups were only matched on self-reported hearing loss grade. Such subjective criteria could be advantageously replaced in future research by objective audiological assessments such as at least an audiogram and perhaps more elaborated hearing tests.

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#### 4.4. Suggestions for Future Research

In addition to previously mentioned suggestions for future research, it should be advised for future studies to define more objective selection criteria to discriminate SIT patients. Defining a threshold on the degree of variability of tinnitus loudness across several morning and evening measurements of MML or VAS-L appears to be a good approach to defining such a discriminative criterion.

Another suggestion in order to better understand the underlying pathophysiological mechanism provoking these intermittent sleep variations would be to switch from a night polysomnography paradigm to a short nap observation paradigm. In fact, as could be observed in the etiological analyses, the prevalence of nap-related modulations of tinnitus in the SIT population is striking. A protocol following a similar design yet organized for naps would enable us to narrow down more effectively the key mechanisms at play behind these modulations. Such short naps (15 min or less) would constitute a more focused approach to enable better control over adverse events and biases compared to 7 or 8 h night sleep recordings.

Similarly, following the latter discussion that a potential root pathophysiological mechanism modulating tinnitus affects both REM sleep and naps sleep, in such a nap condition new protocol, it could be interesting to multiply objective physiological and functional measurements before, during and after each nap. Notably, to complete previous suggestions, blood testing and functional imagery would be relevant additional measurements.

#### 5. Conclusions

The present study presented the specific sleep characteristics of patients exhibiting important sleep-driven modulations of their tinnitus, referred to here as SIT patients, compared to matched Non-SIT patients. It showed that while there are no differences in sleep quantity nor in sleep apnea syndrome prevalences between the two groups, the SIT group's sleep appeared more deteriorated than the sleep of the matched Non-SIT group. REM sleep deterioration potentially plays an important role in these modulations, as suggested by several correlations which were observed. Future research should further investigate these modulations on larger cohorts and in more longitudinal modalities to confirm these preliminary results.

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**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of CPP Iff2 2018 A01034-51.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient concerned by the Appendix A to publish this paper.

**Data Availability Statement:** Data available on request due to ethical restrictions.

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**Conflicts of Interest:** Damien Léger declares that in the past 5 years, he has been employed as an investigator or a consultant by Actellion-Idorsia, the Agence Spatiale Européenne, Bioprojet, iSommeil, ESAI, Jansenn, Jazz, Vanda, Merck, Philips, Rythm, Sanofi, Vitalaire, and Resmed. Robin Guillard declares that he is a shareholder and president in Siopi SAS and has a professional activity



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as independent as Robin Guillard EIRL. Louis Korczowski declares he is a shareholder in Siopi SAS employed by Robin Guillard EIRL. The other authors did not declare COI.

## Appendix A

Longitudinal 7 days polysomnography assessment of a sleep intermittent tinnitus patient—a case report.

### 1. Subject Presentation

This appendix presents a case report of seven nights of longitudinal polysomnographic recordings of a 50-year-old 1.78 m man reporting sleep intermittent tinnitus (SIT). The subject had started presenting sleep intermittent modulations of tinnitus six months before his first polysomnographic participation. He presented a right unilateral high pitch (around 10 kHz) tinnitus that was continuous when present and yet that could totally disappear upon awakening and stay absent until a subsequent sleep occurrence. He described pseudo-cyclic though random alternances of 2 to 4 days “on” and “off” periods of tinnitus. The subject presented notable retrognathism without temporo-mandibular or headache complaint. According to his description, tinnitus could also sometimes rise spontaneously after lunch during the post-prandial period. He presented only slight somatosensory modulations of his tinnitus, as he described being able to reduce the tinnitus when advancing the jaw slightly. No other maneuver of the jaw or neck elicited any change in his tinnitus percept. The patient described important rises of his tinnitus after short naps, notably in the evening while his television remained on. He described his tinnitus as very bothersome in the first months after its onset and was prescribed 10 mg of mianserin per day to cope with his tinnitus. This treatment gradually helped him, yet without successfully suppressing tinnitus. When he applied to participate in the present study, his treatment was stable for more than three months, and his THI score was 36. The patient’s audiogram was normal for both ears, with a slight hearing loss of 8 kHz in both ears.

### 2. Polysomnographic Recordings and Methodology

The subject participated in the present clinical study and subsequently manifested the will to participate in further longitudinal explorations of his sleep in order to understand better why his tinnitus was such drastically influenced by sleep. He thus participated in two additional nights of polysomnography at the hospital in the same experimental conditions as the study. He was then lent one Nox A1 and all necessary materials to continue polysomnographic measurements at home. He was advised how to minimally install the material by himself to perform the polysomnographic recordings with autonomy. Consequently, for his recordings at home, C3, C4, O1 and O2 electrodes were not recorded; he did not use an airflow cannula for these recordings either. Five recordings were performed by the patient in autonomy with this setup.

Out of the eight recordings cumulated, seven were exploitable (a battery issue occurred in one of them) and were analyzed following the same methodology as in the observational group study. To score recordings when C3, C4, O1 and O2 were not available, the experimenters used bipolar channels F3-M2 and F4-M1 to assess sleep stages.

The subject did not record his MML levels during his polysomnographic recordings at home and hence only reported VAS-L and VAS-I measurements before and after each recording. In his opinion, VAS-L and VAS-I measurements were always identifiable and scored them always equally.

To try to evaluate the potential link between sleep characteristics and the overnight modulation of tinnitus, we performed spearman correlation tests.

### 3. Results

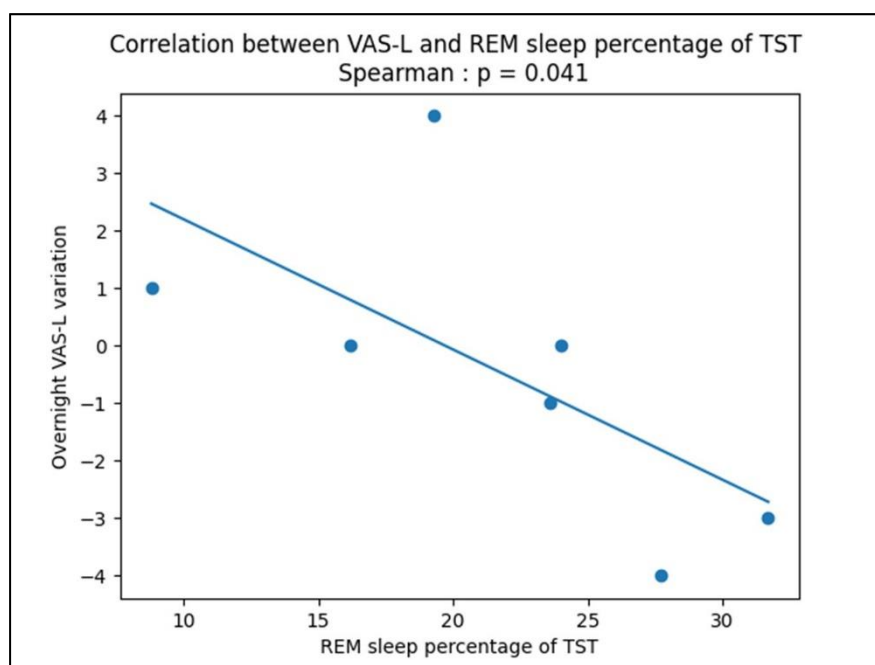
The sleep characteristics of the seven exploitable recordings are presented in Table A1. As can be seen, one night with a consequent rise of tinnitus was recorded (night 2), as well as two nights where tinnitus disappeared at the end (nights 4 and 5) and four nights where the loudness of tinnitus remained approximately the same. It could yet be pointed out that situations are maybe dissimilar between night 3, where tinnitus was absent before and after, and on night 6, where it was present with a loudness score of 3 on the VAS-L before and after the night.

**Table A1.** Longitudinal sleep characteristics.

	VAS-L Evening	VAS-L Morning	TST	WASO	Sleep Latency	REM Latency	%N1	%N2	%N3	%REM	%Snoring	%Supine
Night 1	2	1	421	8.3	5.3	71.5	4.9	38.8	32.7	23.6	10.7	97.4
Night 2	1	5	514.5	21.2	6.6	80	11	54.8	14.9	19.3	17.5	94.2
Night 3	0	0	423	22.6	7.7	70.7	6.4	39.4	38	16.2	6.1	78.9
Night 4	3	0	358	22.5	2.4	44.4	6	39	23.3	31.7	2.8	72.8
Night 5	4	0	464	27	8	70	5.6	37.4	29.3	27.7	3.6	75.9
Night 6	3	3	339	7.2	15.9	96.9	5.7	29.6	40.6	24	30.1	82.7
Night 7	0	1	297	2.9	2.4	91.4	3.5	32.3	55.4	8.8	30.6	75.6

Abbreviations: TST: total sleep time, WASO: wake time after sleep onset.

An important was observed variability in almost all sleep characteristics. While testing for correlations between sleep characteristics and overnight VAS-L variation, overnight VAS-L variation displayed a significant correlation with REM sleep percentage of total sleep time (anticorrelation,  $p < 0.05$ , illustrated in Figure A1) and with a percentage of snoring (correlation,  $p < 0.05$ ).



**Figure A1.** Anticorrelation between REM sleep percentage of total sleep time and overnight VAS-L variation, TST: total sleep time.

#### 4. Discussion

The present case report displays the longitudinal evolution of tinnitus across days in a patient identified to have SIT. As it could be observed, on 5 out of the 14 VAS-L measurement occasions, tinnitus was completely absent. On the other hand, when present, tinnitus loudness was scored by the subject between 1 and 5. The subject described that historically, his tinnitus could get louder than during the present recordings.

Polysomnographic characteristics of the patient revealed important (yet potentially normal) variability. Correlations were identified between the overnight tinnitus loudness variation measured by the VAS-L and the REM-sleep percentage of total sleep time. This result matches the similar anticorrelation observed over the whole group of SIT patients and is comforting the hypothesis that REM sleep may play a role in the observed tinnitus loudness variation. On the contrary, the observed correlation between the percentage of time snoring and overnight VAS-L variation has not been found for the group analysis.

Such longitudinal measurements appear all the more essential to carry out knowing the day-to-day variability of this specific type of tinnitus described by patients.

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## 5.2 A longitudinal polysomnographic study of a TIAN patient sample to study physiological correlates of NITM

In this last study, we intended to test correlations between polysomnographic characteristics and overnight tinnitus modulation within each group, yet we faced a major limitation : for both sample we only recorded one time point of measurement (one night of polysomnographic measurement). Yet, the precise characteristic of SIT patients is that depending on nights, they can wake up with or without their tinnitus percept. This implies that most probably there is intra-individual variability in some sleep characteristics of these patients which accounts for such difference of outcomes depending on nights. Such intra-individual variability cannot be explored by only night of polysomnographic assessment and requires a longitudinal protocol design. We partially addressed this limitation by publishing as an appendix of the last study a case report of a seven-night polysomnographic exploration of such a SIT patient.

In the study presented hereafter, we attempted to replicate this longitudinal methodological framework of multiple consecutive polysomnographic assessments of the same patients at the scale of a whole sample. We hence designed a six-nap polysomnographic protocol for which patients of the TIAN population were recruited to participate into. In this protocol, each patient was its own control. Over the six naps each patient could perform, there was a variability of NITM outcomes that could be correlated with the polysomnographic characteristics of each nap. Our methodological approach was then to perform individual correlations between each feature of the nap assessments and try to correlate them with NITM measurements. Subsequently, the Stouffer combination method was employed to draw conclusions at the level of the entire sample.

# Why does tinnitus vary with naps?

## *A polysomnographic prospective study exploring the somatosensory hypothesis.*

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**Abstract:** (1) Background: Tinnitus, defined as the conscious awareness of a noise without any identifiable corresponding external acoustic source, can be modulated by various factors. Among these factors, tinnitus patients commonly report drastic increases of tinnitus loudness following nap sleep. Previous studies have suggested that this clinical pattern could be attributed to a somatosensory modulation of tinnitus. To our knowledge, no polysomnographic study has been carried out to assess this hypothesis.

(2) Methods: For this observational prospective study, 37 participants reporting frequent increases of tinnitus following naps were recruited. They participated to six full-polysomnography nap attempts over two days. Audiological and kinesiological tests were conducted before and after each nap attempt.

(3) Results: 197 naps were collected. Each nap at each time of day elicited an overall significant increase in tinnitus minimum masking level (MML). Each inter nap period elicited a significant decrease. Tinnitus modulations were found significantly correlated with nap sleep duration (Visual numeric scale on tinnitus loudness, VNS-L,  $p < 0.05$ ), with snoring duration (MML,  $p < 0.001$ ), with snoring average sound level (VNS on tinnitus intrusiveness, VNS-I,  $p < 0.05$ ) and with sleep apnea count (VNS-I,  $p < 0.001$ ).

(4) Conclusions: This study confirm objectively that tinnitus may increase following naps. No association was found between these modulations and somatosensory modulations involving the temporomandibular joint and cervical areas. However, it may be possible that nap-induced tinnitus modulations are a hidden form of somatosensory modulation as snoring and sleep apnea events are often related to tensor veli palatini muscle dysfunction.

**Keywords:** Tinnitus, nap, somatosensory modulations, polysomnography, sleep apnea, snoring

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## List of abbreviations

CRF : Case Report Form  
ET : Eustachian Tube  
ECG : ElectroCardioGraphy  
EEG : ElectroEncephaloGraphy  
EMG : ElectroMyoGraphy  
EOG : ElectroOculoloGraphy  
MML : Minimum Masking Level  
NITM : Nap-Induced Tinnitus Modulation  
SIT : Sleep-Intermittent Tinnitus  
SPO2 : Blood-oxygen saturation level  
THI : Tinnitus Handicap Inventory  
TIAN : Tinnitus Increases After Naps  
TMA : Tinnitus Momentary Assessment  
TMM : TurboManoMetry  
TT : Tensor Tympani  
TVP : Tensor Veli Palatini  
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 form [2].

Patients often report that perception of tinnitus can vary over time [3,4]. Multiple sources of tinnitus modulations have been identified: somatosensory modulations [5–7], stress modulations [8], noise modulations [9,10], specific food intake modulations [11], atmospheric pressure modulations [12]... Another cause of modulation of tinnitus reported by roughly a third of the tinnitus population is sleep, and more specifically napping sleep [5,13]. Surprisingly, twice as much patients report increases of tinnitus following naps compared to decreases of tinnitus after naps [14,15]. Three studies have suggested that this pattern could be associated to somatosensory modulations of tinnitus [5,13,16], and even that these modulations could be more frequent when tinnitus patients sleep in a seated position. To the best of the authors’ knowledge, no polysomnographic exploration has been led to better understand these nap-induced tinnitus modulations (NITM).

We believe that such a study has several theoretical methodological benefits.

First, it focuses on a homogeneous sub-phenotype of patients that share a least a similar pattern of tinnitus modulation. Indeed current guidelines in tinnitus research encourage an in-depth study of homogeneous subgroups of patients [17–19].

Second, collecting longitudinal data in individual patients offers the possibility to test intra individual correlations between tinnitus modulation and other physiological parameters. Last, NITM in patients of the Tinnitus Increases After Naps (TIAN) population have the advantage to trigger long and stable modulations of tinnitus. This should make it possible to perform long lasting post-nap tests in the tinnitus-modulated state.

There are several potential physiological events that can happen during naps that could explain NITM. A first possibility are bruxism events. It has been shown that tinnitus is significantly higher in the bruxism population [20,21]. One could hypothesize that bruxism events occurring during naps could constitute trigeminal nerve stimulations

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that could result in a somatosensory modulation of tinnitus upon awakening. Similarly, changes in cervical and masticatory muscle tonus, associated with long lasting inclined positions during sleep could be another potential somatosensory source of modulation explaining NITM. Last, one could argue that sleep apnea and snoring could be the source of NITM. Both of which have been shown to be related to tinnitus [22,23] and both implicate the tensor veli palatini, another trigeminally innervated muscle.

In a previous study, we investigated a subgroup of TIAN patients : sleep-intermittent tinnitus (SIT) patients (i.e. patient who occasionally describe a total disappearance of the tinnitus after night sleep) [24]. We compared, over a whole night of polysomnographic exploration, the sleep characteristics of a sample of this population to controls (tinnitus patients without any sleep-induced modulation). We did not identify any differences between these two populations with regard to sleep apnea, snoring, bruxism or sleep position during the night. We did not find any correlation between these variables and night sleep-induced tinnitus modulation either. Yet a strong limitation for the calculation of these correlations was the fact we only studied one-night of measurement per patient. A longitudinal set of measurements for each patient would appear necessary to be able to conclude upon what physiological mechanism correlates with sleep-induced tinnitus modulations. Indeed, in a seven-night longitudinal case-report of a SIT patient (supplementary material: Appendix), we identified that snoring weakly correlated with night-induced tinnitus modulations.

The present study was aimed at addressing the methodological limitations of our previous study by identifying the physiological correlates of NITM and more specifically test if NITM are linked to somatosensory modulations of tinnitus. To achieve this goal, longitudinal assessments of tinnitus were performed through 6 naps per patient in a cohort of TIAN patients, along with a large set of audiologic, kinesiological and polysomnographic explorations.

## **2. Materials and Methods:**

### *2.1. Participants :*

One cohort of 37 TIAN patients (mean  $\pm$  standard deviation age:  $55.24 \pm 10.70$ , 27 men, 10 women) were recruited to participate for two days of polysomnography examination at Hôtel-Dieu hospital sleep department (VIFASOM) in Paris, France. Most of these patients were recruited by ENT M.D. (A. L.), whereas some enrolled in the study spontaneously after a communication was made to social media platforms with the help of a French patient tinnitus association (France-Acouphènes) and the mutual help digital community Siopi [25].

Inclusion criteria were: subjects aged between 18 and 75, reporting noticeable modulations of tinnitus following naps which can be masked by 85 dB broadband white noise, affiliated to the French social insurance and having signed informed consent. Non-inclusion criteria were: change in tinnitus treatment in the last 3 months, patients under guardianship or with important cognitive impairment or not able to do naps easily, or having been diagnosed with Ménière disease, acoustic schwannoma, severe hyperacusis or pulsatile tinnitus; as well as patients who reported epilepsy seizures, non-stabilized metabolic or cardiovascular conditions, or superficial scalp wounds or latex allergy and at last subjects pregnant or breastfeeding. Demographic and symptomatologic characteristics of the sample are presented in tables 1 and 2.

### *2.2. Ethics :*

All patients gave their informed consent to participate to the present clinical trial, which 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

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participants' best interests into consideration. Participants were compensated 100 euros for their participation and transportation fees were reimbursed up to 100 euros.

### 2.3. *Clinical assessment* :

#### 2.3.1. Anamnesis case report form:

The participants completed a comprehensive Case Report Form (CRF). This CRF included a comprehensive description of tinnitus and its somatosensory modulations, history of comorbidities and associated pain symptoms (jaw, cervical area and headaches). CRF also included screening questions on sleep disorders and how tinnitus was modulated by night sleep and naps, and by sleep positions. Last, it included Visual Numerical Scales on tinnitus Loudness and Intrusiveness (VNS-L and VNS-I), following the methodological advice of the Comit'Id consensus [26]. Finally, the Tinnitus Handicap Inventory (THI) was administered. The THI is a 25-item questionnaire yielding a score between 0 and 100 classically used in tinnitus clinical studies to assess the impact of tinnitus on quality of life [27]. The main clinical characteristics of the sample are presented in Tables 1 and 2.

#### 2.3.2. Protocol:

##### Napping

All participants were asked to perform six nap attempt cycles over two days in VIFASOM sleep lab. Each day had a similar planning. Minimal duration between the two days of participation at the hospital was of three days.

Participants were first equipped with polysomnographic material (as described hereafter in section 2.2.3), then they went through a first nap attempt cycle in the morning starting 11am. Then came lunch, during which a selection of several menus with similar nutritional properties were proposed. The afternoon started by a second nap attempt cycle near 2pm, then a one-hour break, then a last nap attempt cycle near 4pm.

7 patients among the 37 recruited TIAN patients only participated to one day of clinical assessment, resulting in only 3 naps attempts performed for each of them.

Each nap attempt cycle was similar. A set of examinations were performed in the order hereafter before the nap, then in mirror order after the nap.

Napping occurred in an EEG quiet room. If the participant fell asleep, nap was interrupted after a maximum 15 min of N2 and/or N3 sleep to the best of the experimenter's ability to score sleep in real time. Participants were awoken by a gradual light bulb lighting over 1 min to minimize brutal awakening. The nap attempt stopped in all cases after 45 min, whether the participant fell asleep for less than 15 min or not. After the end of the nap attempt, participants performed the same set of examinations, in mirror order, so that the same time distance between examination and sleep was preserved before and after the nap (e.g. EEG resting state was the last examination before the nap and the first one upon awakening).

Polysomnographic recordings were performed using four Nox A1 devices (Resmed, San Diego, California, United-States). The sampling rates of the four devices were 250 Hz. EEG channels were positioned as usual at scalp locations F3, F4, C3, C4, O1, O2, and referenced to the opposite mastoid M1 and M2 according to the 10-20 system for electroencephalography (EEG) positioning [28]. Two electrooculography (EOG) channels were positioned diagonally: one externally above one eye and the other externally under the other eye. as well as seven electromyography (EMG) sensors, two placed on the right and left suprahyoid muscles with one on the chin as reference, as well



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as two bipolar electrodes to measure left and right masseter activity, each referenced to the chin as well.

All EEG, EMG and EOG electrodes were gold cup electrodes filled with conductive paste (Weaver and Company - Ten20 Conductive Neurodiagnostic, Aurora, Colorado, United States), except for masseter bipolar electrodes which were consumable gel electrodes (Medtronic - Kendall - hydrogel ECG electrodes H92SG, Watford, United Kingdom). Epiderm was initially cleaned with alcoholic solution (Alcohol 70% vol.) and then dried before conductive paste application and electrode positioning. Electrodes were held in place using adhesive conductive cream (Natus Genuine Grass EC2 electrode cream, Middleton, Wisconsin, United States) on the top and adhesive band (Mölnlycke - Mefix - Self-adhesive fabric Gothenburg, Sweden).

Two electrocardiography (ECG) sensors were placed in left arm/right leg positions. Single-use humid electrodes were used as reference (on the forehead) and for ECG measurement (Medtronic - Kendall - hydrogel ECG electrodes H92SG, Watford, United Kingdom).

The Nox A1 units are equipped with additional sensors: accelerometers in the 3 dimensions, activity measurement, angular position of the device, dB audio measurement.

Sleep apnea was assessed by means of two plethysmography belts on the thorax and abdominal regions. Furthermore, oximetry and pulse were measured continuously by NONIN 3150 bluetooth oximeter (Nonin: Plymouth, Minnesota, United States) and nasal airflow was measured by a nasal cannula connected to the pressure sensor of the polysomnographic NOX A1 device. Naps were recorded with an infrared video camera.

Polysomnographic recordings were scored for sleep stages and sleep apnea following the ASSM recommendations by two experienced polysomnography technologists. A consensus scoring session was performed at the end of the 2 independent scorings to agree on epochs in which scorers had responded differently. For bruxism scoring, automatic scoring was first performed with the Tinnitus-n-sleep toolbox (<https://github.com/lkorcowski/Tinnitus-n-Sleep>) and then reviewed manually. Bruxism scoring procedure for bursts and episodes followed the scoring rules advised by [29]. This toolbox enables to automatically label EMG jaw muscles signals for EMG bursts and scores bruxism events accordingly, following the recommendations given in [29,30]. This task was performed while rejecting artifacts provoked by body movements (measured by the accelerometer embedded on the NOX A1), and faulty electrode contact with the skin (measured by electrode impedance).

Snoring events were manually scored from the decibel channel of the Nox devices. Cumulated duration and average snoring decibels were calculated from this scoring. Sleep apnea events were manually scored according to ASSM recommendations from air cannula airflow measurements, oxygen desaturation events (SPO2) and plethysmography measurements. SPO2 oxygen desaturation events and position assessment (supine, right, left, prone) were labeled automatically during the nap by the Noxturnal software (v6, Resmed, San Diego, California, United-States) respectively from the SPO2 signal and the accelerometers measurements, according to ASSM recommendations.

When a part of more than 60 seconds (2 epoch) of a nap had a missing signal, due to faulty or malfunctioning sensors, the feature it would enable to calculate was not evaluated for this nap. For example, if during a nap, the SPO2 sensor malfunctioned or fell from the finger for more than 60s, the number of desaturations was not assessed. This resulted in having a different number of data points for each test for each variable.

#### Auditory assessments

First a tonal audiometry at 250Hz, 500Hz, 750Hz, 1kHz, 1.5kHz, 2kHz, 3kHz, 4kHz, 6kHz and 8kHz auditory thresholds was collected for each ear with a descending

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procedure [31]. Koalys online digital audiometer was used to acquire these audiograms, using Telephonics TDH-39 with noise-attenuating shells [32].

Multifrequency impedancemetry, also called wideband tympanometry, was measured twice for each ear with a TITAN device (Interacoustics, Middelfart, Denmark) [33].

Tubomanometry (TMM) is an Eustachian tube (ET) function testing method. The principle of TMM is to deliver defined pressures of 30, 40 and 50 mbar to the epipharynx through a nasal applicator. Swallowing triggers the opening of the cartilaginous part of the ET and at the same time temporarily seals the epipharynx towards the pharynx. If the ET opens during swallowing, the defined pressure applied to the epipharynx is transmitted to the middle ear. Pressure curves of the epipharynx and the ear canal are displayed on the monitor of the TMM device, and various measuring values are calculated [34]. In the present study, TMM measurements were acquired three times before and after each nap with a TMM device from DTF Medical (Saint-Etienne, France).

### Physical examination

Neck mobility was assessed through the Neckcare device [35], by recording range of motion of the neck in the three rotation directions, measured as angles in degrees. 3 measures were taken for each direction of rotation through an assisted and automatized procedure.

Muscular trigger point tests were then performed to assess masticatory and neck muscular sensitivity and its relation to tinnitus. These examinations were mainly realized by V.P. who had a physiotherapist background, who trained the other experimenters to perform the tests whenever he was not available. It consisted in the experimenter applying a defined and standard amount of pressure over the trigger points of a set of masticatory and neck muscles and asking the patient two questions. First question was to rate on a scale from 0 to 10 how much pain this pressure would induce, and then second to describe if it would elicit either an increase (encoded as +1), a decrease (encoded as -1) or no effect on his/her tinnitus loudness (encoded as 0) to test somatosensory modulation. Muscles were tested on the left and right side separately in the following order: trapezius muscles, sternocleidomastoid muscles, masseter muscles, temporalis muscles, splenius capitis muscles. All answers were collected in real time by experimenters on a dedicated Psychopy python interface.

An adapted Spurling test to assess pain elicited by compression of the cervical facet joints was applied on the left and right side [36]. Again, for each test, patients were asked if this maneuver would modify tinnitus loudness.

Next examinations were a set of assessments of jaw mobility. Range of motion of the jaw were measured in millimeters by a ruler for jaw maximum opening and laterotrusion to the right and left. Last, a jaw jerk test was performed [37]. Again, for each test, patients were asked if the performed movements would modify tinnitus perceived loudness.

### Tinnitus momentary assessment (TMA)

Then, except before the first nap attempt cycle, the patients were left in autonomy to perform TMA. TMA consisted first in reporting VNS-L and VNS-I. Then, a minimum masking level (MML) procedure was performed to estimate tinnitus loudness. MML was assessed with a MP4 device (Mobile Gear MP4 player, On-EARZ) and intra-auricular JBL Wired Headset (Harman International Industries). The masking stimulation was a broadband white noise (20 Hz to 10 kHz). MML procedure starting 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 volume where you cannot discriminate your tinnitus perception from the sound stimulus, without actively focusing to do so”. This procedure for MML assessment was performed

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and reported three consecutive times in order to ensure stability of the measurement. This set of procedures and how to fill their answers on the dedicated Psychopy python interface was taught to the patients just before the first nap attempt.

Last, patients went through an EEG resting state measurement. After a last verification of the quality of the signal, the advice given to the patient was to stare at a cross on the screen of a computer, staying still and without thinking about anything in particular for 90 seconds, and then when a bip sound would occur, to close their eyes and remain still without thinking about anything in particular until a second bip sound would end the EEG resting-state measurement.

During the period of time between the two days of participation, participants were asked to fill two short questionnaires one before going to bed and one shortly after awakening. These two questionnaires assessed tinnitus loudness and its associated intrusiveness using visual analog scales (respectively VNS-L and VNS-I), as well as Minimum Masking Levels (MML) of their tinnitus (with the method described in 2.3.4). In addition, the morning short questionnaire included a sleep agenda set of questions. Patients 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.

A tinnitus matching procedure was performed to assess tinnitus pitch characteristics at the end of the first or the second day of participation depending on participant availability.

#### 2.3.4. Experimenters blinding:

In order to limit bias, the experimenters were blinded to the variations of tinnitus perceived by patients over the course of the day. To ensure this, from the start of the day in hospital to the end of the last third of the day's nap cycle, participants reported their TMA autonomously on a custom-designed Psychopy interface [38].

### 2.4. Preprocessing :

#### 2.4.1. Assigning side variables according to tinnitus side :

Some of the variables used in this study are lateralized (for example left or right muscle, left or right hearing threshold) and so was tinnitus (left, right or bilateral). It appeared more valuable to measure the variables of interest relative to the tinnitus side. This is why we calculated metrics as “ipsilateral” or “contralateral” to the participant’s tinnitus side. If a participant reported tinnitus “inside the head” or “in both sides”, we used the average of left and right measurements.

#### 2.4.2. Somatosensory assessment variables computation:

The answers collected during muscular trigger point tests were processed before statistical analyses. First, each right or left measurement was converted to a tinnitus ipsilateral or contralateral measurement according to the procedure described above. Then cumulated scores were calculated as the sum of the records for each muscle (trapezius muscle, sternocleidomastoid muscle, masseter muscle, temporalis muscle, splenius capitis muscle). These sums were calculated separately for ipsilateral and contralateral measurements for both sensibility scales and somatosensory modulation records. It resulted in four different cumulated scores.

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## 2.5. Statistical analyses:

Data were centralized on a common anonymized CSV (Comma Separated Value) file and analyzed using Python, pandas library [39] and Scipy library [40].

Before any correlation tests, a z-scoring procedure was applied for all features. This procedure was as follows: centering and standardization was applied for all measurements of a feature on the set of naps from each patient separately. For example, for snoring duration, for each patient, Z-scoring was applied on the distribution of snoring durations of all his/her naps, independently from one patient to the other. TMA were performed between the two days of participation at the hospital: TMA included MML, VNS-L and VNS-I, which were assessed every morning and every evening for at least three days per patient. These additional measurements were included in the Z-scoring procedure to have better distribution granularity on these important TMA features.

A first set of tests were conducted to evaluate how naps and pauses between naps affected tinnitus intensity measured by MML. Wilcoxon paired-tests were used to evaluate the overall effect of naps on MML as well as between each distribution of MML values at each sequential time point of the day.

A second statistical analysis was led to evaluate the absolute amount of variation between each paired point for each time point of the day. Again, Wilcoxon paired-tests were used between each distribution of absolute difference of MML values between each sequential time point of the day.

Cohen-d effect size calculations were systematically performed for each Wilcoxon tests.

Features concerning the polysomnographic events measured during the nap (referred hereafter as intra-nap measurements) were correlated with TMA over the nap. As the dataset consisted of sets of naps of patients, Spearman correlation tests were performed between intra-nap measurements and TMA for each set of naps for all patients. Pearson correlation statistics were then extracted and aggregated in one list for all patients. Fisher Z-transform was then applied to this list of statistics. Then a Stouffer combination method was utilized on the given list of Z-transformed statistics to derive a single p-value for correlation group-wise. In cases where a Z-score value in the list exceeded 5 or fell below -5, it was assigned the value of 5 or -5, respectively.

Regarding the audiological and kinesiological explorations conducted before and after the nap (referred to as extra-nap measurements), their features were correlated with TMA scores before and after the nap. However, as these features' values were collected both before and after the nap, a Pearson 2D correlation test was employed. The resulting 2D individual correlation statistics were then compiled into a single list. The subsequent steps followed a similar procedure as described above: Fisher Z-transform was applied to this list of correlation statistics, followed by the application of the Stouffer combination method to obtain a final p-value for correlation group-wise. If any Z-score in the list exceeded 5 or fell below -5, it was respectively assigned the value of 5 or -5.

Holm-Bonferroni method [41] was applied to control for multiple statistical testing on correlation tests. Such control was applied for each TMA feature set of tests separately, as TMA measurements were highly correlated one to the other (high correlation between MML, VNS-L and VNS-I measurements).

Last, the effect of naps on extra-nap measurements was assessed using a one-sided Stouffer combination of p-value method over the list paired t-tests p-values for each participant scores before and after each nap.

## 3. Results :

### 3.1. Global effect of naps on tinnitus :

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Figure 2 displays the representation of the Z-scored MML variation before and after a nap on a total of 193 naps (4 missing values for MML measurements). Naps that fall above or very close to the diagonal line indicate no variation in MML between before and after the nap. The majority of naps, as depicted in the top left corner, demonstrate an increase in MML after the nap, compared to the value before. This observation was further supported by a comprehensive test conducted on the 195 paired-values of MML, revealing a significant result ( $p < 0.001$ , Cohen-d: 0.55). However, it is important to note that not all naps resulted in an increase in MML. 23% of naps actually led to a reduction in MML, with certain participants reporting different outcomes across their 6 naps.

### *3.2. Effect of consecutive naps over the day on tinnitus :*

Figure 3 illustrates the changes in the MML measurements distributions throughout the day, encompassing all the days of participation from all participants. All three naps across the day elicited a significant increase of MML after the nap compared to the value before the nap (first nap :  $p < 0.001$ , Cohen-d : 0.59 , second nap :  $p < 0.001$ , Cohen-d : 0.59, third nap :  $p < 0.001$ , Cohen-d : 0.47). The first break of the day (2 hours during which patients had their lunch) elicited a significant reduction of tinnitus ( $p < 0.001$ , Cohen-d : 0.7), as well as the second break (1 hour, no systematic food intake,  $p < 0.05$ , Cohen-d : 0.34).

Figure 4 illustrates the absolute magnitude of MML variation between paired MML values for each time interval of the day. As the day progressed, there was a gradual decrease in the impact of naps. We observed a notable decrease in the absolute paired-difference of MML between before and after the first nap and before and after the second nap ( $p < 0.05$ , Cohen-d: 0.41). Similarly, we also observed a significant decrease in magnitude between the first and the third nap ( $p < 0.01$ , Cohen-d: 0.49). However, there was no significant reduction observed between the second and third nap of the day.

### *3.3. Effect of naps on extra-nap measurements :*

Effect of naps was tested on extra-nap measurements. Only a significant effect of naps was observed for ipsilateral ( $p < 0.01$ ) and contralateral ( $p < 0.05$ ) measurements of resonance frequency measured by multifrequential impedancemetry. The effect of the nap on this metric was a reduction of resonance frequency.

Tubomanometry measurements appeared unexploitable for analysis due to poor signal quality and test reliability.

### *3.4. Correlations of TMA metrics with intra-nap measurements :*

Table 3 displays the outcome of the correlation analysis conducted on the intra-nap measurements and TMA measurements. We provide further information regarding each measurement subsequently.

#### *3.4.1 Correlations with nap sleep duration:*

Light sleep (N2 stage) was reached for at least 1 epoch (30s) in 169 out of the 197 nap attempts performed (85, 7 %). Deep sleep (N3) was present in 21 out of the 195 naps (10 , 7%) performed. No participant reached REM sleep stage in any epoch during any of the nap attempts. After Holm-Bonferroni statistical correction, significant positive correlations were found between N2 duration during the nap and VNS-L variation ( $p < 0.05$ ) and N2 and N3 durations during the nap and VNS-L variation ( $p < 0.05$ ). We also performed a supplementary correlation test between the nap attempt total duration

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(independently of sleep duration) and VNS-L variation and we did not find significant, even without any correction for statistical testing.

#### *3.4.2 Correlations with sleep breathing disorder metrics:*

Another important issue of this experiment was to determine the correlation between the variation in MML and the count of apnea and hypopnea events throughout the nap. However, no significant correlation was found between these metrics, even without applying the Holm-Bonferroni correction. However, a significant positive correlation was observed between the variation in VNS-I and the count of apnea and hypopnea events ( $p < 0.001$ ). In the initial questionnaire, 8 participants (24.32%) reported being diagnosed with sleep apnea. However, we did not include full night polysomnography or polygraphy in this protocol to confirm objectively these diagnoses. Besides, during the nap recordings, 34 participants (91.89%) exhibited 15 or more sleep apnea or hypopnea events per hour of sleep during at least one of their naps.

Different sleep breathing disorder metrics were examined in this study. Firstly, the SPO2 desaturation count was tested, followed by the duration of snoring and the average sound intensity of snoring (in dB). The results revealed significant positive correlations between the duration of snoring and the variation in MML ( $p < 0.01$ ), as well as between the average sound intensity of snoring and the variation in VNS-I ( $p < 0.05$ ). To further validate the findings, a supplementary control test was conducted to assess the correlation between the general average sound in the room during the nap (in dB) and each TMA metric. However, even without applying any statistical correction, no significant correlation was observed. Interestingly, in the initial questionnaire, 19 participants (51.35%) reported snoring, but during the naps recording, 33 participants (89.19%) exhibited more than 30 seconds of cumulative snoring during at least one of their naps.

#### *3.4.3 Effect of Sleep position on tinnitus modulation :*

Out of the 37 participants who took part in this study, a mere 2 participants (5.41%) stated that taking a nap while seated tended to exacerbate their tinnitus. On the other hand, a majority of 31 participants (83.78%) reported that their tinnitus remained unaffected by their sleeping position. This initial finding was further supported by the absence of any significant correlation between the sleep position during the nap and any of the TMA metrics. Detailed analysis of the head position during the nap, as determined through manual scoring of video camera footage, can be found in the supplementary material.

#### *3.4.4 Effect of bruxism on tinnitus modulation :*

Out of the 37 individuals who took part in this study, merely 7 participants (18.92%) disclosed that they had been diagnosed with sleep bruxism. Throughout the nap recordings, 6 participants experienced 5 or more episodes of sleep bruxism in at least one of their naps. There was no observed correlation between the number of sleep bruxism episodes and any of the TMA metrics.

#### *3.5. Correlations of TMA metrics with extra-nap measurements :*

No statistically significant correlation was found between any of the extra-naps measurements (trigger point tests measurements, neck and jaw mobility, auditory thresholds nearest to tinnitus frequency, average tone loss, multifrequency impedancemetry measurements) and any of the TMA metrics after statistical correction. It is important to note that despite the fact nap showed a significant effect on multifrequency impedancemetry resonance frequency as mentioned above, no significant

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correlations were found between TMA and this variable.

Correlations of TMA and extra-nap measurements are presented in greater detail with all individual items instead of aggregated scores in supplementary material table 2 to this study. Such a supplementary analysis was purely exploratory and thus no statistical corrections were applied.

#### **4. Discussion**

This study is the first to demonstrate and quantify in a controlled clinical environment that naps can increase tinnitus. It gives objective ground to the experiences frequently reported by tinnitus patients seeking medical advice.

This study is indeed the first to investigate correlates of Naps-Induced Tinnitus Modulations (NITM) in the Tinnitus Increases After Naps (TIAN) population. It has successfully identified potential factors that correlate with NITM, such as snoring and sleep apnea. Our study involved a longitudinal analysis of a sample of patients, who underwent six nap attempts over two days in a sleep laboratory. The results revealed that NITM is not a consistent phenomenon, as we observed different variations of tinnitus in the same individuals during the six nap attempts. However, we observed at a group level that each nap, regardless of the time of day, led to a significant increase in mean tinnitus loudness. Interestingly, these increases were temporary, as we also remarked significant decreases in tinnitus loudness between naps.

We believe that the introduction of longitudinal measurements of NITM in the TIAN population offers several methodological advantages. Firstly, it allows for a comparison of participants with themselves, this allows for more statistically robust pairwise comparisons by eliminating many confounding factors, since the patient is his or her own control. It is important to emphasize that the majority of previous protocols have focused on comparing a tinnitus sample to matched controls in order to identify physiological correlates of tinnitus. [42–45]. But such comparison between different groups of participants brings unpaired measurements that can hardly be perfectly matched, a key example being different patterns of hearing loss, or unknown amounts of auditory nerve deafferentation [46,47]. Indeed, a variety of studies have already tried to compare tinnitus patients to themselves in a tinnitus modulated state, often through sound stimulation. Examples are residual inhibition [48], Zwicker tone [49], mechanical stimulation of the middle ear [50]. Such modulation techniques have at least two limitations: first, the modulation is very short, not leaving enough time to perform time-consuming audiologic tests. Second, as the technique used to induce the modulation is sound based, any test aiming at probing the auditory system suffers the bias of the sound stimulation. NITM solves these limitations as patients of the TIAN population often report that NITM are long and stable modulations of tinnitus.

Additionally, the transition from a normal tinnitus state to a modulated state during naps is relatively short (15 minutes of sleep). Lastly, as demonstrated in this study, naps have minimal physiological effects apart from NITM. The only significant change observed was a modification in the resonance frequency of multifrequency impedancemetry, although it was shown that this metric did not correlate with NITM. Such a significant reduction in resonance frequency of multifrequency impedancemetry following naps could be explained by a residual effect of middle-ear pressure elevation during sleep [51,52]. Overall, NITM provides a valuable framework for studying and identifying the physiological factors associated with tinnitus. This study contributes to the understanding of NITM and its potential links to somatosensory triggers, furthering the knowledge in this field.

NITM and the somatosensory hypothesis :

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The motivation behind this study was to identify the physiological correlates of NITM, and more specifically to test if NITM were a hidden form of somatosensory modulation [5,13,16]. We systematically tested a variety of physiological correlates that could be involved in generating somatosensory modulations of tinnitus. We performed some of these assessments during the naps: sleep apnea, snoring, bruxism and sleep position. Other assessments were tested before and after the nap along with TMA: neck and jaw mobility, neck and jaw muscle sensitivity and susceptibility to elicit somatosensory modulations and middle-ear multifrequency impedancemetry.

Somatosensory modulations of tinnitus are believed to be triggered by somatosensory information transmitted by the muscles and joints innervated by the mandibular branch of the trigeminal nerve to the cochlear nucleus via the caudal spinal part of the trigeminal complex (Sp5) and by dorsal root ganglions [7,53]. If NITM were indeed a hidden form of somatosensory modulation, it would be expected that naps would alter the somatosensory signal transmitted by at least one muscle or joint structure innervated by the trigeminal nerve. This change in the afferent somatosensory signal would consequently lead to a corresponding change in tinnitus loudness.

The present results tend to invalidate this hypothesis when considering the overall cumulated somatosensory information transmitted by the tested muscles. Indeed, no significant correlations were observed between TMA and the cumulative scores of trigger point sensitivity or somatosensory modulations of tinnitus. Further analysis, as described in the supplementary material, showed that even when examining each muscle individually, only the sensitivity changes in the contralateral trapezoid muscle and contralateral sternocleidomastoid muscle exhibited a significant correlation (without statistical corrections) with TMA.

Moreover, it seems that temporomandibular joint and masticatory muscles are not involved in NITM. Indeed, neither jaw mobility nor bruxism episode counts significantly correlated with TMA.

However, the mandibular branch of the trigeminal nerve does not solely innervate the masticatory muscles. It also innervates the tensor veli palatini (TVP) and tensor tympani (TT). Previous studies have shown that they could play a role in tinnitus generation and/or modulation, notably in the case of the tensor tympani syndrome or in case of acoustic shock [54,55]. A review conducted by Norena et al. proposed that the excessive use of the TT muscle can give rise to a chronic neurogenic inflammation. This inflammation would lead to the continuous transmission of somatosensory information to the trigeminal complex (acoustic shock model) [56].

#### Tensor veli palatini overuse hypothesis :

In the present study, we found significant correlations between snoring duration and MML variation, between average snoring sound intensity and VNS-I and between apnea count and VNS-I. These findings provide support for the notion that a similar model to the acoustic shock model could be applied to the TVP instead of the TT for the TIAN population. Sleep apnea and snoring are both very often related to TVP tonus dysregulations during sleep [57,58]. In fact, some studies suggest that people with snoring and/or obstructive sleep apnea syndrome (OSA) have by nature a narrower pharyngeal airway section [61]. Consequently, this would result in a higher tonic tonus of the TVP in the awake state to maintain airway patency. A study conducted by Mezzanotte et al. [62] also suggested this possibility, showing that apneic patients display a more significant decrease in electromyographic tonus upon sleep onset compared to healthy controls. Consequently, this would lead to an increase in somatosensory information transmitted by the muscle to the trigeminal complex, thereby altering its structure. Evidence of this phenomenon has been demonstrated in rodent models of sleep apnea, where an increase in noradrenergic terminals in the Sp5 region of the trigeminal complex



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was observed [60]. In this model, sleep occurrences, such as naps, would constitute triggers for changes in TVP tonus. This would result in changes of somatosensory information afferent signal and as a result of tinnitus perception through somatosensory modulation of the auditory signal in the central auditory pathway.

Additionally, in alignment with the acoustic shock model, chronic apnea and/or chronic snoring could trigger a chronic neurogenic inflammation, reactivated night after night. This possibility is strongly supported by the report of proliferation of receptors for nociceptive agent substance P, in the palatal mucosa of apneic patients and chronic snorers [59].

Furthermore, snoring activity during sleep could constitute abnormal afferent proprioceptive signals that could contribute to somatosensory modulation of tinnitus. Indeed, one definition of simple snoring consists of a fluttering sound created by the vibrations of pharyngeal tissues [63]. Such vibrations would generate a proprioceptive excitation of the TVP and the TT, then transmitted to the trigeminal complex. This proprioceptive disturbance could in itself be a source of modulation of tinnitus as a past study has hypothesized that proprioceptive signal disruption within the middle ear could trigger tinnitus [50].

#### Alternative possibilities :

Another alternative explanation for the observed association between sleep apnea and VNS-I could be the potential impact of both hypoxia or hypercapnia induced by these events on NITM. Recent research has indicated a link between sleep apnea and hearing loss [64]. Similarly, sleep apnea appears to be highly co-prevalent with tinnitus [23]. It would be plausible to consider that following a nap with sleep apnea episodes, patients may experience a temporary deterioration in their hearing, leading to an increase in tinnitus intensity. However, this particular scenario is unlikely based on the findings of the present study. We did not find any correlations between the number of SPO2 desaturation events and TMA. Furthermore, naps did not appear to have any impact on audiogram.

Then, another explanation for the observed relationship between the duration of snoring and MML, as well as the average sound intensity of snoring and VNS-I, could be attributed to the potential increase in tinnitus intensity caused by exposure to sound during the nap. We there hypothesized that patients may unknowingly subject themselves to some form of acoustic trauma/shock, resulting in an elevation of their tinnitus loudness upon waking up. However, it is important to note that this possibility is unlikely, as the control tests examining the correlation between the average sound intensity in the room during the nap and TMA did not yield statistically significant results, even without applying any corrections.

#### Cervical and body position implication in NITM:

Finally we examined the hypothesis of the potential involvement of the cervical area in NITM. Previous research has demonstrated that the second cervical dorsal root ganglion connects to the cochlear nucleus in animal models [65] suggesting that it could play a role in somatosensory modulation of tinnitus [66]. Some studies have proposed that certain forms of tinnitus may be closely related to cervical spine dysfunctions in the upper cervical region, such forms of tinnitus often referred to as cervicogenic somatosensory tinnitus [36,67–70]. Several therapeutic interventions on the upper cervical area have been proposed to alleviate tinnitus [68,71,72].

Previous studies have suggested that NITM may occur more frequently when individuals sleep in a seated position [5,13,16]. Sleeping in the seated position may induce cervical instability and prolonged periods of bad neck posture.

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However, the findings of the present study indicate that the involvement of the upper cervical spine or body position in NITM is unlikely based on the observed results. There were no significant correlations found between neck mobility, body position, and TMA. Additionally, specific trigger point tests conducted on the splenius capitis muscles did not show any correlation with TMA. When examining the correlation between head position during sleep and TMA, only a significant correlation without statistical corrections was found between head tilting towards the same side and opposite side of tinnitus and VNS-L (cf supplementary material). Lastly, only 2 patients (5.41%) reported an increase in tinnitus intensity when sleeping in a seated position.

#### Sleep occurrence and NITM:

An essential question that arises concerning NITM is whether sleep is a prerequisite for its manifestation. The current study provides limited evidence suggesting that sleep is necessary for NITM to take place. To test this question directly, we could have made a comparison between nap attempts with sleep and those without sleep by examining TMA. However, out of the 197 recorded naps, only 10 nap attempts did not involve any sleep, not even the N1 light sleep stage limiting the possibility of comparison. When comparing these 10 naps to the others that included at least one epoch of sleep, we found no significant differences in terms of TMA amplitude.

Nevertheless, indirect tests bring more insights on this question. Significant correlations could be drawn between N2 sleep duration and VNS-L and cumulated duration of N2 and N3 sleep stages and VNS-L. To control if these correlations were not due to the duration spent in a dark and silent room and not because of sleep, we tried to correlate nap attempt duration length and TMA metrics. No significant correlations were found. This suggests a specific dose effect of sleep.

Such a finding opens the door for a potential alternative scenario: NITM may be induced by central mechanisms that are directly linked to sleep-induced changes in brain functioning. Further explorations on electroencephalographic data acquired during the nap and during the resting states measurements before and after each nap are required to give more ground to this possibility.

#### Audiological changes and NITM:

Tinnitus is commonly associated with some form of hearing impairment, even though traditional audiograms may sometimes appear normal [73]. Recently significant loss of auditory nerve fibers were linked to presence of tinnitus in subjects presenting normal hearing audiograms [74]. Transient hearing loss is often accompanied by an increase or onset of tinnitus, particularly in cases of Meniere's disease where low frequency tinnitus coincides with low frequency hearing loss during acute episodes [75,76].

Another interesting result of the present investigation is that, out of all the auditory features examined, only a significant positive correlation (without statistical corrections) was observed between ipsilateral 4 kHz auditory thresholds and TMA metrics VNS-L and VNS-I (as indicated in the supplementary material). However, it is difficult to draw a direct connection between this correlation and the frequency characteristics of tinnitus in the sample, as the average tinnitus frequency was 7155 Hz, as shown in table 1. It is important to note that both the average audiometric loss and the measurements obtained from multifrequency impedancemetry did not demonstrate any association with TMA. Additionally, it is worth mentioning that the audiogram characteristics remained unaffected by naps during the study. This finding suggests that either naps solely induce changes in the perception of tinnitus without affecting hearing abilities, or that potential

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changes in hearing ability are too subtle to be detected through modifications in the audiogram.

#### *4.3. Limitations :*

One of the primary constraints of the current study was the presence of missing or unusable data, which hindered the analysis process. It is important to highlight that out of the 37 participants, 7 individuals were involved in the hospital study for just one day. Since three nap attempts were deemed insufficient to conduct individual correlation tests, this led to a smaller sample size for correlation analysis.

A second limitation of this study was associated with its exploratory nature. Being the first study of its kind to attempt to identify physiological correlates of NITM, numerous hypotheses were tested. However, the moderate sample size that could be recruited within the designated time frame (originally aiming at 40 participants) required statistical corrections for multiple testing, which led to the suppression of many seemingly significant results.

Another limitation was that the study did not assess whether NITM is influenced by circadian rhythms. The experimental design used in this study was unable to separate the effects of repeated naps throughout the day from the circadian effect on NITM. There are multiple ways circadian rhythm could influence NITM. Two basic possibilities are that NITM could increase or could decrease in magnitude as the day progresses due to a circadian effect. As shown in Figure 2, it was observed that the magnitude of NITM decreases over time. This observation suggests that it is unlikely that a circadian effect causes NITM to increase as the day progresses. However, it cannot be concluded whether the pattern observed is due to a circadian amplification of NITM in the morning, a decrease in NITM amplitude with repeated naps, or a combination of both.

Furthermore, the results of this study revealed a minor flaw in the experimental design. The experimenters believed that NITM remained stable over time after a nap based on patients' reports. This led them to confidently perform audiological and kinesiological measurements post-nap, expecting the tinnitus modulated state to remain stable during these assessments. However, the present results showed a significant decrease in tinnitus loudness during the breaks between naps. Since the post-nap measurements of MML, VNS-L, and VNS-I were conducted shortly after participants woke up, it is possible that tinnitus decreased back to its baseline level before the end of the measurements. To address this issue and ensure the stability of NITM, a simple solution would have been to measure MML, VNS-L, and VNS-I both at the beginning and at the end of pre-nap and post-nap measurements.

Then another limitation of the present study is the lack of control procedures on the correlational tests conducted which hinders the ability to ensure independence among variables. For instance, the duration of nap sleep was found to be correlated with VNS-L, and before statistical corrections, such correlation was also present with VNS-I. However, it is important to note that apnea events count and durations of snoring are both variables that are correlated with durations of nap sleep. Therefore, when measuring either of these two variables, a portion of the observed correlation may actually be attributed to the relationship between nap sleep duration and TMA. To address this issue, more rigorous statistical procedures could be employed to eliminate the influence of independent variables on dependent ones. Yet, such additional procedures will require significantly more instances of nap attempts per patient.

#### *4.4. Suggestions for future research:*

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As stated just above, future protocols trying to identify NITM physiological correlates should make TMA measurements at the beginning and the end of the pre-nap and post-nap measurements.

Another suggestion would be to increase the number of naps per patient, as six naps were maybe not enough to test whether or not individual correlations were significant. As the number of days one participant will be motivated to attend to the hospital for a non-interventional study is limited, a good suggestion would be to try to make it possible for participants to perform their nap attempts at home. It would enable performing these naps on a longer time scale, possibly under remote supervision of the experimenters. Such sleep remote monitoring that can be performed in autonomy by participants could involve the use of novel smart medical devices such as smart rings as the Oura ring (Oura Health Ltd., Oulu, Finland), the Circular Ring (Circular SAS, Paris, France) or EEG headsets such as the Dreem headset (Beacon Biosignals, Boston, USA).

Another suggestion would be to combine nap and night measurements in the same cohort of patients so as to test if naps and night induced tinnitus modulations are caused by the same physiological mechanisms.

Last, a subsequent study focusing on analyzing EEG activity of participants before, during and after the nap is planned to address the alternative hypothesis of whether or not NITM are maybe not induced by somatosensory modulations of tinnitus but by central changes of brain activity induced by naps.

## 5. Conclusions

The current investigation is the first polysomnographic exploration of the TIAN population, aiming to elucidate the underlying mechanisms through which naps may influence tinnitus. We particularly emphasized the methodological design of this study to minimize potential sources of bias when evaluating the associations between NITM and potential physiological factors. Substantial increases in tinnitus loudness, as measured by MML, were observed following each nap session (one in the morning and two in the afternoon). The present study aimed at investigating whether or not NITM were a hidden form of somatosensory modulation. Present results tend to show it is unlikely that NITM could be a tinnitus somatosensory modulation triggered by the jaw or the neck. Instead, results suggest a potential correlation between TMA and nap sleep duration, sleep apnea and especially snoring. Such observations suggest a potential involvement of the TVP muscle in NITM. A new hypothesis on how chronic snoring and sleep apnea could constitute a covert form of tinnitus somatosensory modulation is discussed. Further clinical investigations employing the same methodological framework are mandatory to validate these preliminary exploratory outcomes.

**Supplementary Materials:** The supplementary material “Exploratory correlational analyses” is available hereafter

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**Conflicts of Interest:** Damien Léger declares that in the past 5 years he has been employed as an investigator or a consultant by Actellion-Idorsia, the Agence Spatiale Européenne, Bioprojet, iSommeil, ESAI, Janssen, Jazz, Vanda, Merck, Philips, Rythm, Sanofi, Vitalaire, and Resmed. Robin Guillard declares that he is shareholder and president in Siopi SAS, and has a professional activity as independent as Robin Guillard EIRL.

The other authors did not declare COI.

## References

References must be numbered in order of appearance in the text (including citations in tables and legends) and listed individually at the end of the manuscript. We recommend preparing the references with a bibliography software package, such as EndNote, ReferenceManager or Zotero to avoid typing mistakes and duplicated references. Include the digital object identifier (DOI) for all references where available.

Citations and references in the Supplementary Materials are permitted provided that they also appear in the reference list here.

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Table 1, Sample characteristics for quantitative features (N =37)

	<b>Mean</b>	<b>Std</b>	<b>Min</b>	<b>Max</b>
Age (in years)	55.24	10.70	32	75
Tinnitus Handicap Inventory (THI)	48.76	20.43	14	98
VNS scale Tinnitus loudness (0 to 10)	6.24	1.83	3	10
VNS scale Tinnitus intrusiveness (0 to 10)	5.89	2.34	2	10
Tinnitus main frequency	7155.1	3312	275	12000
<i>Abbreviations : VNS : Visual Numeric Scale</i>				

Table 1 – Sample characteristics for quantitative features, N=37, Abbreviations : VNS : Visual Analog Scale

Table 2, Sample symptomatologic characterisation (N = 37)

General tinnitus characteristics	Percentage	Tinnitus comorbidities	Percentage	Tinnitus variation	Percentage	Sleep symptomatologic profile	Percentage
<b>Assumed cause of tinnitus*</b>		<b>Tinnitus Duration</b>		<b>Variation of Tinnitus Over Time*</b>		<b>Sleep parasomnia diagnoses*</b>	
Exposure to loud sounds	21.62 %	Between 6 months and 1 year	10.81 %	From second to second without any reason	10.81 %	Sleep apnea	24.32 %
Changes in hearing	8.11 %	Between 1 and 2 years	2.7 %	Different intensities over different days	72.97 %	Narcolepsy	0.0 %
Exposure to a change in ambient pressure	0.0 %	Between 2 and 5 years	48.65 %	Frequently louder upon waking	51.35 %	Sleepwalking, night terror	0.0 %
Flu, cold, or other infection	2.7 %	Over 5 years	37.84 %	Frequently louder in the evening	21.62 %	Hypersomnia	0.0 %
Feeling of plugged ears	18.92 %	<b>Self-presumed hearing loss</b>	No tinnitus variation or negligible	No tinnitus variation or negligible	0.0 %	Behavioral disorder during REM sleep	0.0 %
Episode of stress	54.05 %	No	29.73 %	Other	5.41 %	Restless legs syndrome	2.7 %
Head trauma	5.41 %	Yes, a slight hearing loss	35.14 %	<b>Variation of Tinnitus with Movements*</b>		Bruxism (teeth grinding during sleep)	18.92 %
Trauma to the neck (e.g., whiplash)	5.41 %	Yes, a moderate hearing loss	13.51 %	When you clench your teeth	35.14 %	No	62.16 %
I don't know	10.81 %	Yes, a significant hearing loss	10.81 %	Mouth opening with resistance	37.84 %	Other	8.11 %
Other	24.32 %	Don't know	10.81 %	Jaw protrusion with resistance	45.95 %	<b>Effect of Sleeping Position on Tinnitus*</b>	
<b>Description of tinnitus sound*</b>		<b>Many everyday noises painful or bothersome</b>		Jaw protrusion with resistance (left)	32.43 %	Increase, when on my back	5.41 %
I perceive only one sound	24.32 %	Yes	54.05 %	Jaw protrusion with resistance (right)	32.43 %	Increase, when on the left side	8.11 %
I perceive several different sounds	29.73 %	No	45.95 %	Head rotation with resistance (left or right)	27.03 %	Increase, when on the right side	2.7 %
The overall tone is high	67.57 %	<b>Cervical History*</b>		Head rotation with resistance (left or right)	32.43 %	Increase, when on my stomach	2.7 %
The overall tone is medium	5.41 %	Cervical osteoarthritis	27.03 %	Lowering the head	13.51 %	Increase, when I sleep in a seated position	5.41 %
The overall tone is low	5.41 %	History of whiplash or cervical trauma	18.92 %	Lower the head with resistance	35.14 %	Increase, when on my back	2.7 %
One sound / hear resembles a pure tone	5.41 %	Hemiated disc	18.92 %	Tilting the head backward	10.81 %	Increase, when on the left side	10.81 %
One sound / hear resembles a whistling	54.05 %	Cervical discopathy	10.81 %	Tilting the head backward with resistance	24.32 %	Increase, when on the right side	2.7 %
One sound / hear resembles a buzzing	21.62 %	Scoliosis	10.81 %	None of the above	40.54 %	Increase, when on my stomach	2.7 %
One sound / hear seems melodious	2.7 %	Kyphosis / kyphotic posture	16.22 %	<b>Loud sounds increase tinnitus</b>		Increase, when I sleep in a seated position	0.0 %
One sound / hear resembles crickets	8.11 %	Surgical intervention at the cervical level	5.41 %	No	48.65 %	No influence of position on my tinnitus	83.78 %
One sound / hear resembles a background noise	18.92 %	Other	37.84 %	Yes	27.03 %	<b>Average hours of sleep per night</b>	
One sound / hear resembles a hissing	29.73 %	No history to declare	5.41 %	Don't know	24.33 %	Less than 6 hours per night	16.22 %
Other	13.51 %	<b>Migraines or headaches</b>		Other sources of tinnitus variation*		Between 6 to 8 hours	72.97 %
<b>Tinnitus localisation (most of the time)</b>		Almost never	45.95 %	Driving or when in a car	24.32 %	More than 8 hours per night	10.81 %
On both sides?	24.32 %	Rarely	32.43 %	Stress or anxiety	67.57 %	<b>Difficulty falling asleep or staying asleep</b>	
On both sides but more to the left?	24.32 %	Sometimes	16.22 %	When tired or very tired	43.24 %	No	45.95 %
On both sides but more to the right?	16.22 %	Often	13.51 %	When I drink alcohol	29.73 %	Yes, in staying asleep	40.54 %
Exclusively to the right?	13.51 %	Very often	0.00 %	When I drink coffee	5.41 %	Yes, in falling asleep	5.41 %
Exclusively to the left?	10.81 %	<b>Feeling of ear fullness or plugged ears</b>		When I take certain medications	2.7 %	Yes, both	8.11 %
In your head?	8.11 %	Almost never	45.95 %	When I use hearing aids	8.11 %	<b>Snoring</b>	
Other	2.70 %	Rarely	18.93 %	After exertion or sports	21.62 %	Yes	51.35 %
<b>Tinnitus onset</b>		Sometimes	8.11 %	Pressing on the head, neck or near the ear	29.73 %	No	29.73 %
Sudden	59.46 %	Often	8.11 %	Other	13.51 %	Don't know	18.91 %
Progressive	40.54 %	Very often	18.93 %	None of these situations	13.51 %		

(\*) For these questions, responders could select multiple answers among the proposed choices

Table 2 – Sample symptomatologic characterization N=37, Abbreviations : VNS : Visual Analog Scale

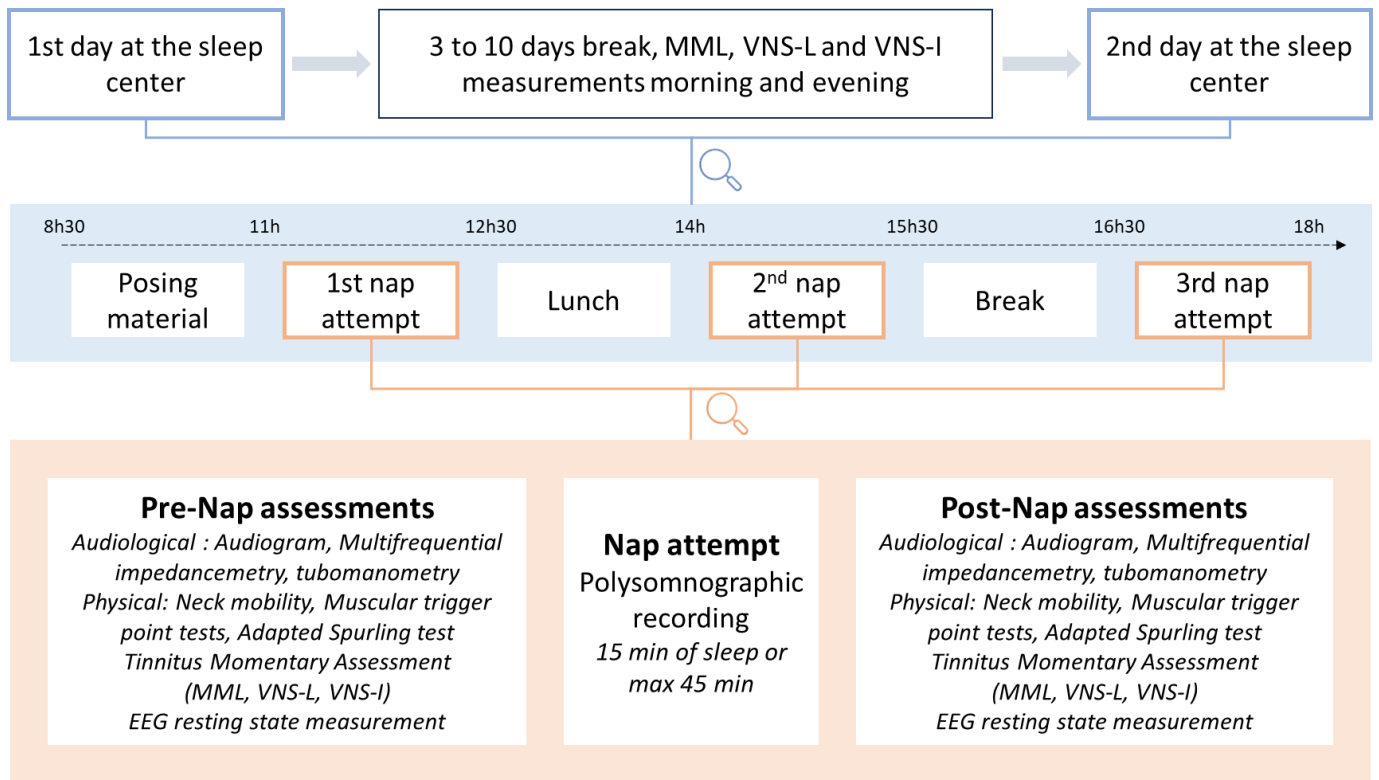
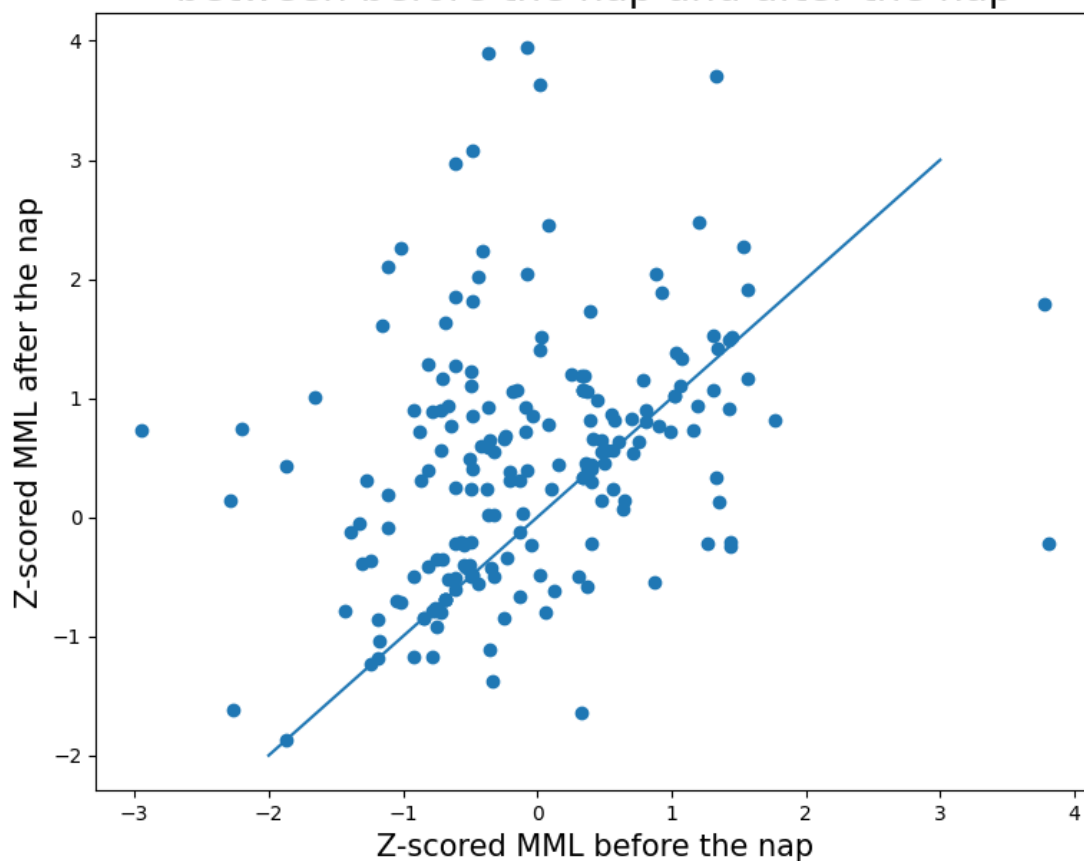


Figure 1: Pipeline of participation of Tinninap subjects, MML : minimum masking level, VNS-L: visual numeric scale on tinnitus loudness, VNS-I: visual numeric scale on tinnitus intrusiveness, EEG: electroencephalography

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Figure 2: Distribution of Z-scored Minimum Masking levels between before the nap and after the nap



*between the two days of participation.*

Figure 3: Evolution of Z-scored Minimum Masking Level (MML) across time of measurement in the day

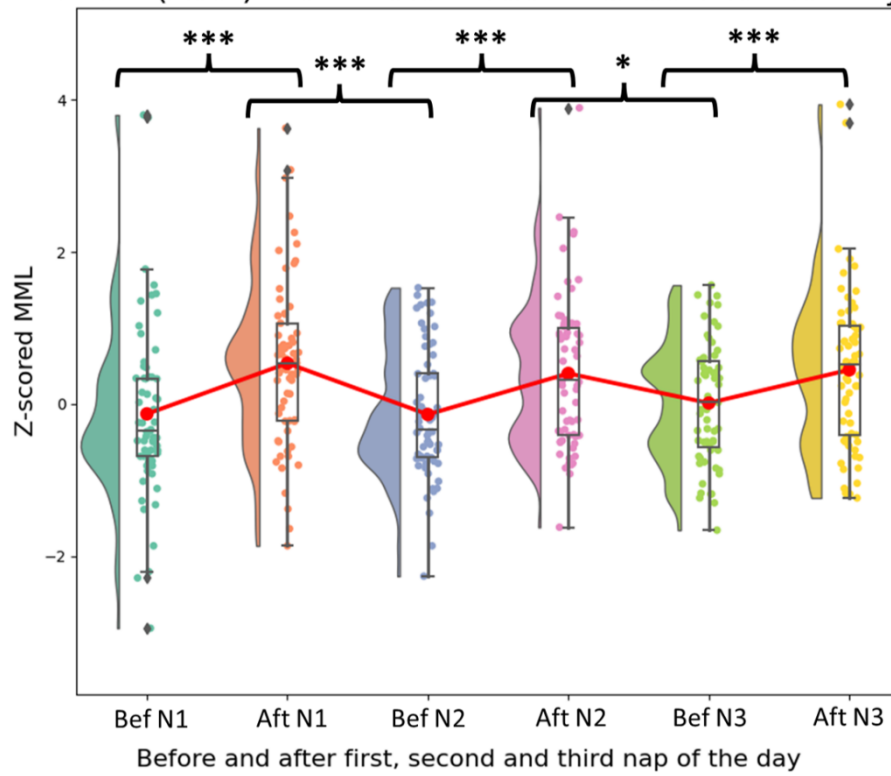


Figure 3: Evolution of Z-scored Minimum Masking Level (MML) across time of measurement in the day.  
Bef: Before, Aft : After N1 : nap 1, N2 : nap 2, N3 : nap 3

Figure 4: Evolution of absolute differences of Z-scored Minimum Masking Level (MML) across time of measurement in the day

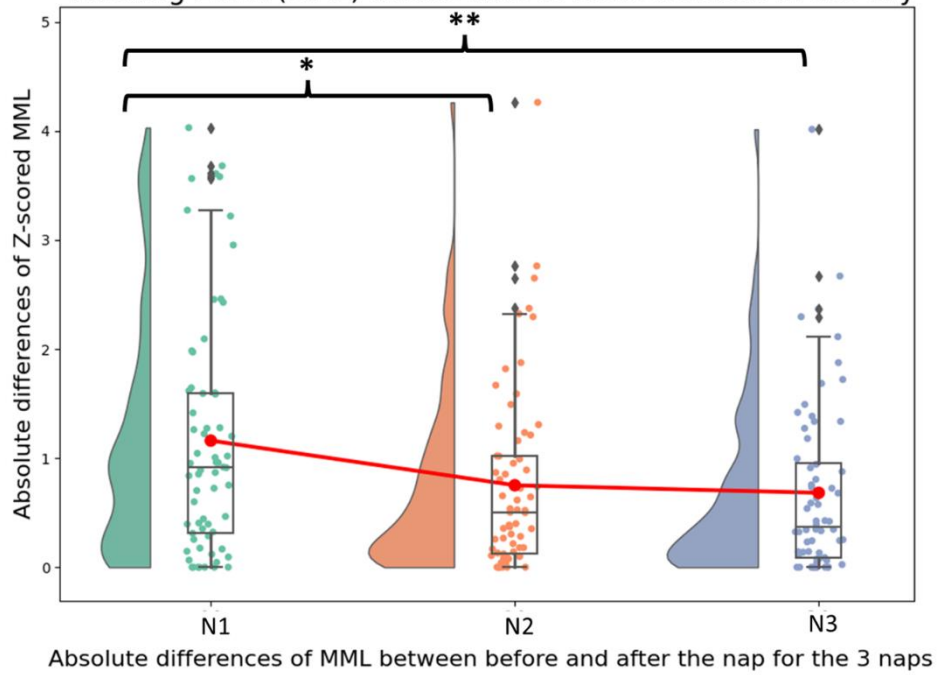


Figure 4: Evolution of absolute differences of Z-scored Minimum Masking Level (MML) across time of measurement in the day. N1 : nap 1, N2 : nap 2, N3 : nap 3



Table 3, Polysomnographic correlates of nap-induced tinnitus modulations

Polysomnographic correlates	Number of patients	Delta MML		Delta VNS-L		Delta VNS-I	
		Correlation dir	P-value	Correlation dir	P-value	Correlation dir	P-value
N2 sleep duration	29	Positive	1.0	Positive	<b>0.011*</b>	Positive	1.0
N2 and N3 sleep duration	29	Positive	1.0	Positive	<b>0.02*</b>	Positive	1.0
Snoring duration	29	Positive	<b>p &lt; 0.001 ***</b>	Positive	0.38	Positive	0.75
Average snore db	29	Positive	0.2	Positive	0.12	Positive	<b>0.012 *</b>
Apnea count	29	Negative	1.0	Positive	0.14	Positive	<b>p &lt; 0.001 ***</b>
SPO2 desaturation count	25	Negative	0.56	Positive	0.75	Positive	0.32
Supine position duration	28	Negative	1.0	Positive	1.0	Negative	1.0
Ipsilateral rotated sleep position	28	Positive	1.0	Negative	0.26	Positive	1.0
Controlateral rotated sleep position	28	Positive	1.0	Negative	1.0	Negative	1.0
Bruxism burst events count	28	Positive	1.0	Positive	0.17	Negative	0.79

Abbreviations : VNS : Visual Numeric Scale, Correlation dir : direction of the correlation, (\*) :  $p < 0.05$ , (\*\*) :  $p < 0.01$ , (\*\*\*) :  $p < 0.001$

Table 3 : Polysomnographic correlates of nap-induced tinnitus modulations. MML : Minimum Masking Level, VNS-L : Visual Analog Scale on tinnitus Loudness, VNS-I : Visual Analog Scale on tinnitus Intrusiveness, SPO2 : Blood-oxygen saturation level, dir : direction (of the correlation)

Table 4, Audiologic and kinesiologic correlates of nap-induced tinnitus modulations (N =30)

Audiologic and kinesiologic correlates	MML		VNS-L		VNS-I	
	Correlation dir	P-value	Correlation dir	P-value	Correlation dir	P-value
Cumulated muscular sensibility ipsi	Positive	0.33	Positive	1.0	Positive	1.0
Cumulated muscular sensibility contro	Positive	0.12	Positive	1.0	Positive	1.0
Cumulated tinnitus modulation ipsi	Negative	1.0	Positive	1.0	Positive	1.0
Cumulated tinnitus modulation contro	Negative	1.0	Positive	1.0	Positive	1.0
Neck extension-flexion amplitude (°)	Positive	1.0	Positive	1.0	Positive	1.0
Neck lateral flexion amplitude (°)	Negative	1.0	Positive	1.0	Positive	0.64
Neck rotation amplitude (°)	Negative	1.0	Negative	1.0	Positive	1.0
Jaw opening amplitude (cm)	Negative	1.0	Negative	1.0	Negative	1.0
Jaw diduction amplitude ipsi (cm)	Positive	1.0	Positive	1.0	Positive	1.0
Jaw diduction amplitude contro (cm)	Negative	1.0	Positive	1.0	Positive	1.0
Intensity threshold closest freq ipsi (dB)	Positive	1.0	Negative	1.0	Negative	1.0
Intensity threshold closest freq contro (dB)	Positive	1.0	Positive	1.0	Positive	0.26
Average tone loss	Positive	1.0	Positive	1.0	Positive	0.62
Multifreq Imp Resonance freq ipsi	Negative	0.91	Negative	1.0	Negative	1.0
Multifreq Imp Peak pressure ipsi	Positive	1.0	Positive	1.0	Positive	1.0
Multifreq Imp Resonance freq contro	Negative	1.0	Negative	0.79	Negative	1.0
Multifreq Imp Peak pressure contro	Positive	1.0	Positive	1.0	Positive	1.0

*Abbreviations : Correlation dir : direction of the correlation, ipsi : measurement performed on the side of tinnitus perception, ipsi : measurement performed on the side contralateral to tinnitus perception, freq : frequency, multifreq imp : multifrequential impedancemetry*

*Table 4 : Audiologic and kinesiologic correlates of nap-induced tinnitus modulations (N=30). MML : Minimum Masking Level, VNS-L : Visual Analog Scale on tinnitus Loudness, VNS-I : Visual Analog Scale on tinnitus Intrusiveness, dir : direction (of the correlation), ipsi : measurement performed on the side of the tinnitus perception, contro : measurement performed on the side contralateral to the tinnitus perception, multifreq imp : multifrequency impedancemetry.*

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## Supplementary Material:

Hereafter in Supplementary Tables 1 and 2 are presented the results of correlational tests between Tinnitus Momentary Assessment (TMA) features (Minimum masking level, Visual analog scales on tinnitus loudness and intrusiveness) and a more extended set of intra-nap and extra-nap measurements. Please note that these tests were purely exploratory, this is why no statistical corrections for multiple testing were applied here.

Hereafter are described the meaning and procedure of obtention of the extended features presented in these tables.

### Extended Intra-nap features

Snore and apnea density: it was calculated as the sum of durations of snores, apneas and hypopneas events during the nap divided by the duration of sleep during the nap.

Head positions durations per nap were manually scored from video recordings of the nap sessions. They were calculated as percentages of the total duration of the nap, as for body positions.

Distinction between sleep bruxism burst events and episodes : applying scoring recommendations from Lavigne and al [29], bursts of bruxism are 250 ms bursts of EMG activity in the suprahyoid and/or masseter muscles, without concomitant body movement. Bruxism episodes were scored from bursts with three different types : phasic (rhythmic), tonic (sustained), or mixed (both phasic and tonic). A phasic episode corresponds to at least three EMG bursts of 0.25 to 2.0 seconds' duration, separated by two inter burst intervals. A tonic episode corresponds to an EMG burst lasting more than 2.0 s.

### Extended extra-nap features

Extended extra-nap features comprise the details of trigger point sensitivity and somatosensory modulations tests for all specific facial and cervical muscles tested, for both ipsilateral and contralateral sides. It also includes results of the adapted Spurling test and whether or not it elicited somatosensory modulations.

Likewise, correlational tests between all intensity thresholds frequencies for both sides ipsilateral and contralateral to tinnitus are detailed.

Correlations tests between TMA and tinnitus furthest frequency auditory thresholds were provided as a control test for closest frequency correlation test. Furthest frequency auditory threshold was the frequency among the ones tested that maximized the distance with tinnitus main frequency calculated from the tinnitus matching procedure.

Two supplementary features are also provided for multifrequency impedancemetry: separation frequency and separation pressure. Normal profiles of multifrequency impedancemetry frequency slices have only one maximum in pressure. This is what is observed classically in tympanograms curves. Yet, in pressure curves of slides of increasing the frequency, gradually the unique maximum in pressure splits in two maxima of pressure. This generally happens between 750 Hz and 3000 Hz and was described in [77]. Separation frequency and pressure was calculated from a custom-made automatic algorithmic procedure as the coordinates in the pressure/frequency plan of the separation between one maximum to two maxima.

Supplementary Table 1, Extended polysomnographic correlates of nap-induced tinnitus modulations

	Number of patients	Delta MML		Delta VNS-L		Delta VNS-I	
		Correlation dir	Pvalue	Correlation dir	Pvalue	Correlation dir	Pvalue
N1 duration	29	Negative	0.066	Negative	0.55	Positive	0.995
N2 duration	29	Positive	0.358	<b>Positive</b>	<b>0.001 **</b>	Positive	0.249
N2+N3 duration	29	Positive	0.373	<b>Positive</b>	<b>0.002 **</b>	Positive	0.278
Nap duration	29	Negative	0.801	Positive	0.449	Positive	0.315
Snore duration	29	<b>Positive</b>	<b>p &lt; 0.001 ***</b>	Positive	0.095	Positive	0.107
Average snore sound intensity during nap	29	<b>Positive</b>	<b>0.023 *</b>	<b>Positive</b>	<b>0.015 *</b>	<b>Positive</b>	<b>0.001 **</b>
Average room sound intensity during nap	29	Positive	0.598	Positive	0.783	Negative	0.417
Apnea count	29	Negative	0.703	<b>Positive</b>	<b>0.024 *</b>	<b>Positive</b>	<b>p &lt; 0.001 ***</b>
Apnea duration	29	Negative	0.51	Positive	0.186	<b>Positive</b>	<b>0.001 **</b>
Snore and Apnea duration	29	<b>Positive</b>	<b>0.004 **</b>	<b>Positive</b>	<b>0.007 **</b>	<b>Positive</b>	<b>0.001 **</b>
Snore and apnea density	25	Positive	0.068	Positive	0.6	<b>Positive</b>	<b>p &lt; 0.001 ***</b>
SPO2 count	28	Negative	0.07	Positive	0.251	<b>Positive</b>	<b>0.04 *</b>
Head upright	29	Negative	0.885	<b>Negative</b>	<b>0.002 **</b>	<b>Negative</b>	<b>0.006 **</b>
Head bent forward	29	Positive	0.811	Positive	0.371	Positive	0.252
Head bent backward	29	Negative	0.738	Negative	0.735	Negative	0.723
Head rotated ipsilateral to tinnitus	29	Negative	0.615	Positive	0.061	Negative	0.949
Head rotated contralateral to tinnitus	29	Negative	0.198	Positive	0.399	Negative	0.188
Head tilted ipsilateral to tinnitus	29	Positive	0.15	<b>Positive</b>	<b>0.002 **</b>	<b>Positive</b>	<b>0.047 *</b>
Head tilted contralateral to tinnitus	29	Positive	0.424	<b>Positive</b>	<b>0.004 **</b>	Positive	0.452
Ipsilateral rotated sleep position	29	Positive	0.251	Negative	0.95	Positive	0.571
Contralateral rotated sleep position	29	Positive	0.329	Negative	0.058	Negative	0.463
Position supine	29	Negative	0.34	Positive	0.905	Negative	0.653
Bruxism burst events count	28	Positive	0.725	<b>Positive</b>	<b>0.026 *</b>	Negative	0.131
Bruxism episodes count	28	<b>Positive</b>	<b>0.028*</b>	<b>Positive</b>	<b>0.002 **</b>	Positive	0.179
Bruxism density of burst events	25	<b>Negative</b>	<b>0.022 *</b>	Negative	0.118	<b>Negative</b>	<b>0.003 **</b>

Abbreviations : VNS : Visual Numeric Scale, Correlation dir : direction of the correlation, (\*) :  $p < 0.05$ , (\*\*) :  $p < 0.01$ , (\*\*\*) :  $p < 0.001$

Supplementary Table 1 : Extended polysomnographic correlates of nap-induced tinnitus modulations. MML : Minimum Masking Level, VNS-L : Visual Analog Scale on tinnitus Loudness, VNS-I : Visual Analog Scale on tinnitus Intrusiveness, SPO2 : Blood-oxygen saturation level, dir : direction (of the correlation)

Supplementary Table 2, Extended audiologic and kinesiologic correlates of nap-induced tinnitus modulations (N=30)

Audiologic and kinesiologic correlates	MML		VNS-L		VNS-I	
	Correlation dir	P-value	Correlation dir	P-value	Correlation dir	P-value
Neck extensionflexion amplitude (°)	Positive	0.971	Positive	0.636	Positive	0.205
Neck lateral flexion amplitude (°)	Negative	0.625	Positive	0.073	<b>Positive</b>	<b>0.043 *</b>
Neck rotation amplitude (°)	Negative	0.129	Negative	0.413	Positive	0.741
TP sensibility trapezoid ipsilateral	Positive	0.119	Negative	0.43	Negative	0.65
TP sensibility SCM ipsilateral	Positive	0.078	Positive	0.278	Positive	0.578
TP sensibility splenius ipsilateral	Positive	0.189	Positive	0.321	Positive	0.162
TP sensibility masseter ipsilateral	Positive	0.245	Negative	0.969	Positive	0.993
TP sensibility temporal ipsilateral	Positive	0.09	Positive	0.477	Positive	0.385
TP sensibility trapezoid controlateral	<b>Positive</b>	<b>0.008 **</b>	Negative	0.482	Negative	0.825
TP sensibility SCM controlateral	<b>Positive</b>	<b>0.03 *</b>	Positive	0.358	Positive	0.723
TP sensibility splenius controlateral	Positive	0.425	Positive	0.352	Positive	0.164
TP sensibility masseter controlateral	Positive	0.109	Positive	0.81	Positive	0.73
TP sensibility temporal controlateral	Positive	0.187	Positive	0.437	Positive	0.232
Jaw opening amplitude (cm)	Negative	0.78	Negative	0.381	Negative	0.992
Jaw diduction amplitude ipsi (cm)	Positive	0.351	Positive	0.39	Positive	0.669
Jaw diduction amplitude contro (cm)	Negative	0.793	Positive	0.383	Positive	0.587
Adapted spurling test ipsilateral	Positive	0.388	Positive	0.112	<b>Positive</b>	<b>0.048 *</b>
Adapted spurling test controlateral	Positive	0.154	Positive	0.574	Positive	0.195
TP SM trapezoid ipsilateral	Negative	0.256	Negative	0.276	Negative	0.143
TP SM SCM ipsilateral	Positive	0.996	Negative	0.769	Positive	0.944
TP SM splenius ipsilateral	Positive	0.406	Negative	0.513	Negative	0.386
TP SM masseter ipsilateral	Positive	0.411	Negative	0.41	Negative	0.4
TP SM temporal ipsilateral	Positive	0.268	Negative	0.402	Negative	0.371
TP SM trapezoid controlateral	Negative	0.393	Negative	0.447	Negative	0.432
TP SM SCM controlateral	Negative	0.905	Negative	0.894	Negative	0.995
TP SM splenius controlateral	Positive	0.428	Positive	0.545	Negative	0.356
TP SM masseter controlateral	Positive	0.769	Negative	0.369	Negative	0.343
TP SM temporal controlateral	Positive	0.395	Negative	0.534	Negative	0.644
Jaw opening SM	Positive	0.094	Positive	0.438	Positive	0.515
Jaw diduction SM ipsi (cm)	Positive	0.775	Negative	0.862	Positive	0.713
Jaw diduction SM contro (cm)	Positive	0.235	Positive	0.965	Positive	0.803
Adapted spurling test SM ipsilateral	Positive	0.757	Negative	0.491	Negative	0.215
Adapted spurling test SM controlateral	Positive	0.931	Negative	0.503	Negative	0.123
Intensity threshold closest freq ipsi (dB)	Positive	0.573	Negative	0.619	Negative	0.899
Intensity threshold closest freq contro (dB)	Positive	0.133	Positive	0.155	<b>Positive</b>	<b>0.015 *</b>
Intensity threshold furthest freq ipsi (dB)	Positive	0.971	Positive	0.921	Negative	0.777
Intensity threshold furthest freq contro (dB)	Positive	0.379	Positive	0.948	Negative	0.782
Intensity threshold 125 Hz freq ipsi (dB)	Positive	0.161	Positive	0.501	Positive	0.649
Intensity threshold 250 Hz freq ipsi (dB)	Negative	0.939	Negative	0.586	Positive	0.758
Intensity threshold 500 Hz freq ipsi (dB)	Positive	0.26	Positive	0.231	Positive	0.126
Intensity threshold 750 Hz freq ipsi (dB)	Positive	0.582	Positive	0.452	Positive	0.33
Intensity threshold 1000 Hz freq ipsi (dB)	Positive	0.521	Positive	0.174	Positive	0.154
Intensity threshold 1500 Hz freq ipsi (dB)	Positive	0.611	Positive	0.585	Positive	0.18
Intensity threshold 2000 Hz freq ipsi (dB)	Positive	0.525	Negative	0.921	Positive	0.898
Intensity threshold 3000 Hz freq ipsi (dB)	Positive	0.717	Positive	0.392	Positive	0.369
Intensity threshold 4000 Hz freq ipsi (dB)	Positive	0.557	<b>Positive</b>	<b>0.043 *</b>	<b>Positive</b>	<b>0.009 **</b>
Intensity threshold 6000 Hz freq ipsi (dB)	Negative	0.684	Positive	0.336	Positive	0.359
Intensity threshold 8000 Hz freq ipsi (dB)	Positive	0.933	Negative	0.724	Positive	0.961
Intensity threshold 125 Hz freq contro (dB)	Positive	0.097	Positive	0.108	Positive	0.361
Intensity threshold 250 Hz freq contro (dB)	Positive	0.178	Positive	0.571	Positive	0.373
Intensity threshold 500 Hz freq contro (dB)	Positive	0.271	Positive	0.266	Positive	0.425
Intensity threshold 750 Hz freq contro (dB)	Positive	0.772	Positive	0.536	Positive	0.631
Intensity threshold 1000 Hz freq contro (dB)	Negative	0.973	Positive	0.218	Positive	0.515
Intensity threshold 1500 Hz freq contro (dB)	Positive	0.522	Positive	0.686	Positive	0.56
Intensity threshold 2000 Hz freq contro (dB)	Positive	0.728	Negative	0.753	Positive	0.792
Intensity threshold 3000 Hz freq contro (dB)	Positive	0.126	Positive	0.795	Negative	0.938
Intensity threshold 4000 Hz freq contro (dB)	Positive	0.538	Positive	0.791	Positive	0.619
Intensity threshold 6000 Hz freq contro (dB)	Positive	0.436	Positive	0.948	Negative	0.954
Intensity threshold 8000 Hz freq contro (dB)	Positive	0.412	Positive	0.545	Positive	0.063
Average tone loss	Positive	0.235	Positive	0.159	<b>Positive</b>	<b>0.039 *</b>
Multifreq Imp Resonance freq ipsi (Hz)	Negative	0.061	Negative	0.079	Negative	0.217
Multifreq Imp Peak pressure ipsi (Pa)	Positive	0.376	Positive	0.557	Positive	0.752
Multifreq Imp Separation freq ipsi (Hz)	Negative	0.556	Positive	0.325	Positive	0.194
Multifreq Imp Separation pressure ipsi (Pa)	Positive	0.473	Positive	0.357	Negative	0.889
Multifreq Imp Resonance freq contro (Hz)	Negative	0.803	<b>Negative</b>	<b>0.046 *</b>	Negative	0.089
Multifreq Imp Peak pressure contro (Pa)	Positive	0.709	Positive	0.481	Positive	0.447
Multifreq Imp Separation freq contro (Hz)	Positive	0.664	Negative	0.581	Negative	0.182
Multifreq Imp Separation pressure contro (Pa)	Negative	0.859	Positive	0.782	Negative	0.785

Abbreviations : Correlation dir : direction of the correlation, ipsi : measurement performed on the side of tinnitus perception, contro : measurement performed on the side controlateral to tinnitus perception, freq : frequency, multifreq imp : multifrequency impedancemetry, TP : trigger point, SCM : sternocleidomastoid, SM : somatosensory modulation

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*Supplementary Table 2 : Extended audiologic and kinesiologic correlates of nap-induced tinnitus modulations (N=30). MML : Minimum Masking Level, VNS-L : Visual Analog Scale on tinnitus Loudness, VNS-I : Visual Analog Scale on tinnitus Intrusiveness, dir : direction (of the correlation), ipsi : measurement performed on the side of the tinnitus perception, contro : measurement performed on the side contralateral to the tinnitus perception, multifreq imp : multifrequency impedancemetry, TP :trigger point, SCM : sternocleidomastoid, SM : somatosensory modulation*

# Chapter 6

## General Discussion

## 6. General discussion

Before the research achieved through the present thesis, clinical reports of sleep-induced and nap-induced modulations of tinnitus had been evoked anecdotally in the scientific literature. In our opinion, **the main merit of this thesis is to provide a first epidemiological and physiological characterization of the TIAN and SIT patients' populations, which was lacking in the literature.** Our research work contributes to the assessment of this characteristic symptomatologic trait in the tinnitus population. We have studied the specificities of these subphenotypes in the heterogeneous context of tinnitus. Furthermore, we analyzed the physiological correlates of such sleep-induced tinnitus modulations.

Major outcomes of this thesis are the assessment of prevalence of the TIAN population in the tinnitus population (one out of five tinnitus patient), the observation that twice as many patients describe increase of tinnitus following naps compared to decrease of tinnitus following naps, the demonstration of the existence of sleep-induced (often drastic) modulation of tinnitus by night and nap under polysomnographic assessment condition and the identification of potential correlates of such modulations : REM sleep duration, snoring, sleep apnea and duration of the nap.

Additional merits of the present thesis are a contribution to the assessment of tinnitus heterogeneity through the validation of a French translation of the European School for Interdisciplinary Tinnitus research Screening Questionnaire (ESIT-SQ) and through a benchmark study of clustering methods to best perform a segmentation of tinnitus patients with regards to their diagnoses (when the diagnoses were available). Moreover, this thesis brings a new methodological framework to analyze tinnitus physiological correlates by studying longitudinally TIAN patients. NITM have the advantage to be stable following the nap, leaving enough time to perform several assessments in the tinnitus-modulated state.

### 6.1 On tinnitus heterogeneity

Studying tinnitus heterogeneity within this thesis exceeded the intent to only scrutinize the characteristics of the SIT and TIAN population. As various studies have stated (Coelho et al., 2020; Simoes et al., 2021) an important step to be taken to unravel the physiological correlates of tinnitus and find cures might rely in relinquishing the hypothesis that unique physiological correlates may distinguish all tinnitus patients from individuals without tinnitus. It cannot be excluded, regarding the amount of evidence of tinnitus heterogeneity (on tinnitus pitch, temporal variability, causes, comorbidities, associated intrusiveness), that several distinct sets of physiological signatures may be at the origin of tinnitus depending on tinnitus subgroups. It is hence our opinion that approaches aiming at studying smaller and more homogeneous subgroups of tinnitus patients may yield better results at identifying clear physiological correlates of tinnitus. In this thesis, we focused on two specific tinnitus subphenotypes, TIAN and SIT patients, as an attempt of such an approach. Additionally, our research work on tinnitus heterogeneity was inspired by the fruitful conceptual framework



provided by Genitsaridi (2021), which theorizes three potentially non-identifiable segmentations of the tinnitus population, into endotypes, subtypes and subphenotypes.

Term	Definition
Subgroup	A part of a population (generic term)
Subphenotype	A part of a population with a distinct set of observable characteristics (based on Lötvall et al., 2011)
Subtype	A part of a population with a condition that can be used to guide treatment decisions (based on Saria and Goldenberg, 2015)
Endotype	A part of a population with a condition with distinct underlying mechanisms (based on Anderson, 2008; Lötvall et al., 2011)

### 6.1.1 Clustering tinnitus patients

In Guillard and colleagues (2023a), we aimed more broadly at trying to identify homogeneous subphenotypes of tinnitus that would reproduce the endotype segmentation. Current knowledge about tinnitus endotypes is only partial : we assume we know a limited number of rare etiologies in which tinnitus is associated with specific physiological correlates (acoustic schwannoma, Ménière's disease, pulsatile tinnitus, otosclerosis...). Our approach tried to take advantage of this partial knowledge to design a compass to guide the clustering algorithms. This compass was the use of the V-measure (Rosenberg and Hirschberg, 2007) between the partial diagnostic labels provided by the ENT doctor who collected the database and the attributed cluster labels of the tested algorithm. We completed the characterization of the quality of the obtained clusterings by assessing their stability over a bootstrapping approach by a stability assessment measure, the adjusted mutual information (Vinh et al., 2010). These two criteria guided our benchmark to identify an optimal combination of dimensionality reduction techniques and clustering algorithm for this task. Our benchmark concluded that better scores were achieved by a combination of t-Distributed Stochastic Neighbor Embedding algorithm (t-SNE) and k-means clustering algorithm.

The nature of the of the t-SNE dimensionality reduction technique is that through this method data points that are close in the original high-dimensional space have a higher probability of remaining close to one another in the two or three-dimensional space of projection. Conversely, data points that are distant in the original space have a low probability of having close representations in the space of projection. As a consequence, in the low dimension space it projects to, the axes of projections have no meaning, only the grouping of data points does, in dense structures that gravitate around one another, forming several clusters of different sizes. In the case of our study, it was interesting to observe a recurrent pattern in the structure of the dataset: a massive group of points surrounded by a couple of smaller satellites. Applying on this reduced dimensionality space the k-means algorithm resulted in an optimal clustering in 20 clusters.

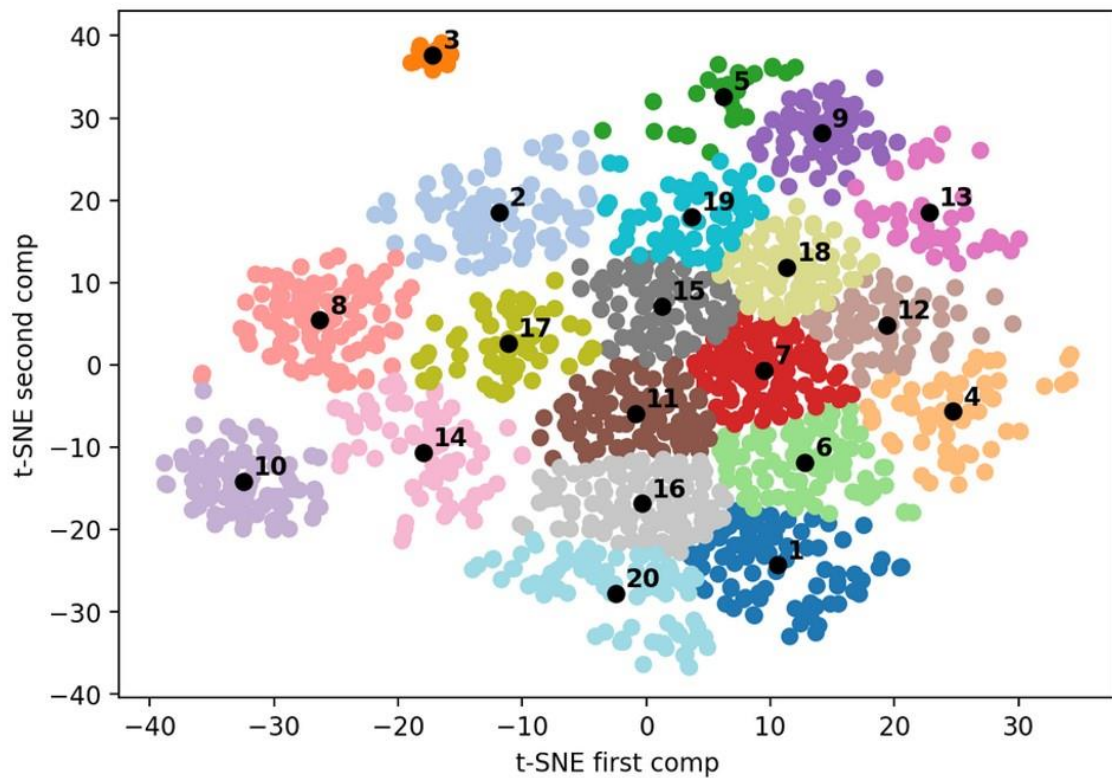


Fig 6.1 selected optimal clustering from (Robin Guillard et al., 2023a)

Retrospectively, such an important number of clusters may appear overrated. Indeed, it is in the nature of the k-means algorithm to form Voronoi-cells-shaped clusters that most often have comparable sizes. The structure of our data was disproportional between a massive central cluster and surrounding smaller satellites. As a consequence, setting the hyperparameters of the k-means to correctly separate each satellite into a distinct cluster resulted in splitting the massive cluster in various subclusters (clusters 1, 4, 6, 7, 11, 12, 15, 16, 18, 19 and 20). Such splitting appears artificial. Indeed, looking at the properties of this central cluster, its structure appeared rather homogeneous, with two interesting gradient axes. First, there was a vertical gradient axis from cluster 20 to cluster 19 that represented tinnitus impact on quality of life. Patients in group 20 were very mildly impacted by tinnitus while patients in cluster 19 were terribly affected by it. Interestingly, a second gradient axis was present and was almost aligned with the first one, although slightly more tilted on the right (from cluster 20 to the 18) and represented sleep quality. Coincidentally, people not bothered by tinnitus were people with a good sleep quality and conversely, people with important sleep deterioration were experiencing distressful forms of tinnitus. Such an alignment confirms the result of the scientific literature concerning the association between tinnitus distress and sleep impairment (Asnis et al., 2018; Crönlein et al., 2007; Folmer and Griest, 2000; Schecklmann et al., 2015), as well as the fact that trying to alleviate one of these symptoms often result in alleviating them both (Marks et al., 2023).

Regarding the purpose of the present thesis, one may question if TIAN and/or SIT patients would constitute separate subphenotypes in such a clustering. First, we cannot conclude concerning the SIT population as there was not a specific set of questions in the questionnaire associated with this database to make such a diagnostic. Concerning the TIAN population,

however, there was indeed a question in the dataset over whether or not naps led to tinnitus increase or not. Yet, a first limitation was the formulation of the question within the questionnaire. The question item asked: “Is tinnitus worse upon awakening in the morning or after a nap?” with only yes or no as possible answers. Such a question does not enable to specifically analyze the TIAN population, but rather all patients presenting with an increase of tinnitus following all sleep episodes. Secondly, this question item could not be included among the set of features used for clustering due missing values (for more than 25% of the dataset). This feature could not be used by the dimensionality reduction techniques, nor the clustering algorithm, to drive the clustering process. Still, one may question whether or not the repartition of TIAN patients was homogeneous in the optimal clustering selected. It appears that TIAN patients were not specifically associated with one of the 20 clusters obtained. Consequently, when modulation by naps is not included as a driving feature for clustering, it seems that a distinct cluster for TIAN patients does not spontaneously appear. This questions the fact that the TIAN patients could be a distinct endotype of tinnitus and interrogates if it is really associated with a specific and distinct profile of symptoms and thus forming a homogeneous subphenotype.

### 6.1.2 Switching to tinnitus trajectories paradigm

Performing this research work has led us to dive into the complexity of tinnitus heterogeneity. A limitation of our methodological approach that we understood only at the end of our work was that we probably did not take into account the time dimension of tinnitus enough. Indeed, as the database we worked on was a database of initial questionnaire records completed at the ENT consultation of Dr Vincent Loche, we assumed that all tinnitus patients that completed the questionnaire were at the beginning of their patient journey. Yet, there was an important variability in duration since tinnitus onset in the sample of the database. For an important amount of tinnitus patients their initial consultation with Dr Loche was not soon after their tinnitus onset (acute tinnitus). It is maybe not their first consultation for addressing their tinnitus complaint. They may have already sought care of a general practitioner or another ENT or already tried some treatment approaches.

The time course of a chronic pathology such as tinnitus is crucial to understand and address the needs of a given patient. The patterns of symptoms of a tinnitus patient can have different starting points and above all evolve differently through time : the tinnitus can start by an initial acute phase of brutal sideration or can be gradual until a precipitating factor. Then, through time, coping mechanism can start to operate with various degrees of success, resulting in habituation, resignation or anchored distress. Hence, it could be postulated that one patient should be assigned into different subphenotypes as time passes and he or she crosses different phases in his or her patient journey. The kinetic of such phase crossing should be assumed to be different from patient to patient.

By not taking into consideration the trajectory through time of tinnitus patients through their journey with this chronic condition, we figuratively took a picture of a set of patients at different steps of their patient journey. Hence, in the clustering obtained, it is impossible to

know with certitude whether the clusters are formed by potentially similar tinnitus patients at different steps of their tinnitus journey, or by patients of initially different subphenotypes.

To illustrate this view, we can mention that in our study Meniere disease patients were dispatched into several clusters. It may be partially due to limitations in the questions asked in the initial questionnaire used in this study (only one question on vertigo), but also, Ménière's disease is an evolutive syndrome by nature : hearing loss, which is initially fluctuant, deteriorates and stabilizes gradually. Ménière's Disease impact on quality of life can vary as vertigo crises transition from rare to frequent. It can also depend on the individual efficacy of the therapeutic strategy chosen. Likewise, acoustic schwannoma patients were grouped in different clusters depending if they completed the initial questionnaire before surgical intervention or post-surgical intervention (which leads to unilateral hearing loss).

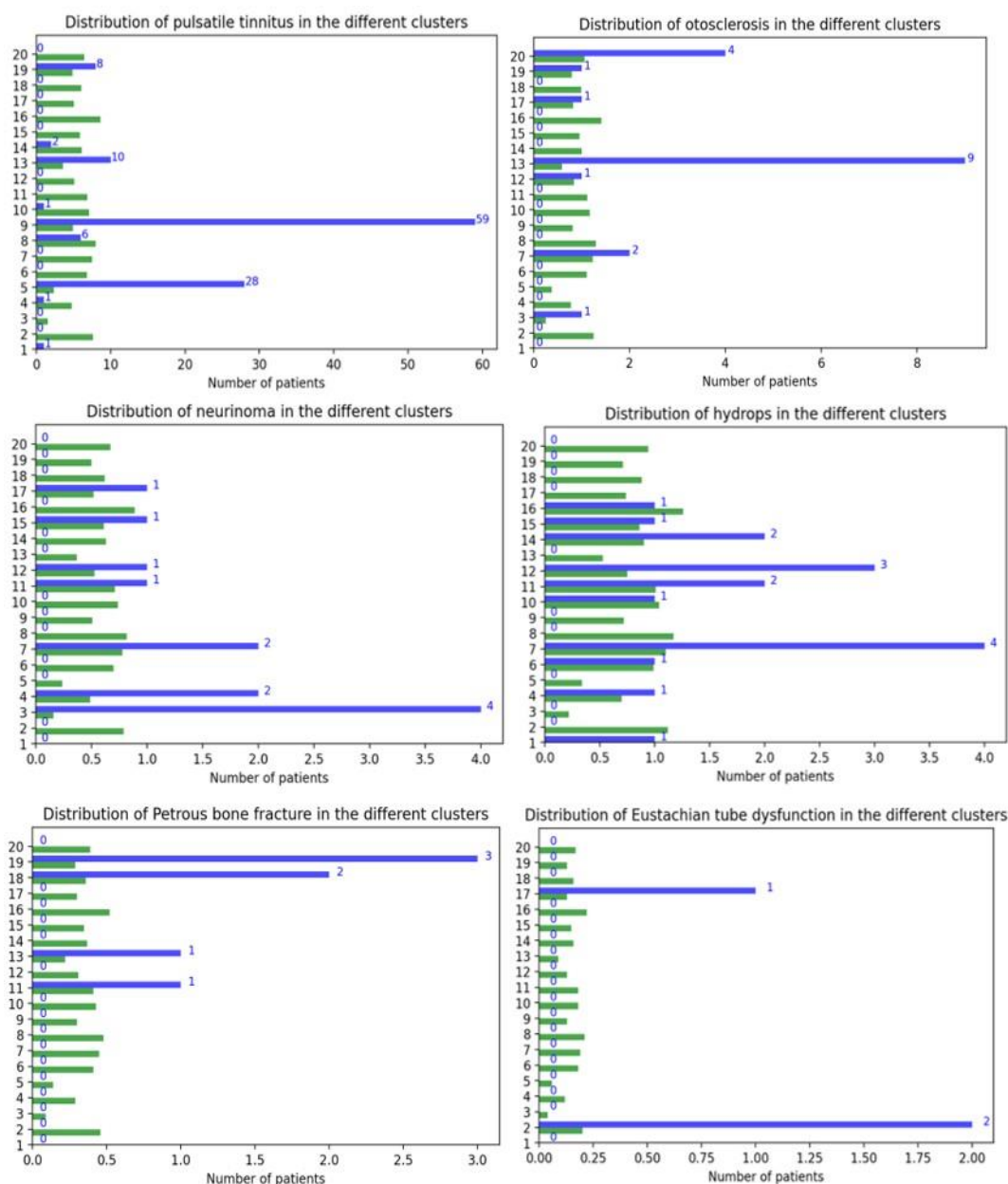


Figure 6.2 repartition of diagnosed patients to different clusters in the selected clustering of figure 6.1

To address this limitation, at least two strategies are possible. A first strategy to try to understand the cartography of tinnitus subphenotypes (and possibly associated endotypes if a similar strategy to the one of our study is applied), would consist in enforcing homogeneity on the time dimension of tinnitus. As kinetics of trajectories of each patient on his/her journey could be heterogeneous, the only viable solution would be to applying a similar clustering strategy to the one of our study on a database of anamnesis questionnaires of early acute tinnitus patients, with a very short duration since tinnitus onset.

A second strategy would be to adapt the clustering strategy to no longer separate tinnitus patients into time-independent clusters, but rather into clustering trajectories of tinnitus patients. An interesting shift would consist in analyzing longitudinal records of the same patients through time to properly analyze trajectories instead of unique time points. An important subtlety would be to use an algorithmic approach that would have the flexibility to allow for forking of such trajectories. A first noticeable step in this direction was proposed by the recent publication of Niemann and colleagues (2024), investigating heterogeneity of treatment response in tinnitus patients depending on tinnitus subphenotypes. Similarly, collecting longitudinally tinnitus ecological momentary assessments on long time scales, as through initiatives such as TrackYourTinnitus (Schlee et al., 2016) and Siopi, could help to build the necessary database to perform such a trajectory analysis.

## 6.2 TIAN epidemiology

Through our analysis of a first sample of responders to the newly translated French version of the ESIT-SQ questionnaire (Guillard et al., 2023) and our larger scale cross-sectional study of the symptom profiles of nap-induced tinnitus modulation populations (Guillard et al., 2023c), we could assess the epidemiological characteristics of the TIAN population, as well as the tinnitus decrease after naps (TDAN) population.

### 6.2.1 TIAN and TDAN prevalence

First, in terms of prevalence, we reported a congruent prevalence on the three datasets analyzed. TIAN population was 23.5% in the French ESIT-SQ sample (N=102), 23% in the Tinnitus Hub survey database (N=6115), and 17.7% in the Tinnitus Research Initiative database (N=3627). TDAN population was 11.8% in the French ESIT-SQ sample (N=102), 8.3% in the Tinnitus Hub survey database (N=6115), and 9.3% in the Tinnitus Research Initiative database (N=3627). These observations concur to highlight that TIAN patients are twice as numerous as TDAN patients.

### 6.2.2 TIAN symptom profile

The general symptom profile of TIAN patients is a global hyper sensibility pattern to external and internal physiological changes. Nap-induced increases rather appear as side manifestation of such an hyper sensitive profile of symptom and is not necessarily at its center. Thus, TIAN patients appear to be more prone to tinnitus modulations by stress, sleep in general,

somatosensory modulations, physical activity and sound exposure than the rest of tinnitus patients. Additionally, TIAN patients report in general more distressful forms of tinnitus than the rest of the population. As a consequence, one may question if TIAN patients are not by nature patients that have an exacerbated consciousness of their tinnitus perception compared to other tinnitus patients and thus have a finer granularity to detect modulations of their tinnitus. This would suggest a specific over-implication of the salience network for these patients, which has more broadly been described for the general tinnitus population (Xiong et al., 2023).

It should also be noted that TIAN patients present signs of middle ear dysfunction. Indeed, an abnormally high number of such patients report feeling plugged ears when stressed and feeling plugged ears after a bad sleep, compared to the rest of the tinnitus patients. In the TinniNap cohort, 27% of patients declared having often or very often plugged ears.

Interestingly, as both observed in the TinniNap study sample and through the cross-sectional study, a high proportion of TIAN patient describe that a stress episode was the initial cause of their tinnitus onset.

Another important epidemiological aspect of the TIAN is the stability of such increases following naps. In a questionnaire published on Siopi, we asked “How is your tinnitus when you wake up from a nap or after dozing off briefly ?” with as possible answers (multiple choices allowed):

- 1) *It neither changes the intensity nor the sound of my tinnitus*
- 2) *I often observe it increases the intensity of my tinnitus for a moment (10 min, 1 hour) then it comes back to normal*
- 3) *I often observe it increases the intensity of my tinnitus, it stays this way until I go back to sleep at night*
- 4) *I often observe it decreases the intensity of my tinnitus*
- 5) *I often observe that it changes the sound of my tinnitus or one new sound appears*
- 6) *I cannot say : I almost never take a nap or doze off since I have my tinnitus*
- 7) *The same things apply when I prolong my sleep when I stay in bed in the morning (week-ends, holidays)*

Interestingly, on a sample of 128 patients, looking at selection of possible answers 1, 2, 3, 4, 6, we obtain the distribution of answers here below in figure 6.3.

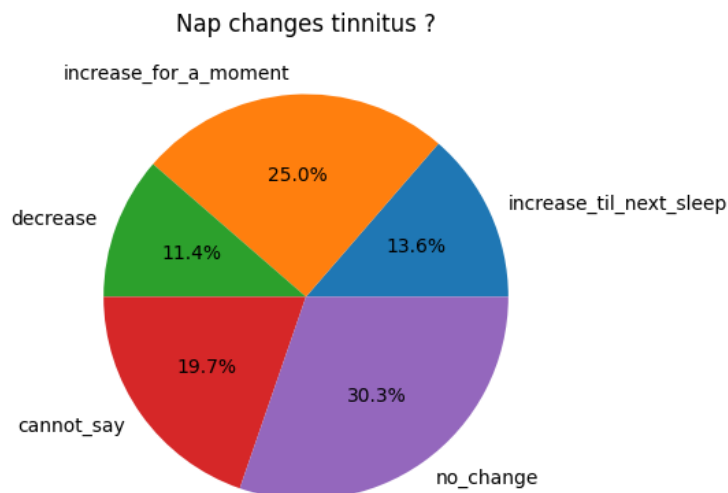




Figure 6.3 Pie chart of answer choices to the question “How is your tinnitus when you wake up from a nap or after dozing off briefly?”, from a survey on Siopi, N=128

The important takeaway knowledge of such a survey is the information that in the majority of cases, increases of tinnitus following naps are transitory and reduce back to baseline intensity 10 min to 1 hour after awakening. This observation has been experimentally confirmed in our TinniNap observational study as shown here below in figure 6.4.

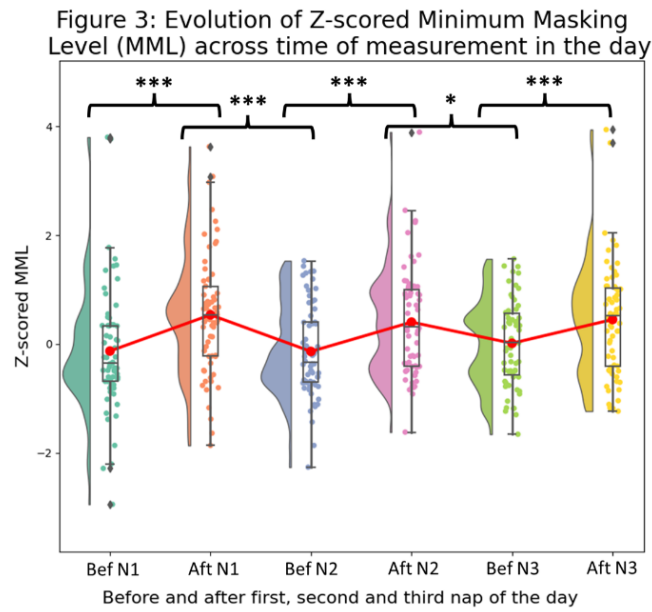
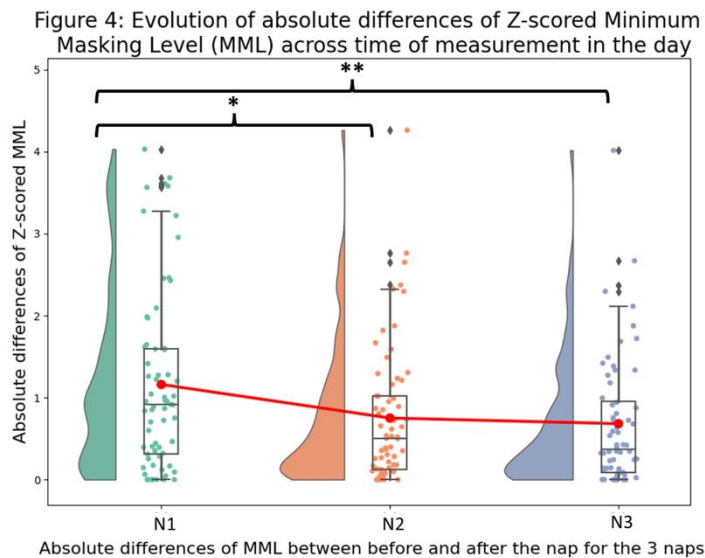


Figure 6.4: Evolution of Z-scored Minimum Masking Level (MML) across time of measurement in the day. Bef: Before, Aft : After N1 : nap 1, N2 : nap 2, N3 : nap 3

Indeed, on figure 6.4, we can observe that between each end of a nap and the beginning of the next one, a significant reduction of tinnitus intensity was observed.

Interestingly, we also learned thanks to the TinniNap study that performing three naps in a row during the same day led to a reduction in the amplitude of the tinnitus modulation with time.



*Figure 6.5: Evolution of absolute differences of Z-scored Minimum Masking Level (MML) across time of measurement in the day. N1 : nap 1, N2 : nap 2, N3 : nap 3*

However, we cannot fully interpret this observation as we cannot disentangle the effect of repetition of the naps along the day from the circadian effect of the day passing.

The TinniNap case report form questionnaire enabled us to also explore the sleep characteristics of TIAN patients on our sample (N=37). It revealed that body position during sleep did not affect sleep-induced tinnitus variation. Patients report relatively good sleep hygiene with only 16% of the sample sleeping less than 6 hours per night. Interestingly, 51% of the sample reported snoring and 24% were diagnosed with sleep apnea. Additionally, 40% of the sample had trouble remaining asleep, a sign that is often associated with sleep apnea. Finally, 19% of the sample reported sleep bruxism. Polysomnographic exploration of these patients during the TinniNap study enabled to highlight that these reports provided underestimations. Indeed, 34 participants (91.89%) exhibited 15 or more sleep apnea or hypopnea events per hour of sleep during at least one of their naps.

### 6.2.3 TDAN symptom profile

As highlighted by our cross-sectional study (Guillard et al., 2023c), TDAN symptomatology appear easier to interpret. In fact, we observe that TDAN patients have a higher prevalence of hyperacusis symptoms than the rest of the tinnitus population, they also report more often pain and/or discomfort when exposed to sounds and their tinnitus worsens with sound exposition. From these observations, it is not surprising that by taking a nap in a calm and quiet environment such patients report improvements in their symptoms.

## 6.3 SIT epidemiology

SIT epidemiology proved difficult. Indeed, contrary to TIAN patients, a single question item was not enough to distinguish such patients from the rest of tinnitus population. No questionnaire has been designed to specifically screen SIT patients. Through the years of this thesis, there were different attempts in the case report forms of the polysomnographic studies and through questionnaires published on Siopi to properly design questions that would enable specific distinction of SIT patients. Such attempts have so far lacked specificity and a shortlisting procedure through oral anamnesis was always necessary to complete the diagnosis. Here is a recent attempt :

Does your tinnitus vary over time?



- From one second to the next for no clear reason
- My tinnitus varies slightly from day to day.
- Depending on the day, I observe very different volumes, and on some days total disappearance, which is generally decided when I wake up
- It's often clearly louder when I wake up
- It's often clearly louder in the evening
- No, my tinnitus varies little or not at all

We expect only SIT tinnitus patients to select answer 3, yet, a proportion of non-SIT patients select it as well.

Very often, oral anamnesis is quite characteristic in the case of SIT patients which describe very similar patient experiences of tinnitus brutal switches on or off upon awakening from sleep. Additional characteristic anecdotes are often reported:

- The majority of patients will report that sometimes even dozing off for a very short moment can activate tinnitus on or off.
- When such patients wake up a first time in early morning without tinnitus (7am for example), if they decide to prolongate their sleep, on their second awakening, very often they report tinnitus switching on upon second awakening
- Such patient sometimes report that pillows shapes or firmness can have an effect on tinnitus modulation. Similarly, some patients report sleeping in the seated position tends to worsen tinnitus or switch on tinnitus upon awakening.
- It is important to mention that SIT patients appear as a subphenotype of the TIAN population. Indeed, the vast majority of SIT patients report that naps can switch on their tinnitus. In (Robin Guillard et al., 2023b) we observed that 87% SIT participants mentioned naps could increase their tinnitus. The rest (13%) declared they never did naps and consequently could not answer. Additionally, such patients often describe a dissymmetry between night sleep and nap sleep. Night sleep can switch tinnitus on or off, while nap sleep only switches it on. Consequently, they naturally avoid naps on days in which tinnitus is off.
- Some of these SIT patients report that tinnitus would be highest when awakening in the middle of a dream.

In our comparative study between SIT patients and controls, we explored some symptomatologic specific characteristics of the SIT population (Robin Guillard et al., 2023b). In addition to largely more increases of tinnitus following naps, SIT group was significantly less sensible to loud sound exposures compared to the control group. Moreover, SIT group reported significantly less frequent neck stiffness compared to controls. Among tendencies that were present, yet not significative on our small samples, jaw clenching, facial/jaw muscle fatigue was more frequent among SIT patients, as well as snoring and self-reported insomnia. Last, it appeared more difficult to mask tinnitus by white noise in the SIT group compared to the control group.

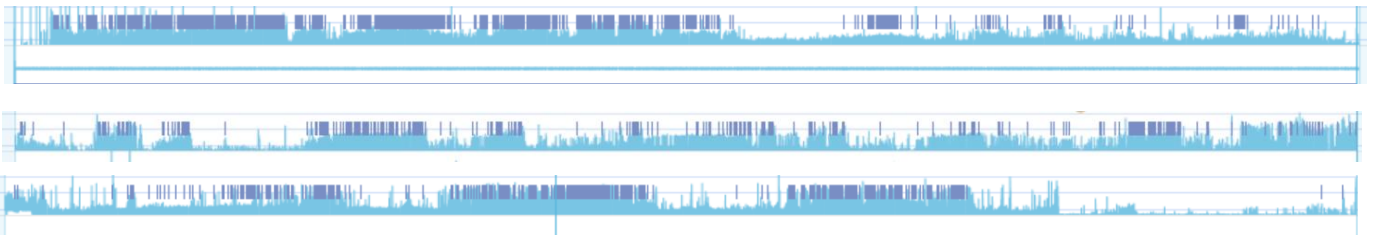
## 6.4 Unifying physiological models accounting for TIAN and SIT subphenotypes

In this section and the following ones, we are going to propose several possible models derived from our experimental observations and scientific literature to try to explain sleep-induced tinnitus modulations. In this section, we are going to present models that could both explain TIAN and SIT patterns of modulations.

### 6.4.1 Tensor Veli palatini overuse model

In our 7-night longitudinal case report, we observed a correlation between the number of snoring events over the night duration and the overnight variation of tinnitus. Patterns were strikingly divergent when looking at the number of snoring events as shown hereafter.

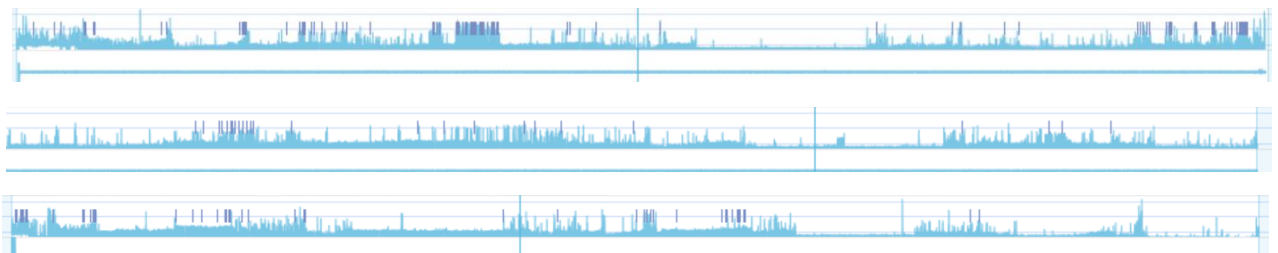
Snoring events distribution during nights leading to intense tinnitus (each vertical blue/purple bar corresponds to one snoring event)



Snoring events distribution during a night with remaining tinnitus at the end but lower loudness:



Snoring events distribution during nights leading to disappearance of tinnitus upon awakening:



In our TinniNap study, we collected three to six naps per patient for a cohort of 37 TIAN patients. Statistical tests combining individual correlations for each patient led us to find a significant correlation between cumulated snoring duration and nap-induced tinnitus

modulation measured by minimum masking level and visual numeric scale on tinnitus intrusiveness. Additionally, we found a significant correlation between number of apnea events and visual numeric scale on tinnitus intrusiveness.

Such observations led us to posit that obstructive sleep respiratory disorders could interfere with tinnitus perception. **We hypothesize that such modulations could be covert forms of somatosensory modulations, involving the tensor veli palatini (TVP) muscle.**

#### 6.4.1.1 Tensor Veli palatini inflammation

Our base of inspiration for this hypothesis is the acoustic shock model proposed by Norena and colleagues (2018). According to this model, excessive use of the Tensor Tympani (TT) muscle can give rise to a chronic neurogenic inflammation. It is then hypothesized that this inflammation could spread to inner ear tissues and alter cochlear functioning or that it could provoke hyperactivation of the trigeminal complex, which projects to the dorsal cochlear nuclei. Both these phenomena could lead to a tinnitus percept generation through hyperactivation of the central auditory pathway.

Likewise, snoring and specifically sleep apnea could nourish chronic inflammation of the TVP and more generally of soft palate and middle ear tissues. Indeed, several reviews and a meta-analysis concluded that obstructive sleep apnea was associated with systemic inflammation (Bergeron et al., 2005; Gnoni et al., 2022; Nadeem et al., 2013; Unnikrishnan et al., 2015). Inflammation is as well present locally as a study reported proliferation of receptors for nociceptive agent substance P and calcitonin gene related peptide (CGRP), in the palatal mucosa of apneic patients and chronic snorers (Friberg et al., 1997). A review even suggested that obstructive sleep apnea could be associated with neuroinflammation (Gnoni et al., 2022). Such neuroinflammation, if it spread to the auditory pathway, could also contribute to the emergence of tinnitus as suggested by the neuroinflammation model of (Adcock and Vanneste, 2022).

Yet, one may question the hypothesis presented in the acoustic shock model that the hyperactivation of the trigeminal complex caused by neurogenic inflammation could provoke a tinnitus modulation. Indeed, inflammatory signaling would probably be signaled to the trigeminal complex by nociceptive receptors and would hence be evaluated as nociception. Yet, two studies showed that the information transmitted by the spinal trigeminal nuclei are not nociceptive but rather more of proprioceptive nature (Shore et al., 2007; Zhou and Shore, 2004).

#### 6.4.1.2 Tinnitus modulation by Tensor Veli palatini through proprioception

More in accordance with this view, sleep apnea and snoring are both very often related to TVP tonus dysregulations during sleep (Patel et al., 2018; Zhu et al., 2022). In fact, some studies suggest that people with snoring and/or obstructive sleep apnea syndrome (OSA) have by nature a narrower pharyngeal airway section (Haponik et al., 1983). Consequently, this would result in a higher tonic contraction of the TVP in the awake state to maintain airway patency. A study conducted by Mezzanotte and colleagues (1996) also suggested this possibility, showing that apneic patients display a more significant decrease in

electromyographic tonus upon sleep onset compared to healthy controls. Consequently, this enhanced tonus during wake would lead to an increase in somatosensory information transmitted by the muscle to the trigeminal complex, thereby gradually altering its structure. Evidence of this phenomenon has been demonstrated in rodent models of sleep apnea, where an increase in noradrenergic terminals in the spinal trigeminal nucleus (Sp5) of the trigeminal complex was observed (Mody et al., 2011). In this model, sleep occurrences, such as naps, would constitute triggers for changes in TVP tonus. This would result in changes of somatosensory information afferent signal and as a result of tinnitus perception through somatosensory modulation of the auditory signal in the central auditory pathway.

Additionally, snoring activity during sleep could constitute abnormal afferent proprioceptive signals that could directly contribute to somatosensory modulation of tinnitus. Indeed, one definition of simple snoring consists of a fluttering sound created by the vibrations of pharyngeal tissues (Deary et al., 2014). Such vibrations would generate a proprioceptive excitation of the TVP and the TT, then transmitted to the trigeminal complex. This proprioceptive disturbance could in itself be a source of modulation of tinnitus as a past study has hypothesized that proprioceptive signal disruption within the middle ear could trigger tinnitus (Job et al., 2016). Last, snoring acoustic properties in tinnitus patients could be different from the rest of the population and this could contribute to TIAN, as a study showed higher power density for high frequencies in snoring sound of tinnitus patients versus control (Lu et al., 2022).

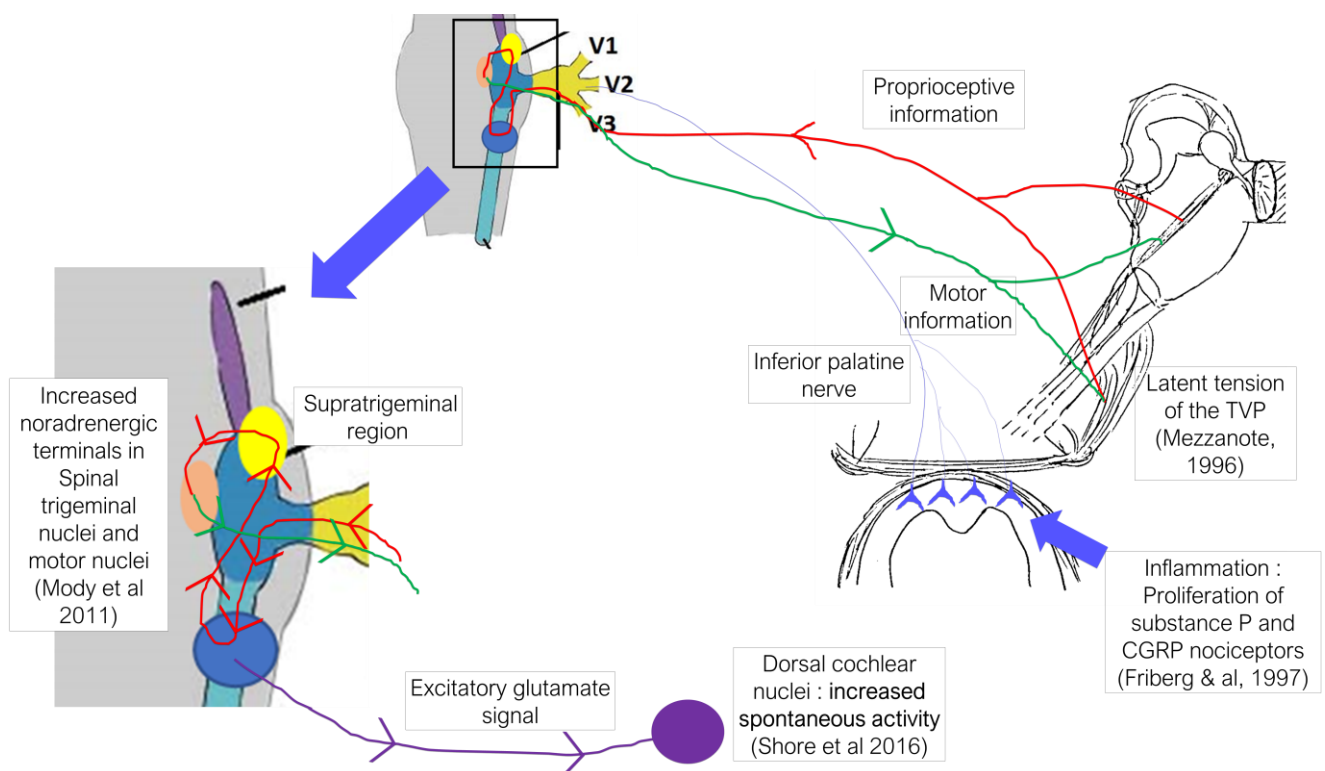


Figure 6.6 Illustration of the tensor veli palatini overuse model, CGRP : Calcium Gene Related Peptide, TVP : tensor veli palatini

## 6.4.2 Theta bursts induced modulations model

We could also hypothesize that sleep-induced tinnitus modulations could be induced by modulations of the EEG theta band power activity along the central auditory pathway. Indeed, according to the updated thalamocortical dysrhythmia model (De Ridder et al., 2015), in case of important hearing loss transposing to important central deafferentation in the central auditory pathway, missing auditory information is retrieved from the parahippocampus (De Ridder et al., 2006). This retrieval is postulated to be piloted through theta activity.

Clinical observations in TIAN and SIT patients include notably that there seems to be a relation between REM sleep duration and night sleep induced tinnitus modulations and that NITM can be triggered even after very short sleep occurrences (patients declaring only dozing off). Indeed, as an illustration, during the TinniNap protocol, a TIAN patient who presented SIT characteristics made his second nap and transitioned from a masking level of 53 dB to 62 dB, which is a non-negligible increase in loudness. Interestingly, the nap lasted for 40 min and only slight dozing off occurrences of a less than 15s were observed, as this one:

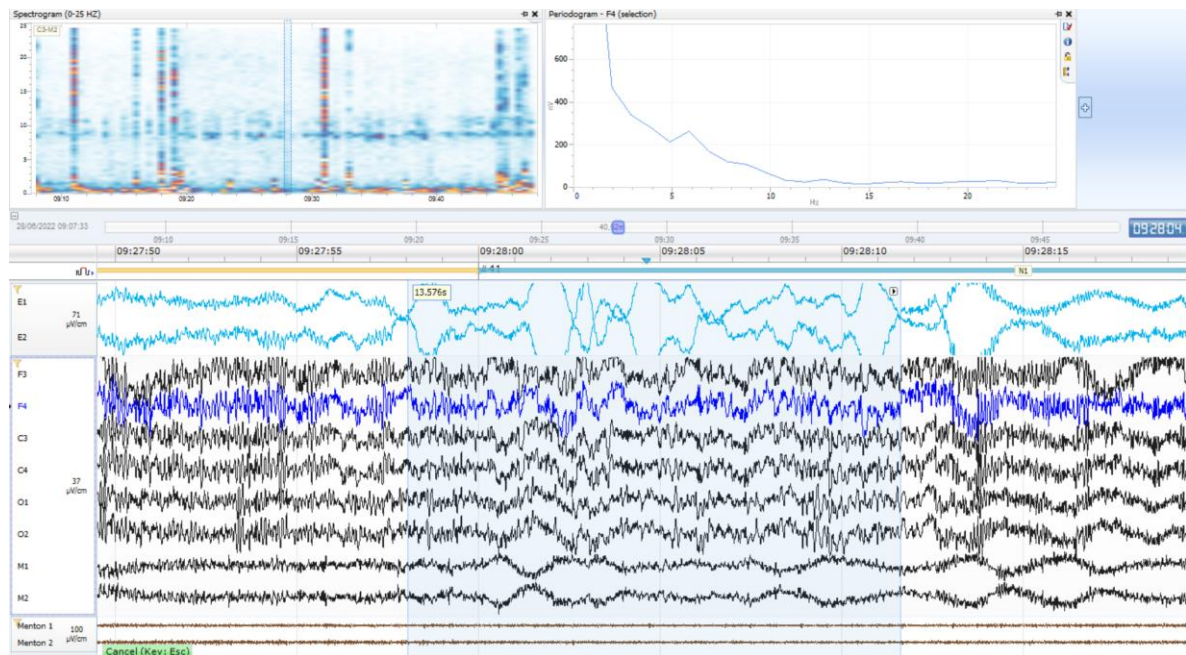


Figure 6.7 30s epoch of subject 5DR18 nap 2, in the middle a short dozing off event of 13.58s, characterized by intense eyes movements, low jaw EMG and a burst of theta activity near 6Hz specifically in the frontal areas as shown from the periodogram of the F4 channel on the top right.

Please note that the hour was not 9h28 but rather 14h28.

Interestingly, both sleep onset and REM sleep have a common feature: a rise in the theta band power activity (Blumberg et al., 2020; Zhuo Zhang et al., 2014). In addition, it has been demonstrated that theta activity during REM sleep is generated by the hippocampal network and has a critical role for memory, and notably contextual and emotional memory (Boyce et al., 2017, 2016; Hutchison and Rathore, 2015). Moreover, when awakening from a nap, patients can often remain in a transitory state of sleep inertia, which has been characterized by increase of theta band activity, notably in the temporal area (Gorgoni et al., 2015). Last,

evidence was provided by Velluti and colleagues (2000) that both during sleep phases and wakefulness there was a firing phase locking of auditory neurons along the auditory pathway on the hippocampal theta rhythm, suggesting that such activity could have an important role in organizing sensory information in visual and auditory systems, in all behavioral states and adding a temporal dimension to the sensory processing.

**For these reasons, it can be hypothesized that sleep-induced modulations of tinnitus may occur as a consequence of modulations of theta band power activity between the hippocampal/parahippocampal regions, the central auditory pathway and conscious enabling networks.** This hypothesis could be tested through the TinniNap resting states recordings, although we could not achieve it in the time lapse of the present thesis.

### 6.4.3 Serotonin drive modulations model

Fluctuating levels of central serotonin has been proposed to result in intermittent gating of tinnitus signal by the thalamic reticular nucleus (TRN), which could result in intermittent tinnitus perception (Rauschecker et al., 2010). The authors of this study suggested that in subjects presenting hearing loss but not experiencing tinnitus, a central gating mechanism potentially involving the Thalamic Reticular Nuclei (TRN) could inhibit hearing-loss-related increased spontaneous activity of the brainstem auditory nuclei. According to this hypothesis, tinnitus conscious perception would be the result of a dysfunction of this gating mechanism, letting the increased spontaneous activity to propagate to the auditory cortex. Rauschecker and colleagues suggest that such dysfunction could be due to a lack of excitatory serotonergic drive from Raphe nuclei and nucleus accumbens to the TRN in tinnitus subjects. Although serotonin implication in tinnitus has been suggested in past studies (Dobie, 2003; Simpson and Davies, 2000), despite some encouraging results (Lee et al., 2007) there is currently no consensual evidence that has been published to support this hypothesis (Deniz et al., 2010; Sachanska, 1999). However, it should be noted that was recently published a first post-mortem cerebral morphometric analysis of tinnitus patients versus controls (Almasabi et al., 2022). This study reports that in tinnitus patients the number of neurons of the dorsal and obscurus Raphe nuclei using serotonin as a neurotransmitter were drastically reduced as compared with controls.

Nonetheless, what is not certain for the general tinnitus population may be accurate for the SIT and TIAN populations. In their publication, Rauschecker and colleagues (2010) also hypothesized that patients with intermittent tinnitus could have fluctuating levels of serotonin, resulting in fluctuating gating performance and thus a fluctuant or intermittent perception. Such scenario fits very well the observed sleep-induced tinnitus modulations as serotonin is deeply involved in wake-sleep transitions and REM sleep duration through the Raphe nuclei (Monti, 2011; Monti and Jantos, 2008). More specifically, serotonergic neurons from the dorsal Raphe nuclei are known to exhibit a tonic continuous firing across wake at a rhythm around 3 Hz, decrease their activity to 34 to 68 % of this rate during Slow Wave Sleep and virtually stop firing during REM sleep (Linley and Vertes, 2019; Trulson and Jacobs, 1979). As a consequence, transition from sleep to wake (after a nap or after night sleep) is normally characterized by an important excitatory serotonergic drive from the Raphe nuclei, with a

greater change when transitioning between REM sleep and wake (Sakai, 2011). It should be noted that several SIT patients describe that tinnitus is louder when awakening from a dream. It is also important to mention that the serotonergic system does not only afferent the auditory system through the TRN. Direct excitatory connections between the Raphe nuclei and the cochlear nucleus have been identified (Felix et al., 2017; Thompson and Thompson, 2001), as well as with the inferior colliculus (Hurley et al., 2002; Peruzzi and Dut, 2004) and the auditory cortex (Rouiller et al., 1989) and could be alternative pathways of modulation of the auditory system by the serotonergic system. **We hence hypothesize that sleep-driven central serotonergic excitatory activity fluctuations in SIT and TIAN patients may explain the observed tinnitus percept modulation.**

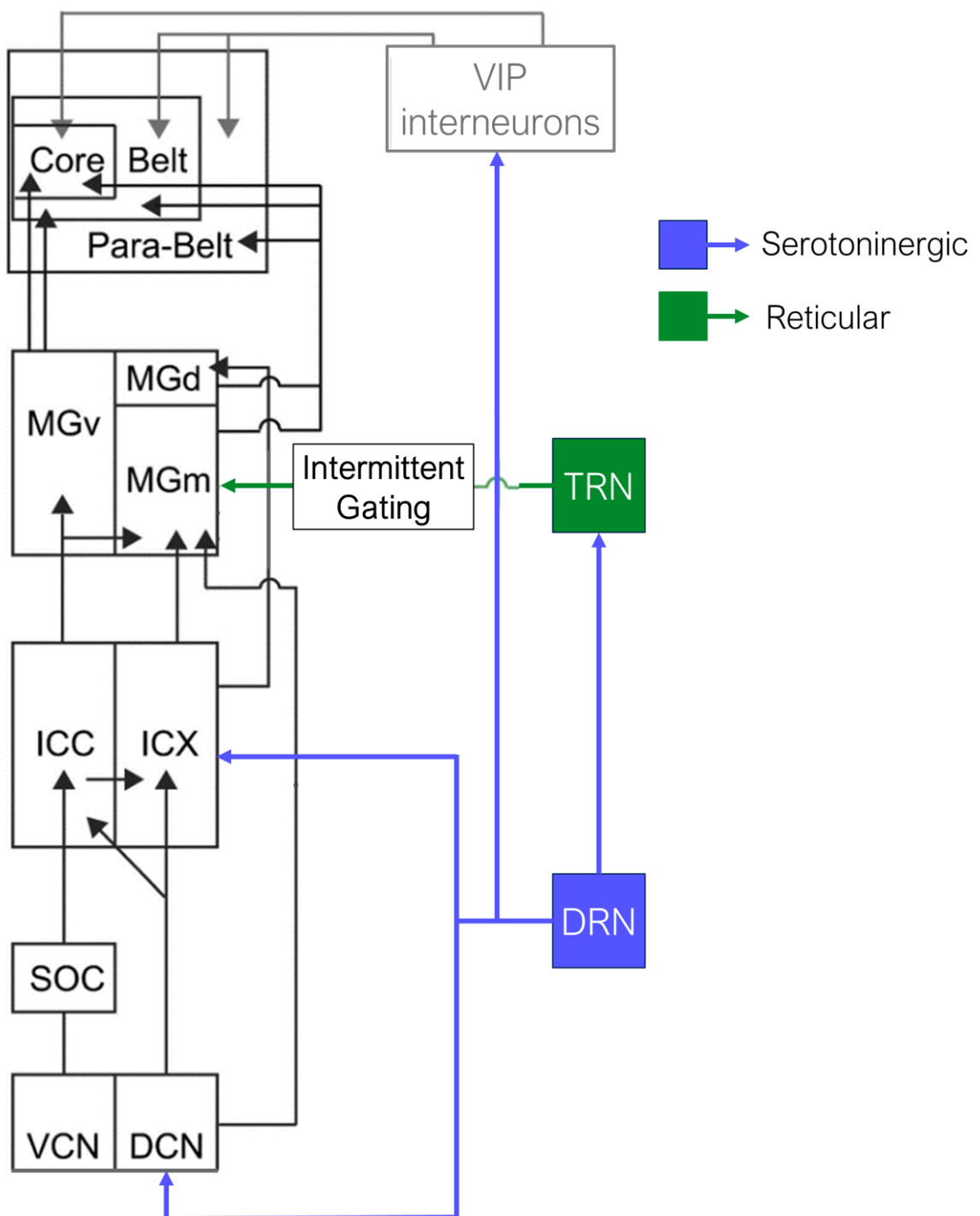




Figure 6.8 Proposed model for serotonergic modulation of the central auditory pathway activity, on the left the central auditory pathway and associated auditory relays, DRN : dorsal Raphe nuclei, VIP: vasoactive intestinal polypeptide.

## 6.5 Pathophysiological models accounting for transitory nap-induced tinnitus modulation

As exhibited by the survey answers to the Siopi questionnaire on variation of tinnitus following naps, the major part of TIAN patients reports only a transitory increase of tinnitus loudness following naps, which then comes back to baseline loudness. This phenomenon was confirmed by experimental data acquired during the TinniNap protocol : tinnitus significantly decreased during breaks between naps. We propose here models that could explain for such transitory tinnitus modulation.

### 6.5.1 Transitory NITM as a byproduct of sleep inertia

In our TinniNap study, we found that nap duration was correlated with nap-induced variation of the visual numeric scale on tinnitus intrusiveness. As participants performed short naps (between 1 and 25 min of length), the longer was the nap, the deepest sleep they reached.

Awakening from a nap and specifically from deep stages of sleep often leaves oneself in a transitory state of hypovigilance, confusion, disorientation of behavior and impaired cognitive and sensory-motor performance, which has been designated as sleep inertia (Tassi and Muzet, 2000). It has been hypothesized that such state is related to the fact that parts of the brain during this transitory period keep presenting physiological characteristics of sleep, which can be referred to as local sleep (Hofer-Tinguely et al., 2005). Neural correlates of sleep inertia have been studied. A disrupted functional connectivity was observed on fMRI and an increased delta band power activity was the main effect observed on EEG (Vallat et al., 2019).

During Non-REM sleep, neurons are known to have a synchronized bursting activity. Notably, along the central auditory pathway, such synchronous bursting has been reported in unitary neurons recordings at least in MGB and the auditory cortex A1 during Slow Wave Sleep (Edeline et al., 2001, 2000). If during sleep inertia, auditory neurons keep functioning with similar patterns as during preceding sleep, then one could hypothesize that they would keep exhibiting increased burst firing compared to normal wake. However, increased burst firing and thus increased firing synchrony in the auditory cortex has been proposed to be a neural correlate of tinnitus (Noreña and Eggermont, 2003). **Hence, we could hypothesize that during transient sleep inertia, auditory cortex neurons have an abnormally high synchronized burst firing activity which could result in a transitory enhanced tinnitus loudness perception.**



For note, this hypothesis would be in opposition with the model proposed by Milinski and colleagues (2022). Indeed, in their study, the authors support the idea that sleep homeostasis and associated synchronized activity would interfere with tinnitus signal and provoke its disappearance during sleep.

Additionally, theta band activity was also found to be increased during sleep inertia (Gorgoni et al., 2015). As presented in the theta bursts model in section 6.4.2, such phenomenon could also contribute to transitory NITM.

In future analyses of resting state data of the TinniNap study, we will analyze the correlation between relative increases of delta and theta band power activities during post-nap resting states compared to pre-nap activity and NITM in an attempt to provide evidences for the present model.

## 6.5.2 Evil gating hypothesis

Continuing on the idea that following a nap TIAN patients could wake in a state of transitory sleep inertia, another phenomenon could occur that could result in increased loudness tinnitus perception. Indeed, another attribute from the Non-REM sleep stages that could remain active during the sleep inertia period is the partial gating of auditory information as described in sections 1.4.1. Indeed, it has been described that during Non-REM sleep, auditory information is partially gated to access the consciousness network, whether at the level of the thalamus (Coenen, 2022) or later at the level of the auditory cortex (Andrillon and Kouider, 2020). In both cases, such gating could transitorily simulate an increase in central deafferentation. Yet, it has been proposed that deafferentation of at least tonotopically-restricted regions of the auditory cortex contributes to increases in uncertainty on sensory perception, increasing prediction error according to the Bayesian brain model of tinnitus (De Ridder et al., 2014b), described in section 1.2.4.7 and the predictive coding model of tinnitus (Sedley et al., 2016), described in section 1.2.4.8. **We hence hypothesize that increased auditory deafferentation due to transitory sleep-inertia-induced gating of auditory information could hence result in transitory increased tinnitus perception.**

The fact that in our TinniNap study NITM was not correlated with variations in auditory detection thresholds is not in support of such a theory. Yet, audiograms are known to be imprecise estimates of auditory function. Another limitation of this absence of correlation is that audiograms were performed after tinnitus momentary assessments, it could be hypothesized that engaging in an auditory attentional task “wakes the auditory system up”. As tinnitus momentary assessments were not performed after the audiograms, it cannot be excluded that engaging in an audiogram examination triggered the disappearance of sleep-inertia-related gating of auditory information and that consequently, in the same time, NITM vanished and auditory performances returned to normal. More accurate assessment of potential remanence of auditory gating during sleep inertia should be performed to better test this hypothesis. For example, one could perform middle latency auditory evoked potentials shortly after the nap and try to reproduce results from (Hulse et al., 2011). In this study, 12 subjects had performed an auditory oddball paradigm test before sleeping and 30 min after

awakening (in the sleep inertia period). Their results showed a reduction in amplitude of the middle latency complex N1-P2 response.

### 6.5.3 Synaptic downscaling as a potential cause to NITM

In section 1.3.1.1 we presented the synaptic homeostasis hypothesis presented as the physiological reason mammals need Non-REM sleep (Tononi and Cirelli, 2006). According to this hypothesis, Non-REM sleep is characterized by a process of synaptic downscaling, during which synaptic weights are pruned down with respect to their weights before sleep onset. It has been hypothesized that during wake some synapses can be selected and receive specific marks that protect them from selective pruning (Cirelli and Tononi, 2022). One would assume that such protected synapses are those deemed “important” during wakefulness, notably those recently activated by learning. As tinnitus perception is omnipresent in non-intermittent tinnitus patients, one can assume that signals conveyed on tinnitus frequencies are statistically more used and heard during wake than any other frequencies. Moreover, an important part of tinnitus patients pathologically focuses their attention on tinnitus perception (Newman et al., 1997). This exacerbated salience on tinnitus perception is an additional factor that could contribute to the protection of tinnitus signal supporting synapses against synaptic pruning during Non-REM sleep. This would result in a relative increase in synaptic weights of the tinnitus supporting neuronal network with accumulation of slow wave sleep. **Consequently, we propose that tinnitus perception could be magnified upon awakening as a result of an accumulated duration of selected synaptic downscaling of auditory non-tinnitus network synapses during slow-wave sleep.** Increase of tinnitus following naps would then gradually extinguish following awakening as the result of sound perception during wakefulness. Auditory non-tinnitus network would then be used for auditory perception. Synaptic potentiation learning would take over and would diminish the relative weight mismatch between synapses of auditory tinnitus and non-tinnitus networks, resulting in tinnitus returning to baseline.

The present model should be also considered more generally in the context of tinnitus to account for how sleep could accentuate the anchoring of tinnitus and contribute to its transition from acute to chronic.

The fact that in our TinniNap study, duration of sleep during naps was correlated with NITM is also in support of such a theory. Accumulated quantity of delta band power during nap sleep should also be considered for correlation to bring additional support to this hypothesis.

## 6.6 REM sleep role in SIT on-off transitions

Our current observations concerning REM sleep and its role in the specific case of SIT patients are somehow puzzling. First, we showed that night duration of REM sleep was inversely correlated with overnight tinnitus modulation, meaning that less REM sleep would lead to higher tinnitus upon awakening. Abnormal decrease of REM sleep duration had already been reported in the general tinnitus population by two studies (Attanasio et al., 2013;

Teixeira et al., 2018b). At the same time, we collected reports of SIT patients that awakening from a dream, hence most probably from REM, would lead to higher tinnitus. We conducted a small analysis on how tinnitus varies overnight depending to which sleep stage patients wake up in. We separated the case of patients having multiple awakenings after 4am. We conducted this analysis on a small sample of SIT patients and obtained the results presented here below in figure 6.9.

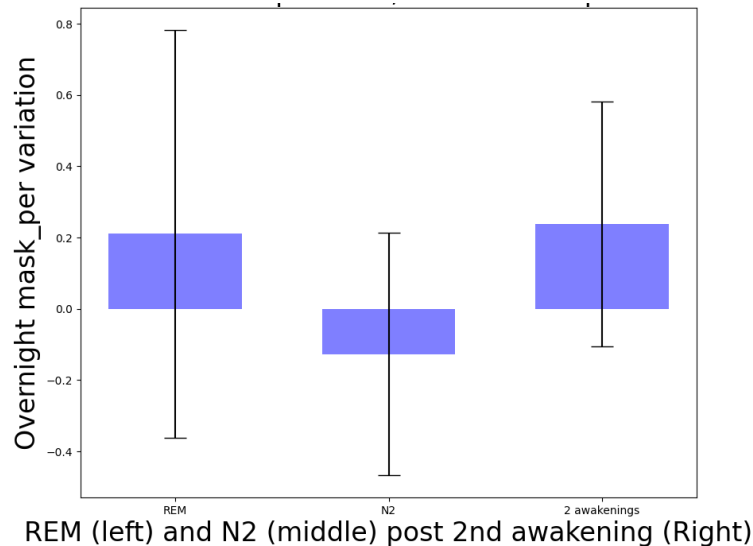


Fig 6.9 comparison of percentages of overnight minimum masking level variations depending on which sleep stages SIT patients (N=16) woke up in. Left bar : patients woke up in REM sleep stage, middle: patients woke up during N2 sleep stage, right : patients had at least two successive awakening of more than 3 min after 4am. Mann-withney tests were used for comparison, REM VS N2 :  $p=0.3$ , >2 awakenings VS N2 :  $p=0.1$

Although, the sample was too small for conclusive significant results, it indicated marginally a tendency for lower tinnitus when waking from N2 sleep as compared to REM or after 2 or more awakenings. Interestingly, when including all the tinnitus patients we explored for night polysomnography over the last years, we observed a general similar effect as shown here below in figure 6.10.

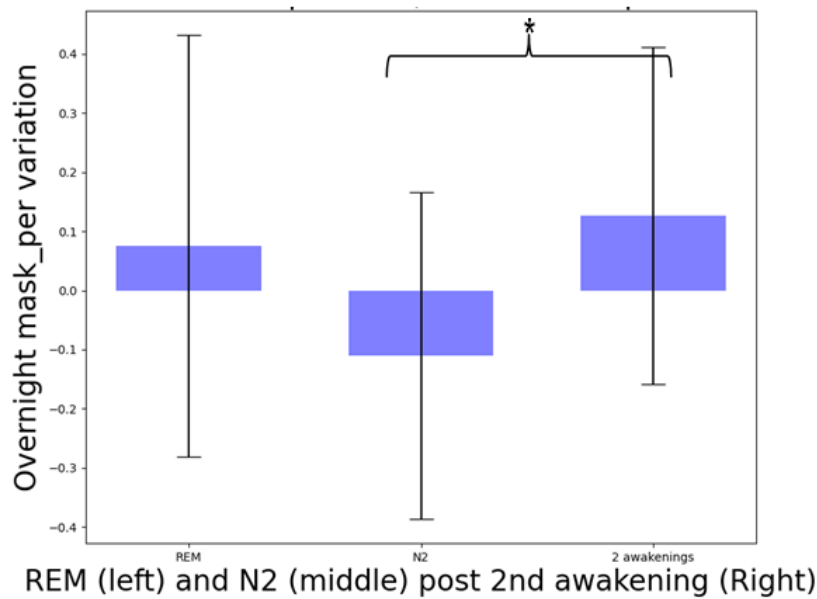


Fig 6.10 comparison of percentages of overnight minimum masking level variations depending on which sleep stages tinnitus patients from the general population (N=41) woke up in. Left bar : patients woke up in REM sleep stage, middle: patients woke up during N2 sleep stage, right : patients had at least two successive awakenings of more than 3 min after 4am. Mann-withney tests were used for comparison, REM VS N2 :  $p=0.083$ , >2 awakenings VS N2 :  $p=0.02^*$

Last, we observed in our comparative study of polysomnographic characteristics between SIT patients versus controls that 87% of SIT patients reported switch on of their tinnitus following naps. Such SIT patients report switches on of their tinnitus perception after short dozing off episodes. Yet, short naps and (above all) dozing off episodes do not contain REM sleep.

These three reasons (less REM sleep implies more tinnitus, waking up in REM sleep worsens tinnitus and waking up of naps without REM sleep worsens tinnitus) appear hard to conciliate. Of course, it cannot be excluded that one of these findings is untrue. Therefore, these findings should be replicated. Nonetheless, we present here below a model that account for all these observations.

### 6.6.1 Non-REM as a negative drive for tinnitus loudness

As mentioned before, an important observation in SIT patient is an apparent dissymmetry between nap sleep that only triggers onsets of tinnitus and night sleep that can trigger both onsets or offsets of tinnitus. This dissymmetry could be explained by the absence of REM sleep during nap sleep and this would mean that, globally, the occurrence of REM sleep can have a positive impact on tinnitus. Conversely, as a corollary hypothesis, we could assume that in the case of SIT patients (and possibly TIAN patients), Non-REM sleep tends to have negative impact on tinnitus, resulting in an increased loudness of the percept.

## 6.6.2 Tinnitus-free dreams, intact body representation and predictive coding: positive effect of REM sleep in tinnitus patients

Two studies showed that tinnitus patients do not report hearing their tinnitus during dreams (Aazh et al., 2021; De Ridder et al., 2014a). We conducted a similar survey on Siopi and we could observe on 108 patients that declared remembering some of their dreams that 92,6% report not hearing tinnitus during their dreams (non-published data). Besides, it has been reported that individuals have an intact body representation in their dreams. As an illustration, amputees often report having an intact body representation during their dreams, and not experiencing phantom limb pain in dreams (Alessandria et al., 2011; Brugger, 2008). Similarly, we could postulate that patients displaying acquired hearing loss after their youth have an intact auditory system representation during their dreams. Indeed, a study showed that in contrast to congenitally deaf subjects, subject that acquired deafness after the age of five had most often sound content in their dreams (Mendelson et al., 1960).

In chronic tinnitus patients, according to the predictive coding model (Sedley et al., 2016), tinnitus patients' prediction of silence may be compromised due to settled deafferentation. This results in the brain shifting its basal prediction of absence of sound from silence to predicting the tinnitus sound percept instead. As developed later by Hullfish and colleagues (2019), in predictive coding model refinements intact body representation during dreams could result in the brain being able to make an accurate prediction of silence in the context of dreams. As a consequence, without any representation of deafferentation in dreams, tinnitus would not be perceived. Yet, what Hullfish and colleagues did not develop is the potential beneficial effect that REM sleep could have following these postulates. Indeed, the role of REM sleep has been hypothesized to be the optimization of our prediction models (Hobson and Friston, 2012). If this hypothesis holds true and REM sleep is the only moment of the day in which silence in absence of noise is correctly predicted, then, we could assume that REM sleep could have a beneficial role for tinnitus patients : their brain would learn to shift their representation of absence of noise from "tinnitus percept" to "silence". Hence, the longer tinnitus patients would stay in REM sleep, the longer their brain would learn to have a good representation of silence and hence the lower their tinnitus would result upon awakening. This would match the experimental data observed in the SIT group.

## 6.6.3 In the remedy may lay the poison

Waking up from REM sleep means leaving a REM sleep episode unachieved during the night, hence reducing its potential duration. As a consequence, if our previous hypothesis about positive dose effect of REM sleep duration on tinnitus is true, then waking from REM sleep could be a sign of shortened REM sleep duration and hence of higher tinnitus loudness upon awakening.

We could also posit a second hypothesis. An interesting attribute of central auditory activity during REM sleep is an increase of spontaneous activity in the last relays of the central auditory pathway : the inferior colliculus (Tortorolo et al., 2002), the MGB (Edeline et al., 2000) and the auditory cortex (A1, belt and parabelt), as described by Issa (2008). As a

consequence, waking from REM sleep may result in sleep inertia conveying remanence of REM sleep physiological correlates, such as a hyperactivity of these auditory system relays. Yet, increased spontaneous activity in the central auditory pathway has been posited as the main correlate of tinnitus or at least of auditory deafferentation constituting a tinnitus perception predisposing factor in at least four of the models we presented (Adcock and Vanneste, 2022; Knipper et al., 2020; Krauss et al., 2016; Norena, 2011). As a conclusion, waking up from REM sleep could induce a sleep inertia state characterized by a transitory increase of spontaneous activity in the auditory pathway, resulting in an increase in tinnitus loudness perception.

**As a conclusive statement on REM sleep role in SIT patients, we may hypothesize the best scenario for such patients to experience a low tinnitus intensity day upon awakening would be to awaken during N2 sleep stage after a restful night containing an important REM sleep duration.**

## 6.7 Invalidated hypotheses concerning TIAN and SIT correlates candidates

We had initial hypotheses concerning potential role of bruxism or cervical area musculature and/or joints in NITM and SIT on-off modulations. Indeed, in both our polysomnographic studies we tested correlations between bruxism and cervical area related assessments and tinnitus momentary assessment attributes to evaluate if they had a role in sleep-induced tinnitus modulations.

Concerning bruxism, two studies had drawn associations between tinnitus and bruxism (Camparis et al., 2005; Fernandes et al., 2014). We had hypothesized that jaw clenching during sleep could result in jaw musculature rigidity and pain upon awakening. These would translate into delayed somatosensory modulations of tinnitus. However, in both our experimental work, we found either weak or absent associations between features associated with bruxism (duration, number of episodes, associated power on EMG, density of episodes) and tinnitus modulation. From our work, it appears hence unlikely that bruxism is driving sleep-induced tinnitus modulations.

Concerning the involvement of the cervical area in NITM and SIT modulations, we initially wanted to explore this possibility as two studies mentioned that making naps in the seating position specifically more often worsened tinnitus loudness (Levine, 2013; Ralli et al., 2017a). Indeed, sleeping in the seating position is unstable for the neck and very often results in bent positioning of the neck during sleep. In our comparative study of SIT patients versus controls, we only tested correlations between body position (supine or non-supine) and overnight tinnitus modulation and found no results. During the TinniNap study, we conducted several tests to explore the potential role of cervical area involvement in tinnitus modulations : we tested neck mobility, adapted Spurling test, splenius and trapezoid muscles trigger points before and after each nap and we also tried to correlate head and body position during the nap with modulations of tinnitus by the nap. Again, we only found weak and incongruent

correlations, which do not support any cervical area involvement in sleep-induced tinnitus modulations.

## 6.8 Perspectives

We will dedicate this last section to present suggestions for future research that we hope we will address in the coming months or years. Some of these ideas are already ongoing work. We will present these points very succinctly as a list.

- As presented in the discussion in the section on tinnitus heterogeneity, it would be interesting to perform a clustering analysis on a database of longitudinal assessments of tinnitus patients, in which we would apply clustering on trajectories of tinnitus patients. The TRI database could be used for this purpose. Another interesting project would be the tinnitus Biobank project, which will be launched soon by tinnitus UK.
- We could also try to perform a clustering analysis similar to what we have done not using endotypes/diagnoses as guiding compass for semi-supervised labels, but responses to treatments instead. Similarly, several databases in which patients reported treatments outcomes could be used for this, notably the one we acquired through Siopi.
- An important set of analyses remains to be performed on TinniNap dataset. Currently, polysomnographic recordings and resting states recordings before and after the nap have been poorly exploited. We could analyze the resting state recordings to test our hypotheses of sleep inertia involvement in NITM (delta band power increase post nap would correlate with increased tinnitus loudness upon awakening, as presented in sections 6.5.1 and 6.5.2), or of potential theta band power modulations in correlation with NITM (as presented in section 6.4.2). Likewise, we could analyze in more depth the EEG content during the nap. We could for example assess cumulated delta band power during the sleep of the naps to test the hypothesis on synaptic downscaling involvement in NITM (as presented in section 6.5.3). In addition, in collaboration with Mr MinChul Park, Pr Greg O’Beirn and Pr Mike Maslin, we performed an analysis of the sleep spindles characteristics during the naps. We aimed at testing the changes of their characteristics in relation with NITM to test the potential involvement of the Thalamic Reticular Nuclei (TRN, which is the generator of sleep spindles). Indeed, the underlying hypotheses would be to test the gating hypothesis proposed by Rauschecker and colleagues (2010) and possibly the involvement of the serotonergic system in sleep-induced tinnitus modulations (as serotonin drives TRN activity). Our results did not highlight any changes in sleep spindles in correlation with NITM. We hope to publish soon these results.
- To test more thoroughly serotonergic involvement in sleep-induced tinnitus modulations, several studies have shown in animals and humans that serotonergic activity from dorsal Raphe nucleus is driving arousal response to hypercapnia in situation of sleep apnea (Buchanan et al., 2015; Kaur et al., 2020; Mateika, 2019).

Notably, in case of central serotonin depletion, mice tend to less often wake up from sleep apnea events, which become more frequent and of longer duration. Additionally, in this condition of serotonin depletion, CO<sub>2</sub> concentration in blood is hence higher, and consequently O<sub>2</sub> concentration would appear lower. We could hence analyze the average duration of sleep apnea events and average SPO<sub>2</sub> levels during the nap in order to correlate them with NITM.

- We could also test intensity dependence of cortical auditory evoked potential (IDAP, on N1 and P1 waves), which have been considered an index of central serotonergic activity in the auditory cortex (Cartocci et al., 2012; Gopal et al., 2017; Hegerl and Juckel 1993; Manjarrez et al., 2005). Indeed, the seminal work of Hegerl and colleagues (1993) showed that serotonergic depletion leads to a steeper amplitude over stimulus intensity function. Yet, this would require a new protocol on naps recordings of TIAN or SIT patients.
- If we perform a new set of naps recordings on TIAN and SIT patients including auditory evoked potential (AEP) recordings, we could test additional sleep inertia markers derived from such AEP recordings as performed by Hulse and colleagues (2011).
- An important question that remains to be settled is whether or not on-off switches of tinnitus on SIT patients happen erratically depending on whether or not a phenomenon happens during sleep or if it follows an oscillatory process with a predetermined time constant. We recently started to investigate this question by recording tinnitus loudness each morning and each evening in 5 SIT patients during at least one month and a half. We were surprised to observe that in all 5 SIT patients, using cosinor test (Moškon, 2020), there was a significant oscillatory rhythm with a time constant between 2.9 days and 3.1 days. Following this pilot observations, we could try to verify this preliminary result on a larger cohort of SIT patients. We could combine this longitudinal follow-up of SIT patients with additional measurements such as snoring assessments and/or polysomnographic measurements, to try to reproduce our findings on snoring and REM sleep on these patients on longer time scales of longitudinal measurements. These longitudinal polysomnographic measurements could be achieved thanks to lighter assessment material such as Oura or Circular rings, or Dreem headband.
- If we were to perform such longitudinal polysomnographic measurements, we could additionally continue to analyze in which sleep stages patients wake up in, with regards to potential correlation with overnight tinnitus modulation, to investigate further more the preliminary results we observed and reported in section 6.6. Such an investigation could contribute in bringing new arguments on the question of whether tinnitus activity lies on increased synchronized bursting activity of auditory neurons as posited by Noreña and Eggermont (2003) or on increase of spontaneous activity of auditory neurons as supported by several tinnitus models (Knipper et al., 2020; Krauss et al., 2016; Noreña, 2011).



- We initiated a study on tinnitus and dreams as well as tinnitus behavior during awakenings (nocturnal awakenings and morning awakenings). We launched a survey on Siopi and collected more than 120 answers. We started the analysis of this ongoing work and we observed surprising results, notably on the subject of tinnitus perception during lucid dreaming. We will shortly present our findings in annex of the present thesis. They will be presented more thoroughly during the TRI 2024 meeting in Vancouver.
- In order to test more thoroughly our hypothesis on Tensor Veli Palatini (TVP) involvement in SIT patient, a minimally invasive test would be to perform oral massage of the TVP at the level of the soft palate on SIT patient and evaluate if it elicits on-off switches of the tinnitus perception. Such massaging techniques have been developed by a Brazilian ENT doctor and disseminated in Europe by Dr Boedts.
- Eggermont (2021) presented a model of tinnitus in which tinnitus signal could be located in the non-primary auditory pathway. This is an interesting hypothesis that remains currently untested. Recently, Arnal and colleagues developed a non-invasive technique to explore the specific correlates of the non-primary auditory pathway (or of the non-canonical auditory pathway), which relies on a non-linear response to different frequency of click trains by the means of auditory steady state responses (Arnal et al., 2019). Interestingly, this technique was used in sleeping patients and showed that such responses remained specifically active during sleep (Legendre et al., 2022). We have started a research project in collaboration with their team to explore tinnitus patients with this technique and thus explore the involvement of the non-primary auditory pathway.
- Finally, exploring the functioning of the unitary firing behaviors (spontaneous and evoked) of the neurons of the different central auditory pathway nuclei and crossing these findings with theories on Non-REM and above all REM sleep and theories about auditory gating during these sleep stages, we came to posit testable hypotheses on how auditory gating during REM sleep could work. Indeed, Andrillon and Kouider (2020) suggested that gating functioning could be different between Non-REM and REM sleep. Notably, during REM sleep they suggested that an informational gating could take place, in which the brain would be “distracted” by the emission of Ponto-Geniculo-Occipital (PGO) waves by the reticular nuclei and would not be able to properly process exterior sounds as a consequence. They suggested that such gating should operate at the cortical level. Yet, by exploring the scientific literature on the unitary firing properties of the auditory nuclei during REM sleep, we came to posit a slightly different alternative hypothesis. Indeed, such studies have shown that spontaneous unitary firing properties in the inferior colliculus, medial geniculate body and auditory cortex (A1, belt and parabelt) are globally increased (Edeline et al., 2000; Issa, 2008; Torterolo et al., 2002). At the same time, unitary evoked activity by clicks remains unchanged in amplitude (contrary to Non-REM sleep). This results in a decreased signal to noise ratio between evoked responses and spontaneous activity, which has been described as significant in at least two studies (Edeline et al., 2000; Torterolo et al., 2002). This leads us to believe that there is a form of informational

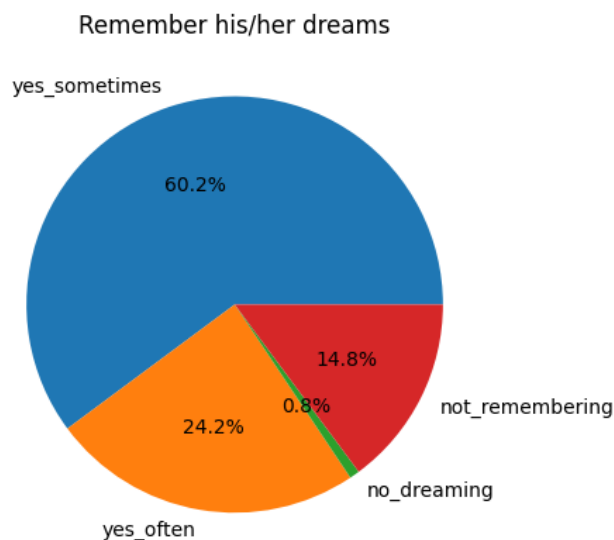
gating of auditory information during REM sleep, but it may not take place at the cortical level. Rather, it could start in sub-cortical nuclei, at least down until the inferior colliculus and maybe even down to the cochlear nuclei. One may wonder what would be the cause of the enhancement of such spontaneous activity in the central auditory pathway during REM sleep. A good potential candidate would indeed be PGO-like waves, as presented by Fazen (1987). Such PGO waves would be associated with middle-ear muscle activity (MEMA) which would appear as the phasic auditory equivalent of rapid-eye movements during REM sleep. Interestingly, it would match the theory proposed by Hobson and Friston (Hobson and Friston, 2012) on the role of rapid-eye movements and PGO during REM sleep. In fact, they posit, according to the Bayesian brain framework, that during REM sleep the brain optimizes our prior belief model. Physiologically, it would rely on the deactivation of the supra-granular layer of the sensory cortices by an interruption of aminergic excitation. This would lead to the interruption of the computation of prediction error at the level of the sensory cortices. Yet, they mention that on the contrary proprioceptive processing of the muscles associated with sensory acquisition, such as the orbital muscles of the eyes, remain active and even enhanced during REM sleep and would actually substitute real sensory information processing during REM sleep. Such muscles movements would be activated by PGO waves. Such proprioceptive information would hence be normally processed (and even enhanced) and be interpreted at the level of the sensory cortices as sensory information that would take meaning in the context of the dreams and contribute to prior belief model optimization. They describe this view as a revisited interpretation of PGO waves and thoroughly describe it for the visual modality. The authors did not propose that a similar functioning could take place for the auditory modality as they maybe were not aware of specific REM sleep MEMA activity. Indeed, MEMA activity could truly be the equivalent of rapid-eye movements for the visual modality during REM sleep. Indeed, they could be elicited by PGO-like activity generated by the reticular nuclei and then propagate within the central auditory pathway, resulting in the observed enhanced spontaneous activity. Proprioceptive information from MEMA could be enhanced such as what happens in the visual modality. This would result in a decrease of signal to noise ratio of real sounds processing, as was reported in the inferior colliculus (Tortorolo et al., 2002), medial geniculate body and auditory cortex (Edeline et al., 2001, 2000). This proprioceptive signal would then be interpreted as sensory auditory information at the level of the auditory cortex in the context of the dream. As such proprioceptive information would be somehow amorphous, it could account for intact body representation during REM sleep as it would not reflect any tonotopically-restricted deafferentation. Alternatively, if an individual presented a lesion only at the level of the middle-ear muscles and yet have an intact auditory system (cochlea and auditory nerve), one could suppose that REM sleep may have a negative effect on hearing by using deteriorated proprioceptive information as base for auditory prediction model fitting. Such a set of hypotheses deserves further clinical investigations. We recently started a collaboration with Thomas Andrillon to investigate them.

# Appendices

Here we will present an additional unpublished research project as well as preliminary results of two ongoing studies.

## Appendix 1 : Ongoing study - Tinnitus, dreams and awakening

We conducted a survey on Siopi on the theme of “Tinnitus dreams and awakening”. We collected and analyzed the 128 first answers to this survey. Such survey is still ongoing. A first part of this survey at a reproducing the results presented in previous studies (Aazh et al., 2021; De Ridder et al., 2014a). We first asked whether the participants remembered their dreams. Figure A1.1 presents the obtained results.



*Figure A1.1 : Pie chart of the answers of the sample to the survey question “Do you remember your dreams?”, N=128.*

We then asked if they heard their tinnitus during their dreams. So as to reproduce the results of De Ridder and colleagues (2014a), we present in figure A1.2 only the answers of the patients that remembered at least sometimes their dreams. We hence have N=108 answers.

### Hear tinnitus in dreams ?

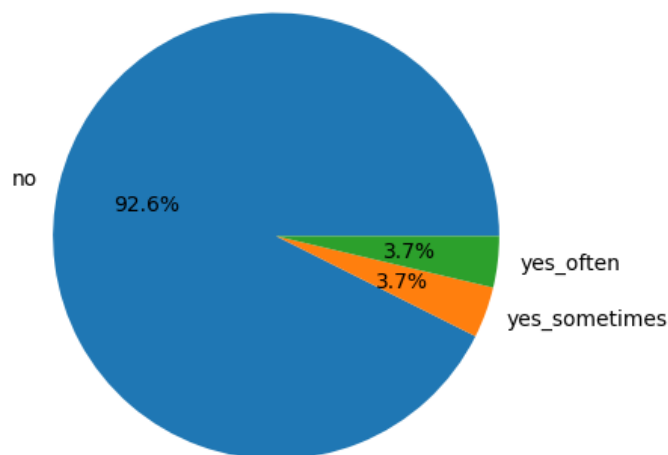


Figure A1.2 : Pie chart of the answers of the sample to the survey question “Do you hear your tinnitus during your dreams?”, N=108.

We then asked if patients made dreams on the topic of their tinnitus (without necessarily hearing it). We present the results collected on the 108 patients who remembered their dreams at least sometimes in figure A1.3.

### Dreams about tinnitus ?

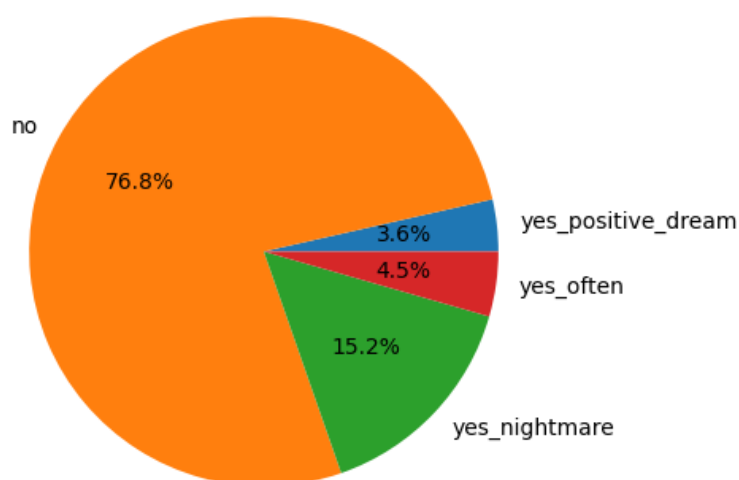
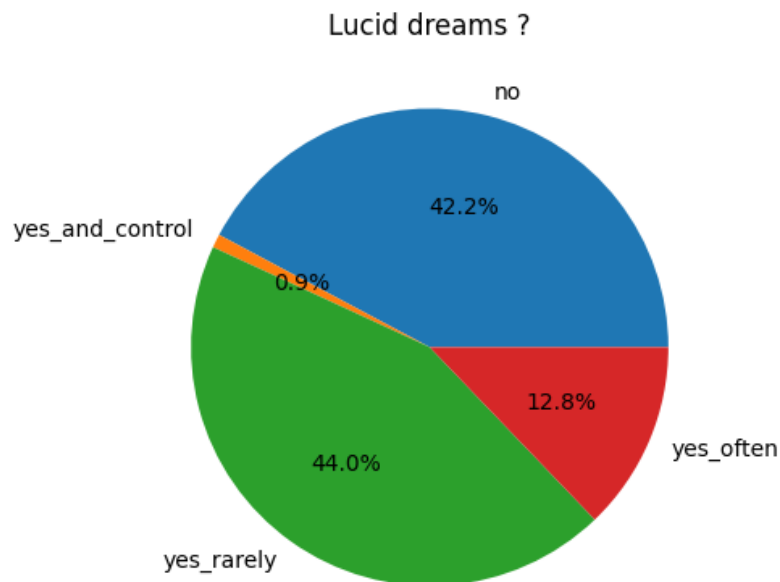


Figure A1.3 Pie chart of the answers of the sample to the survey question “Do you make dreams about your tinnitus?”, N=108.

We also asked patients if they experienced sometimes lucid dreams, that is to say dreams in which you are aware you are dreaming. We present results for the 108 patients in figure A1.4.



*Figure A1.4 Pie chart of answers of the sample to the survey question “Do you make lucid dreams?”, N=108*

12 patients reported they often made lucid dreams about their tinnitus. 10 out of these 12 patients answered two additional questions. We asked them if they heard their tinnitus specifically during lucid dreams and we also asked them if they were able to hear external surrounding noises (e.g. sounds in their bedroom) during their lucid dreams. Out of the 10 patients, 6 patients answered they were neither able to hear their tinnitus during their lucid dreams nor hear external surrounding noises and 4 patients reported they were both able to hear their tinnitus during their lucid dreams and to hear external surrounding noises during such lucid dreams.

As a consequence, these preliminary results suggest that the ability to hear tinnitus during a dream is linked with the auditory gating mechanisms during REM sleep. Conversely, tinnitus perception seems intimately linked with the processing of external auditory sounds and absent in internally generated sound content of dreams.

The survey also asked if patients perceived louder tinnitus when awakening in the middle of a dream. Due to a survey malfunction on this specific question, we only could recover 44 out of the 108 answers on this specific question. Results are presented in figure A1.5.

## Tinnitus higher awakening from a dream ?

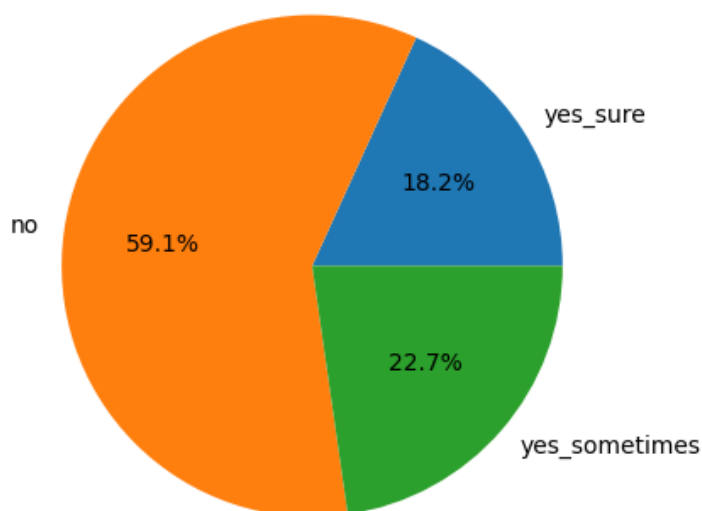


Figure A1.5 : Pie chart of the answers of the sample to the survey question "Is your tinnitus louder when you wake up in the middle of a dream?", N=44

These preliminary results suggest that a non-negligible proportion of tinnitus patients report louder tinnitus when awakening from a dream.

We also asked the responders of this survey how tinnitus tends to arise following awakenings, depending on if it is an awakening in the middle of the night or if it is the classic awakening in the morning. Results are presented jointly hereafter in figure A1.6.

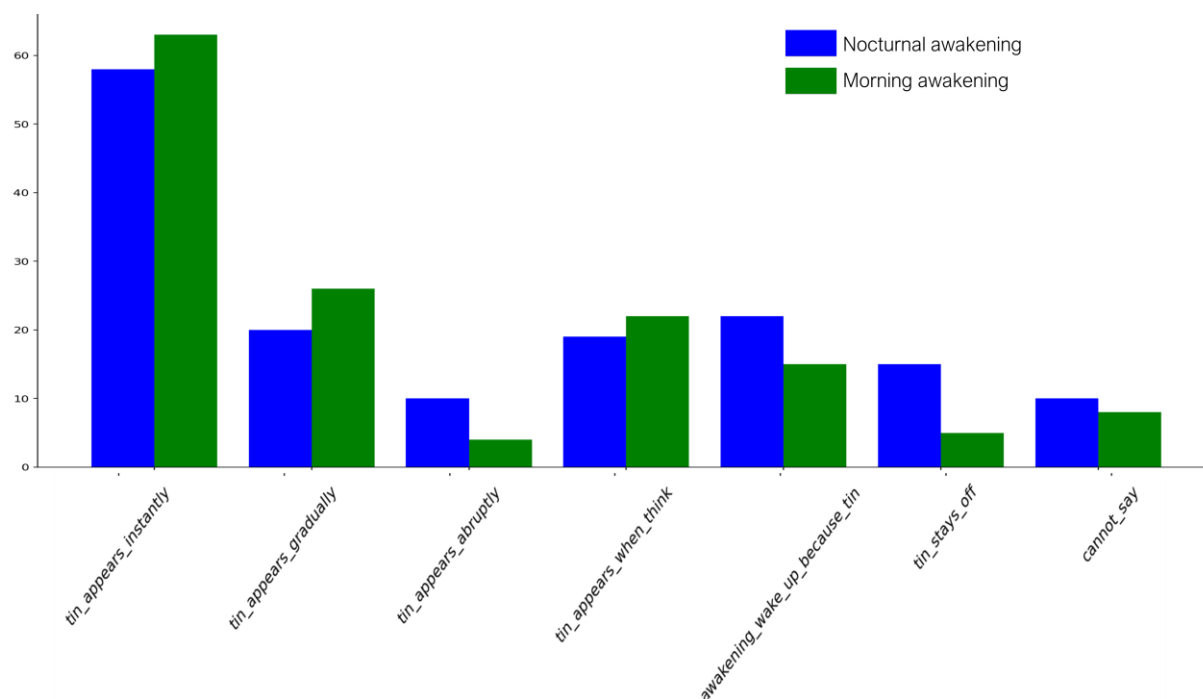
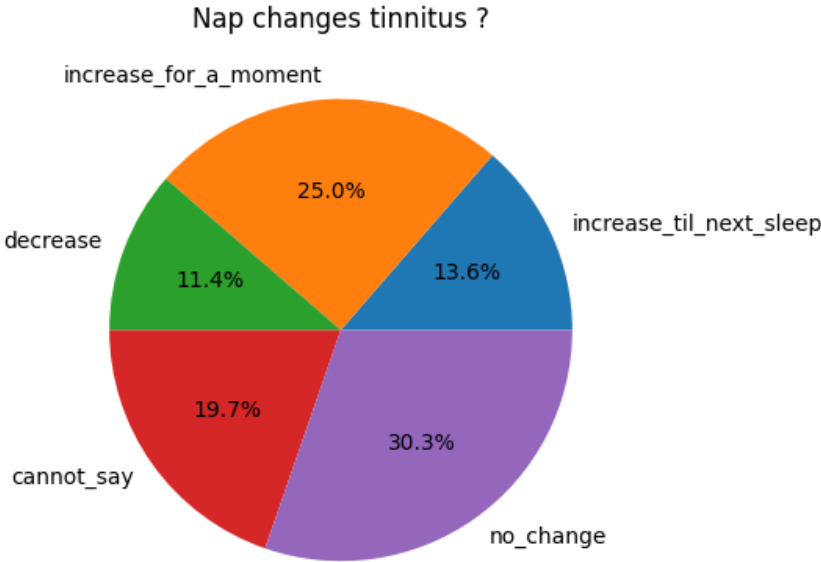


Figure A1.6: Bar charts of the answers of the sample to the survey question "How is your tinnitus when you wake up in the morning /during the night?", N=128

Interestingly, a notably higher proportion of responders reports absent tinnitus during nocturnal awakenings compared to morning awakening.

Last we asked to the responders of the survey how their tinnitus changed after a nap or after dozing off briefly. Results are presented hereafter in figure A1.7.



*Figure A1.7: Pie chart of the answers of the sample to the survey question “How is your tinnitus when you wake up from a nap or after dozing off briefly?”, N=128*

Such results tend to suggest that among TIAN patients there seems to be two groups of patients: patients reporting transient increases of their tinnitus and patients reporting stable increases following naps.

# Appendix 2

## Modulation of tinnitus perception by nocturnal masking stimulation during NREM 1-2 and REM sleep stages. A pilot study.

Robin Guillard, Alexandre Maurel, Louis Korczowski, Alain Londero, Marco Congedo, Damien Léger and Daniel Pressnitzer

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### 1 Abstract

**Background:** A variety of sound stimulation protocols are proposed to reduce subjective tinnitus intrusiveness. Among them, total or partial tinnitus masking is commonly used. In most cases these therapeutic auditory stimulations are delivered during patients' awake time, yet other studies highlight the potential of nocturnal sound stimulation. Moreover, research on auditory cortex function during sleep suggests that specific sleep stages such as NREM1, NREM2 and REM should be better suited to improve efficacy of nocturnal sound stimulation or masking.

**Objective:** In this study, experimenters tested a one-night nocturnal tinnitus masking (NTM) sound stimulation protocol performed during awake, NREM1, NREM2 and REM sleep stages. The aim was to assess whether this could result in an observable tinnitus perception reduction.

**Methods:** A pilot clinical study was conducted on 14 subjective tinnitus patients who reported their initial tinnitus intrusiveness through the Tinnitus Handicap Inventory (THI) and numeric rating scales (NRS) on loudness (NRS-L) and intrusiveness (NRS-I). Sleep schedules via sleep logs, tinnitus minimum masking level (MML), (NRS-L) and (NRS-I) of tinnitus perception were assessed daily for 2 weeks. At the end of the first week, one observational night of full polysomnography was conducted (PSG). A second PSG intervention night followed during which a personalized masking sound stimulation was applied to each patient during their sleep, in wake, NREM1, NREM2 and REM stages, while silence was applied during NREM3 sleep. By the end of the second week, they completed again the THI, NRS-L and NRS-I again (T2). Primary outcome was MML evolution following intervention, secondary outcomes were tinnitus impact on quality of life evolution, measured through NRS-L and NRS-I evolution following intervention and global assessment by THI, NRS-L and NRS-I between T0, T1 and T2.

**Results:** A significant reduction of MML was observed between the morning before intervention and the morning after intervention ( $p < 0.05$ ), as well as between the morning after intervention and the mean MML of the first week ( $p < 0.05$ ). Such reduction could neither be observed between the evening before intervention and the evening after intervention, nor on subjective ratings. Besides, patients got an overall significant improvement of their quality of life between (T0) and (T2), yet no specific improvements between (T1) and (T2) were observed, as seen by THI, NRS-L and NRS-I evolutions.

**Conclusion:** This study suggests that NTM sound stimulation during wake, NREM1, NREM2 and REM has a significant effect on tinnitus sound perception upon awakening after only one night of stimulation. Future research should investigate whether a longitudinal protocol of nocturnal sound stimulation would draw more effective and sustainable effects.

*Keywords: Tinnitus, sleep, REM sleep, masking*



## 2 Introduction

Subjective tinnitus (ST) is a phantom auditory percept that cannot be linked to any objective physical sound source (Baguley and al, 2013). ST is a frequent and widespread symptom experienced by 14 % of the world population, with 2% of the population suffering from a severe form of it (Jarach et al 2022). Tinnitus is assumed to be the consequence of multiple and intertwined dysfunctions of the peripheral and central auditory systems, with several different subtypes that have been only partially elucidated to date (Langguth and al 2013, Coelho et al., 2020).

Several attempts have been made to sustainably alleviate tinnitus perception through sound stimulation (Pienkowski 2019, Searchfield et al., 2017). One such broadly used approach is tinnitus masking, defined as acoustical suppression of tinnitus (Hazell and Wood, 1981), which usually consists of presenting a continuous physical sound stimulus that has the spectral ability to mask tinnitus perception of the patient. The aim of such an approach is not only to mask ST when the sound stimulus is applied but also to hope to attain sustainable reduction of the tinnitus percept when sound stimulation is no longer present (Jastreboff 2007). One well-known temporary phenomenon of such prolonged effect of ST reduction after the end of a sound stimulus is denominated residual inhibition (Roberts, 2007).

Most attempts to treat ST with tinnitus masking were performed during ST patient awakening time through the use of tinnitus maskers or hearing aids (Hobson et al., 2012). However, as a major part of ST patient experience insomnia and more generally sleep disturbances (Alster et al., 1993, Asnis and al. 2018, Weber and al 2022) - a frequent strategy used by ST patients to find sleep despite their tinnitus is tinnitus masking while trying to fall asleep (Handscorn, 2006). Following this trend, new approaches of Nocturnal Tinnitus Masking (NTM) were explored. They combined the potential to help patients in finding sleep and aimed for sustainable reduction of ST by long exposition to masking sound during patient sleep time (Pedemonte et al., 2010; Drexler et al., 2016; Pedemonte et al., 2019). Such a procedure was also successfully tested with patient suffering from hyperacusis (Madeira and al 2007).

These pioneer studies have shown promising results on their cohorts on the approach for longitudinal application of whole night NTM stimulation during several months, with stronger changes reported within the first week (Pedemonte et al., 2010; Drexler et al., 2016). To a smaller extent, it was also observed for a single night NTM stimulation (Pedemonte et al., 2019). This latter study was all the more enlightening as it showed that NTM had different outcomes regarding the sleep stages it was applied in. Further exploratory work was performed by the same team on the analysis of the impact of sound stimulation on electroencephalographic (EEG) patterns during sleep on ST patients (Pedemonte et al., 2014). As an outcome, it was reported that NTM sound stimulation seemed most effective during NREM2, showed mixed results during REM and was not effective at all for patients that were stimulated during NREM3.

The results of a recent study led by our team (Andrillon et al., 2017) have motivated our new approach. Andrillon et al. played randomized sounds never heard by participants during different phases of sleep. EEG recordings obtained during the night, combined with behavioral performance measures at awakening, showed that the sounds played during NREM2 sleep - and to a lesser extent in REM sleep - were learned by the participants while the sounds played during NREM3 sleep did not elicit any signs of learning. Moreover, it was harder for participants to learn the same sounds played during NREM3 while awake; this suggests a form of suppressive plasticity during NREM3 sleep. The suppressive plasticity was very specific and has only been observed for the sounds played during NREM3 and not for sounds with overall identical statistics but different in their acoustic details.

These results on auditory plasticity during sleep bring a new insight to the early observations of Pedemonte et al. regarding the disparity of outcomes of NTM stimulation between sleep stages. It further suggests that to better

take advantage of auditory learning and memorization during sleep, the NTM stimulus should be performed during NREM2 and REM sleep and not during NREM3 sleep. As no specific suppressive plasticity mechanism were described for wake and NREM1 stages, in order to limit the number of masking volume transitions overnight it can be assumed that a theoretically more efficient NTM protocol would consist of stimulating patients overnight during wake, NREM1, NREM2 and REM sleep stages and let NREM3 without sound stimulation. This hypothesis was tested in the present study to investigate if such an approach leads to tinnitus alleviation.

### 3 Methods

To test this hypothesis, a cohort of 14 ST patients were consequently recruited to participate for two nights of full polysomnography. The first night was an observational habituation night without NTM sound stimulation, followed by an intervention night of personalized NTM sound stimulation during wake, NREM1, NREM2 and REM sleep stages and silence during NREM3 stage. Tinnitus perception evolution was monitored daily for the week preceding intervention and the week following it. It was done by minimum masking level (MML) measurements and subjective assessment of the loudness and the intrusiveness associated with their tinnitus perception. These assessments served as the clinical outcomes of the intervention.

#### 3.1 Participants

105 ST patients applied to participate and were screened, from which 14 ST patients fitting the inclusion and exclusion criteria given in table 1 were included. The sample (5 females, 9 males) had a mean age of 50,1 (std 14,2). Each participant gave their written consent. Screening procedure (T0) consisted in the completion of an online e-Case Report Form (e-CRF). Heterogeneity of tinnitus patients' profiles and limitation of available slots for night sessions at the hospital led to the important discrepancy between the number of screened patients and the number of patients included. Demographics about ST patients are given in table 2. Every patient participated in a 14-day protocol, an overview of the schedule of their participation is given in figure 1.

#### 3.2 Evaluation criteria :

Tinnitus minimum masking level (MML) and numeric rating scales (NRS) on loudness (NRS-L) and intrusiveness (NRS-I) were assessed each morning during the week before intervention and the week after intervention. Moreover, MML was assessed each evening during the same time period. Tinnitus Handicap Inventory (THI), as well as NRS-L and NRS-I were administered to patients at screening (T0), at the initial clinical assessment (T1) and at the final clinical assessment (T2).

Table 1, Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age above 18 years old	Subjects under legal protection (guardianship, curatorship or protection)
French social security affiliation	Mesnière's disease, Chronic or
Written consent to the protocol	Pulsatile tinnitus, highly somatosensorial tinnitus
Permanent, chronic (>6 months) non-fluctuating tinnitus	Unability to wear the polysomnography device
2 consecutive days availability for polysomnographic recordings	Pregnancy or breastfeeding
Tinnitus Handicap Inventory (THI) score superior or equal to 18	Sleep apnea, Restless legs syndrome, somnambulism
(at least THI category 2)	New antidepressant/anti-epileptic drug treatment in the last 3 months

Overnight evolution of MML around the intervention night was the primary outcome of the clinical trial (MML between the morning before and the morning after intervention, as well as MML between evening before and after intervention). Comparing MML between similar times of the day seemed essential as tinnitus can have a recurring intensity variation pattern over the day in some patients.

A secondary outcome was the comparison of the MML between the days of the week after intervention and the baseline of MML calculated from measures the week before intervention.

Table 2, Demographics and tinnitus characteristics of the study sample

	Mean	Std	Median	Min	Max
Age	48,7	14,7	55	20	65
Tinnitus duration (in years)	11,8	10,7	8,3	0,8	39
Initial THI score	37	11,3	36	22	64
Initial NRS-L score	5,7	1,7	6	2	8
Initial NRS-I score	5,9	2,1	5	3	10

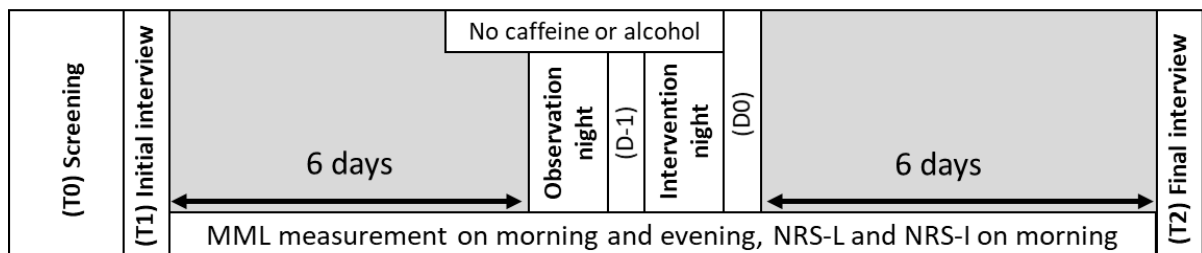
*Abbreviations : Std : standard deviation, THI : Tinnitus Handicap Inventory, NRS-L : numeric rating scale - Loudness, NRS-I : numeric rating scale - Intrusiveness*

Analysis procedures are described hereafter. Similarly to MML, as secondary outcomes, NRS-L and NRS-I were compared before and after the intervention night and compared between the days of the week after intervention and the baseline of NRS-L and NRS-I calculated from measures the week before intervention.

Another secondary outcome was the evolution of THI, NRS-L and NRS-I between screening (T0), initial clinical assessment (T1) and final clinical assessment (T2). These outcomes were individually measured according to the following setups:

Minimum masking level:

Patients were asked to determine the minimum sound level at which their tinnitus perception was masked by a broadband white noise (20 HZ - 10 kHz) on an MP3 device “HIFI WALKER HX” (Letushi Co. Ltd, Shenzhen, China), with intra-auricular earphones “AGPTEK sleep earbuds” (New York, USA). The assessment of tinnitus masking level was performed 3 consecutive times, each time starting at 0 dB Sound Pressure Level (SPL) and rising progressively up to the level at which tinnitus was masked. Precise advice was given to participants: “stop at the volume where you cannot discern your tinnitus perception from the sound stimulus, without focusing on finding your tinnitus”. Conversion from MP3 intensity levels to dB SPL was performed in an anechoic test room (LSP, ENS Ulm) with an artificial ear.



**Figure A2.1: Schedule of subject participation to trial.**

**Legend:** MML: Minimum Masking Level, NRS-L : Numeric Rating Scale – Loudness, NRS-I: Numeric Rating Scale – Intrusiveness. These are simple scales enabling patients to subjectively assess a feature of a symptom (e.g. intrusiveness) and rate it on a discrete 11 grades scale from 0 to 10. NRS have been widely used to assess tinnitus perception in clinical trials on ST patients (Meikle et al., 2008). Two NRS were used in this study: Loudness Numeric rating Scale (NRS-L) and Intrusiveness Numeric Rating Scale (NRS-I). NRS-L was “How loud is your tinnitus? 0 No tinnitus; 10 the louder imaginable tinnitus” and NRS-I was “How intrusive is your tinnitus? 0 : Not intrusive at

all.10: The most intrusive”. Subjects were asked to answer on their perception at the moment where the rating was performed.

Tinnitus Handicap Inventory (THI):

THI is a self-questionnaire of 25 questions rated between 0-100 (Newman and al, 1996) recommended in clinical studies for the clinical evaluation of tinnitus impact on quality of life (Langguth and al, 2007). THI global score was analyzed as assessment of the impact of tinnitus on a subject quality of life, its subscales were not investigated in our analyses.

THI was administered to patients during screening (T0), at the initial clinical assessment (T1) and at the final clinical assessment (T2).

*3.3 Polysomnography material:*

Polysomnographic recordings were performed using 2 Nox A1 devices (Resmed), sample rates of the 2 devices were 200 Hz and 250 Hz. EEG channels were positioned classically in F3, F4, C3, C4, O1, O2, M1, M2 according to the 10-20 system for electroencephalography (EEG) positioning (Jurcak et al., 2007), 2 EOG channels were used. 3 EMG sensors, 2 placed on the right and left suprahyoid muscles and one on the chin as reference.

All EEG, EMG and EOG electrodes were gold cup electrodes which were filled with conductive paste (Weaver and Company - Ten20 Conductive Neurodiagnostic Electrode Paste). (The) Epidermis was initially cleaned with an alcoholic solution (Cooper - Alcohol 70% vol.) and dried before conductive gel was applied and the electrodes were positioned. Electrodes were held in place with the addition of adhesive conductive paste (Natus Genuine Grass EC2 electrode cream) on the top and adhesive band (Mölnlycke - Mefix - Self-adhesive fabric).

2 ECG sensors were placed in left arm/right leg positions. Single-use humid electrodes were used as reference (on the forehead) and for ECG measurement (Covidien - Kendall - hydrogel ECG electrodes H92SG).

Nox A1 had inherent additional biosensors as well: accelerometer in the 3 dimensions, activity measurement, angular position of the device, dB audio measurement.

Table 3, Tinnitus individual characteristics of the study sample

Patients	Tinnitus duration	Tinnitus laterality	Principal tinnitus component frequency	Mixer intensity of principal tinnitus component	Quality factor of principal tinnitus component	Secondary tinnitus component frequency	Mixer intensity of secondary tinnitus component	Quality factor of secondary tinnitus component
1PI07	01/07/2017	L>r	8297	0,0234	103			
1CC05	01/03/2012	Both ears	196,3	0,0343	64			
1PT06	02/01/2006	L>r	3709	0,46	718	1399	0,0033	0
1ZN04	14/11/2018	R>l	5458	0,023	926			
1GB18	01/02/1980	R>l	266,7	0,0029	5	6565	0,0025	114
1RA17	01/01/2019	Both ears	7716	0,0029	138	6687	0,0019	46
1GF14	01/01/1980	L	7817	0,03	981	6791,6	0,004	186
1BA07	04/01/3018	L>r	« Purple noise » ramp	0,6				
1MN09	10/04/2010	Both ears	5500	0,72	338			
1MF19	07/03/2002	L>r	1203,7	0,49	26	2656	0,008	13
1DL12	01/01/1996	R	5236	0,12	467			
1SA14	02/02/2012	Both ears	6080,68	0,012	511			
1DA15	01/01/2000	Both ears	12000	0,005	968	9216	0,005	813
1MA16	01/06/2017	R	6500	0,002	701			

Abbreviations : R : right, L: Left, L>r : laterality rather more on the left, R>l : laterality rather more on the right

Patients participated to the study either after visiting at Georges Pompidou European Hospital (Paris, France) for otolaryngologist tinnitus consultation, or by answering to an online survey questionnaire, which included THI, NRS-L and NRS-I (T0). They were then invited to participate in an initial interview at Hôtel-Dieu Hospital (Paris, France) sleep service (T1) where a doctor tested whether they complied with inclusion and exclusion criteria presented in Table 1. They could then give their informed consent and their night at Hôtel-Dieu Hospital was

scheduled. They were informed not to consume coffee nor alcoholic beverages on the observation day(s) and intervention nights.

Patients completed again the THI, NRS-L and NRS-I. They were given the MP3 device and headphones with preloaded broadband white noise and were instructed on how to perform MML measurements in autonomy, as well as how to fill daily reports of their MML, NRS-L, NRS-I and sleep quality feedbacks.

### 3.4.2 Observation night:

Patients were invited to come upon late afternoon to Hôtel-Dieu Hospital sleep service. They were equipped with NOX A1, and were offered dinner. After dinner, a tinnitus pitch matching procedure was performed manually by the experimenters to assess the pitch of their tinnitus as well as their tinnitus level through tinnitus masking level and NRS-L and NRS-I, (see section 3.2). Tinnitus pitch matching was performed binaurally regardless of tinnitus laterality, following a 3-step procedure: first bandwidth of tinnitus perception was estimated by oral questions and several examples of several bandwidth values for multiple frequencies. When bandwidth was assessed, pitch matching was performed with the “Methods of limits” described in (Tyler and Conrad-Armes, 1983). Last, tinnitus level was assessed by estimating the MML for the obtained sound stimulus. Residual inhibition was tested by creating a sound stimulus with the formerly determined sound characteristics, 5 seconds in duration, 2 seconds pauses and up to 15 dB above formerly determined sound level following (Fournier and al, 2018).

Afterwards, calibration tests to assess polysomnography sensors signal quality were run with the experimenters to test if all recording channels were set up correctly. Each channel was tested individually and for EMG, EOG and EEG channel, channel impedances were controlled to be below 20k Ohms. They were then asked to assess their evening MML.

They could freely decide when to try to fall asleep and were warned against using blue screens that could alter their sleep quality.

Patients were then woken up at 8 a.m. and were served breakfast. They assessed their tinnitus perception level through tinnitus masking and NRS-L and NRS-I. After removing the polysomnographic device and non-disposable electrode components, patients were invited to take a shower to remove remaining conductive gel deposits. Patients were told to come back in late afternoon for intervention night.



*Fig A2.2: polysomnography electrode setup. EEG electrodes in F3, F4 (blue), C3, C4 (yellow), O1, O2 (purple) and mastoids electrodes M1 and M2 (brown). EOG channel in Green, EMG electrodes in red and the red bar for the reference electrode. NOX A1 not shown.*

### 3.4.3 Intervention night:

Similarly to observation night, patients were invited to come upon late afternoon to Hôtel-Dieu Hospital sleep service. They were equipped with NOX A1, and were offered dinner. After dinner, same calibration tests were conducted.

A SoundLink Bose revolve speaker was placed before the head of the patient bed, on the middle plane of the bed for balanced sound stimulation between ears for a normal supine sleep position.

The sound stimulus elaborated with the patient during tinnitus pitch matching procedure was used as the NTM sound, unless patients expressed preference for editing the sound stimulus' characteristics, without changing its ability to mask their tinnitus. Patients were asked to set the speaker volume to a level at which their tinnitus was minimally masked. This volume was set as maximal volume for the night,  $V_{max}$ .

Patients were then asked to assess their evening MML. They were instructed that NTM sound at  $V_{max}$  would be set on when they were ready to find sleep. They were also instructed that they could decide at any point of the night to switch off the sound of the speaker manually if they wanted. Out of the 14 patients who participated, none decided to switch it off.

Patient sleep was monitored during the night by an experimenter through Noxturnal software real time signal visualization tool. All Nox A1 signals were displayed in real time.

The experimenters followed the following procedure during the night: each time the patient entered 30 consecutive seconds of stable NREM3 stage, an automated procedure enabling NTM sound transition linearly from  $V_{max}$  to 0 over 20 seconds would be activated. Likewise, when patients elicited signs of another sleep stage during 30 consecutive seconds, experimenters would launch a symmetric 20-second linear ramp to transition from volume 0 to  $V_{max}$ . An example of stimulation procedure overnight is presented in figure 2.

Patients were then woken up at 8 a.m. and were served breakfast. They could then assess their tinnitus perception level through tinnitus masking and NRS-L and NRS-I. After removing the polysomnographic device and non-disposable electrodes components, patients were invited to take a shower to remove remaining conductive gel deposits. Patients were then free to pursue their daily occupation.

Patients continued to fill daily reports of their sleep quality, MML, NRS-L and NRS-I for one week after intervention night to study the intervention lasting effect.

### 3.4.4 Final interview (T2):

One week after intervention night, patients went back to Hôtel-Dieu Hospital sleep service for a final interview (T2). They handed back the MP3 device and headphones, and were asked to complete one last time the THI, NRS-L and NRS-I. They could then share their feedback over the clinical procedure and ask questions to experimenters about the study design and analysis procedure.

Data from patients were filed and pseudo anonymized for future analysis. Participating patients received a gratification of 100 euros for their participation.

### *3.5 Preprocessing:*

We analyzed data with Anaconda Python 3.7 software and jupyter notebook tool for visualization of the results. Analyses and anonymized data are available on the repository "tinnitus-nocturnal-stimulation" on GitHub (<https://github.com/lkorcowski/tinnitus-nocturnal-stimulation.git>).

Data preprocessing consisted in creating 2 folders for morning and evening daily measurements and a CSV file for clinical assessments measures at screening (T0), initial interview (T1) and final interview (T2). Each folder contains 1 csv file per patient, where are gathered all the patient's daily reports, sorted chronologically. Reports were tagged with a relative date to locate the report compared to the intervention night. In the following analyses, Day 0 (D0) refers to the day following the nocturnal stimulation (intervention night), Consequently, (D-1) refers to

the day after the observation night and before the intervention night and D-7 to D6 are the participation days to the protocol. Each CSV file for morning measurements gathers daily self-measurements of MML, NRS-L and NRS-I, while evening measurements gathers daily self-measurements of MML.

### 3.6 Analyses:

3 types of analyses were led on clinical data associated with our study.

#### 3.6.1 Over-night intervention effect analysis:

Overnight effect of the masking sound stimulation intervention was evaluated through MML, NRS-L and NRS-I evaluation between (D-1) and (D0) on morning measurements, and MML on evening measurements. (D0) measurements were also compared to the individual average values of MML (morning and evening), NRS-L and NRS-I over the week before intervention.

#### 3.6.2 Global intervention effect analysis:

Patients' overall quality of life was evaluated through THI, NRS-L and NRS-I between (T0), (T1) and (T2). Statistical tests were led between paired distributions of scores between (T0) and (T2), (T0) and (T1) and (T1) and (T2).

#### 3.6.3 Polysomnographic analysis:

All Polysomnographic recordings were scored manually by a unique scorer applying AASM (American academy of sleep medicine) scoring guidelines on 30s epochs. Analyses were led to compare if sleep architecture characteristics differed between the paired values of observation nights and intervention nights for all patients. These analyses had the purpose to show if NTM intervention significantly interfered with sleep architecture (deteriorated or improved).

### 3.7 Statistics:

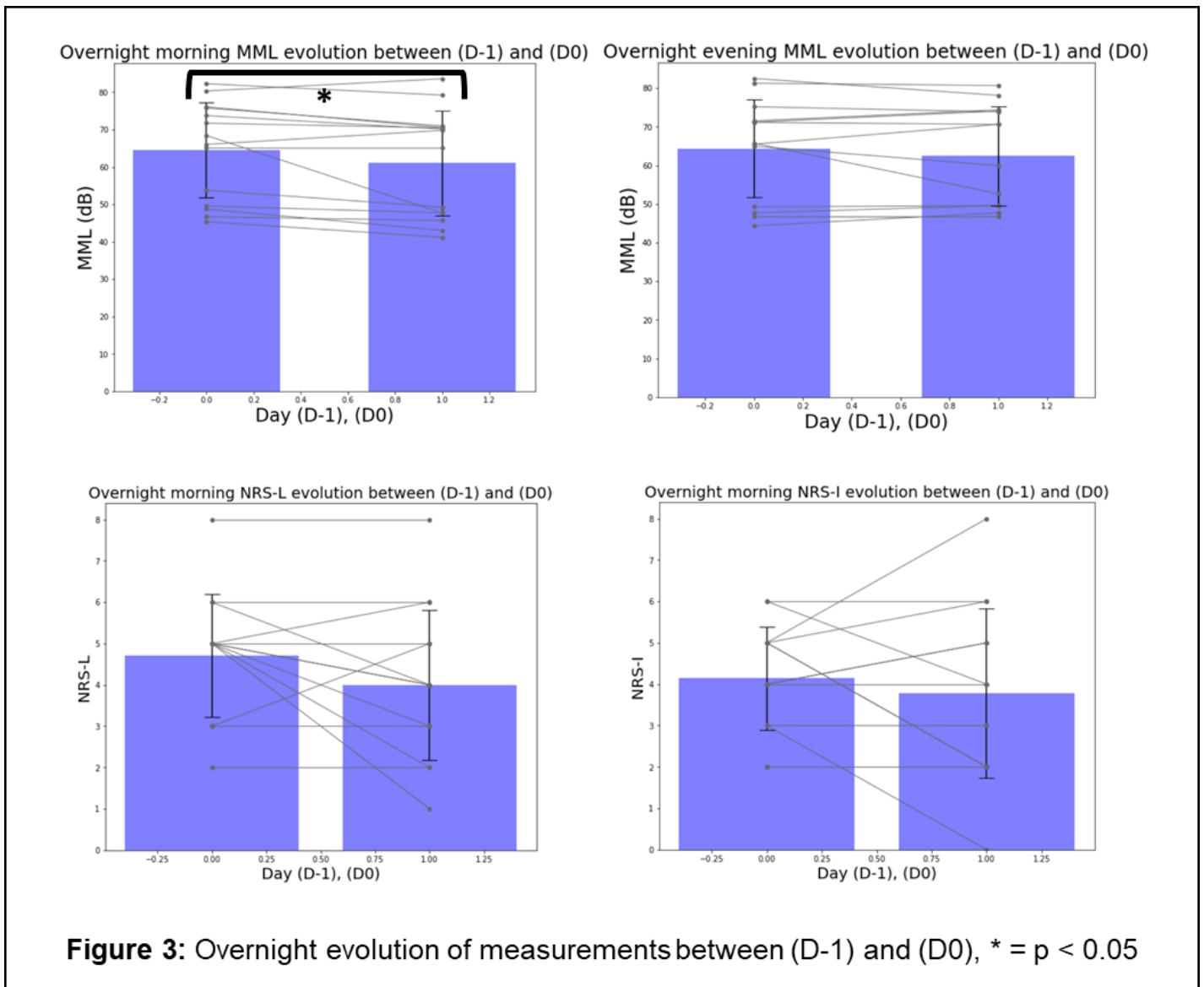
We used the Python library `scipy.stats` functions for statistical testing (Virtanen et al, 2020). As normality hypothesis could not be verified in most cases to perform parametric tests (due to the small sample size of our cohort), all tests performed were Wilcoxon signed rank non-parametric tests to compare between the paired distributions of samples (Wilcoxon, 1945), with Cohen's d effect size measure (Cohen 1992).

## 4 Results

### 4.1 Overnight intervention effect:

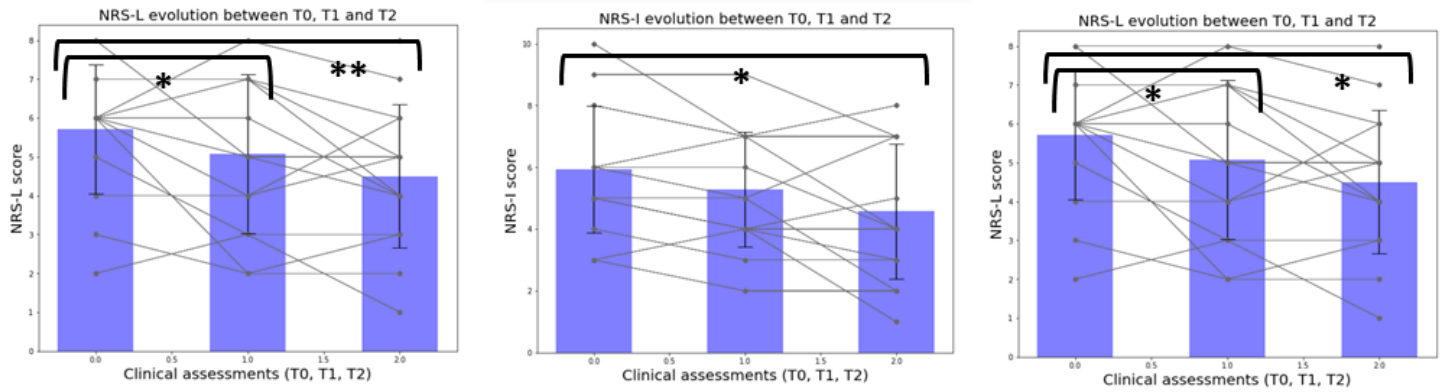
Overnight effect of the masking sound stimulation intervention showed a statistically significant decrease between morning MML scores between (D-1) (M = 64.56, std = 12.68) and (D0) (M = 61.04, std = 14.00),  $t(13) = 12.0$ ,  $d = -0.25$ ,  $p < 0.05$ . Neither NRS-L, nor NRS-I, nor MML evening measurements decreases were statistically significant.

A significant decrease of morning MML between reference distribution  $\mu_{Ref}(MML)$  ( $M = 64.77$ ,  $std = 12.72$ ) and (D0) distribution  $\mu_{D0}(MML)$  ( $M = 61.4$ ,  $std = 13.$ ) was observed,  $T(13) = 15.0$ ,  $d = -0.27$   $p < 0.05$ . Although the effect was not present for NRS-I, it was also significant for NRS-L between reference distribution  $\mu_{Ref}^{i \in [0,14]}(NRS\_L)$  ( $M = 4.84$ ,  $std = 1.70$ ) and (D0) distribution  $\mu_{(D0)}^{i \in [0,14]}(NRS\_L)$  ( $M = 4.17$ ,  $std = 1.86$ ),  $T(13) = 9.5$ ,  $d = -0.62$ ,  $p < 0.05$ .



**Figure 3:** Overnight evolution of measurements between (D-1) and (D0), \* =  $p < 0.05$





**Figure 4:** Evolution of secondary judgement criteriae between (T0), (T1) and (T2), \* =  $p < 0.05$ , \*\* =  $p < 0.01$

4.2 Global intervention effect:

THI scores showed a statistically significant decrease between T0 (M = 53.64, std = 11.31) and T1 (M = 31.29, std = 10.84),  $T(13) = 5.5$ ,  $d = -0.50$   $p < 0.05$ , THI scores continued to decrease between T1 and T2 (M = 27.0, std = 11.38) without reaching statistical significance ( $t(13) = 24.5$ ,  $d = -0.37$   $p = 0.14$ ). The overall decrease of 27% of THI scores between T0 and T2 was highly significant  $t(13) = 3.5$ ,  $d = -0.85$   $p < 0.01$ .

NRS-L scores showed only a statistically significant decrease of 21% between (T0) (M = 5.71, std = 1.67) and (T2) (M = 4.5, std = 1.84),  $t(13) = 20.5$ ,  $d = -0.66$   $p < 0.05$ , although it showed continuous decrease between (T0) and (T1) (M = 5.07, std = 2.05) and between (T1) and (T2).

NRS-I scores showed a statistically significant decrease between (T0) (M = 5.93, std = 2.05) and (T1) (M = 5.29, std = 1.87),  $t(13) = 11$ ,  $d = -0.31$   $p <$

$0.05$ , NRS-I scores continued to decrease between T1 and T2 (M = 4.57, std = 2.19) without reaching statistical significance ( $t(13) = 9$ ,  $d = -0.33$   $p = 0.11$ ). The overall decrease of 23% of NRS-I scores between T0 and T2 was highly significant  $t(13) = 7.0$ ,  $d = -0.61$   $p < 0.05$ .

4.3 Sleep architecture:

Sleep architecture parameters mostly didn't show any significant differences between observation night and intervention night, except for REM latency that exhibited a significant decrease between observation night (M = 112,2, std = 65,2) and intervention night (M = 76,5, std = 18,7),  $t(13) = 21$ ,  $d = 0,74$  ,  $p < 0.05$

Table 4, Polysomnographic characteristics

Night	Observation night	Intervention night	Wilcoxon test p-value
Mean TST (min)	419,9 (+/-94,4)	421,4 (+/-53,1)	0,71
Mean WASO (min)	93,1 (+/-75,4)	69,6 (+/-37,2)	0,35
Mean Sleep latency (min)	11,8 (+/-8)	15,7 (+/-11,2)	0,5
Mean REM latency (min)	112,2 (+/-65,2)	76,5 (+/-18,7)	0,049*
Mean %WAKE	20 (+/-15,6)	16,3 (+/-7,4)	0,71
Mean %N1	4,4 (+/-2,9)	4,3 (+/-2,1)	0,97
Mean %N2	37,9 (+/-8,9)	41,7 (+/-8,5)	0,21
Mean %N3	20,4 (+/-7,9)	20,5 (+/-7,2)	0,9
Mean %REM	16,8 (+/-5,5)	17,1 (+/-5)	0,62

Abbreviations : TST : Total Sleep Time, WASO : Wake time After Sleep Onset, REM : Rapid eye movement, \* :  $p < 0,05$

## 5 Discussion

The goal of this preliminary one arm pilot study was to evaluate the feasibility and short-term outcome of a one-night implementation of a nocturnal tinnitus masking (NTM) therapy, aiming to mask tinnitus during wake, NREM1, NREM2 and REM while letting NREM3 without stimulation.

### *Merits:*

The present study has tested the NTM procedure for treating tinnitus on a selected population of patients. Tinnitus masking overnight was manually performed by experimenters through real time sleep staging. Tinnitus evolution was scrutinized granularly through multiple time scales measurements on both objective and subjective assessments, during the week before and after the intervention. A significant effect on the MML was present the morning following intervention night. The sleep architecture wasn't deteriorated by the NTM intervention except a significantly shorter REM latency during intervention night compared to observation night with no clinical significance. This absence of sleep deterioration, notably of REM sleep was positive outcome as previous studies tended to show that night continuous noise exposition tended to damage sleep quality and notably reduce REM sleep, which wasn't the case in the present study (Scott and al 1972, Griefahn 2002, Messineo and al 2017).

Tinnitus concerns 14% of the general population (Jarach et al 2020) and is very difficult to treat, with an often-chronical evolution and a major impact on quality of life, sleep and depression (NICE, 2020). Insomnia is one of the most common complaints among people attending tinnitus clinics (Asnis and al 2018) ; the process is thought to be the same as in insomnia in other contexts with psychological factors being the dominant influences in bringing about and maintaining the problem (NICE, 2000). Tinnitus may be considered as altogether a Predisposing, Precipitating and Perpetuating factor of insomnia, These 3 P factors that have be described early in the pathogenesis of insomnia (Spielman et al, 1987). It is also hypothesized that tinnitus and insomnia may both be promoted by hyperarousal caused by enhanced activation of the sympathetic nervous system. There is increasing evidence for hyperarousal in insomnia patients, and animal models of tinnitus and insomnia show conspicuous similarities in the activation pattern of limbic and autonomous brain regions (Wallhäusser-Franke et al, 2013, Milinski et al 2022). Insomnia was also associated with greater perceived loudness and severity of tinnitus (Folmer & Griest, 2000). In this perspective, taking care of insomnia may per se improve tinnitus. This is why cognitive behavioral therapy (CBT), which is the gold standard treatment recommended in insomnia (Rieman et al, 2017) has also been proposed to take care of both insomnia and tinnitus. How the evidence is still low in our knowledge (Curtis et al, 2021). Beside CBT, a recent Cochrane analysis concluded that there was no evidence to support the superiority of sound therapy for tinnitus over waiting list control, placebo or education/information with no device. There was insufficient evidence to support the superiority or inferiority of any of the sound therapy options (hearing aid, sound generator or combination hearing aid) over each other (Sereda et al, 2018). They also recommended the use of validated, patient-centred outcome measures for research in the field of tinnitus. Our survey originally answered to these concerns as it was focused on carefully checked patients with both clinical criteria of insomnia and tinnitus and open the field of masking stimulation during NREM 1-2 and REM sleep stages, a new concept for treating insomnia at night.

Another important step brought by our study is the PSG analysis of patients during the two nights before and after masking. There are relatively few PSG data in patients with tinnitus as only four have been found in a review published in 2018 (Teixera et al, 2018a), with heterogeneous results. The latter review mentions yet that 3 studies

had found that REM sleep of tinnitus patients seemed disturbed (Burgos and al 2005, Attanasio and al 2013 , Teixeira 2018b). Since then, another publication has identified a correlation between REM duration and THI scores (Madhulika et al 2019). Here we found that patients with tinnitus had objective criteria of sleep maintenance insomnia with a high average wake after sleep onset (WASO) of 93.1 +/- 75.4 (Table 4) on D1, reduced but not significantly (69.6 +/- 37.2) on D2. The percentages of NREM stages and TST may be considered in the normal ranges, with REM lower than usually found in the general population (under 20%). PSG was crucial in our survey and we warmly recommend to use it in future studies in the field.

### *Limits:*

This study was a single arm trial without control and did not evaluate placebo effect. The size of the cohort for this feasibility study was limited (14 subjects) and statistical correction for multiple comparisons (as Bonferroni) was not applied in the analyses. Reported uncorrected significant results should thus be taken with caution and awaits confirmation by further research on larger cohorts.

Only one night of NTM stimulation was administered, while past studies (Pedemonte et al 2010, Drexler et al 2016) demonstrated that this kind of intervention's effects tended to strengthen over time through daily longitudinal approaches. THI questionnaire used for global intervention effect evaluation may not have been the best suitable questionnaire as only 2 weeks went by between (T1) and (T2) and THI is not very sensitive to changes in short time-frames. On the other hand, significant THI reductions were observed between (T0) and (T1) (slightly longer time frame as an average), before intervention began. Perhaps observed reduction corresponds to a waiting list effect as described by Hesser and al (2011). Patients' outcomes were overall heterogeneous, highlighting some patients benefited more from this approach than others. This suggests patient cohort inclusion and exclusion criteria might not be optimal (yet). Lastly, although MML overnight reduction was significant, it wasn't the case for NRS-L. This tends to imply that although the necessary masking sound volume to mask tinnitus was lower after intervention, it wasn't clinically significant enough to the point of eliciting significant results on this subjective scale.

### *Future directions:*

The current study is encouraging as it showed a significant reduction of MML the morning after the NTM intervention. The mean reduction of tinnitus observed in the cohort was 24% between mornings of (D-1) and (D0). Past studies (Pedemonte et al 2010, Drexler et al 2016) obtained stronger and more sustainable results on longitudinal procedures with daily intervention for 24 weeks and 1 month respectively, with best improvements observed within the first week (Pedemonte et al 2010). As a result, future protocols testing our NTM procedure should implement longitudinal procedures with daily intervention for at least 1 week. Moreover, a more sophisticated protocol, such as a 2-arm clinical trial with a crossover and 2-week washout procedure that compares between our NTM procedure and a control situation on larger cohorts would greatly contribute to control for placebo effect and bring solid evidence of the clinical efficacy of NTM procedure.

Clinical disparities were observed regarding our intervention. For future research, the selection criteria regarding patients' etiologies should be more strictly defined in order to identify a more homogeneous patient sub-group from our respondents. As such, an etiology-driven group comparison of clinical outcomes could be done with our NTM procedure.

Besides, for future clinical trials to come on this clinical approach, assuming that it chooses similar time-frame measurements to the ones in our study, it should be advised to use the Tinnitus Functional Index (TFI) (Meikle et al 2012) instead of the THI. This would assess the patient's evolution of their quality of life more accurately across the clinical trial, as the TFI appears to be more sensitive on these short time-frames (Newman et al 1998).

It should also be noted that our initial hypothesis which consisted in taking advantage of the auditory plasticity during sleep to try to unlearn tinnitus percept did not elicit a strong different therapeutic effect compared to prior attempts (Pedemonte et al 2010, Drexler et al 2016). Therefore, the extent of the relevance of these auditory plasticity differences according to sleep stages highlighted by Andrillon and al 2017 should be questioned for this therapeutic approach.

In order to test the additional value of the selection of sleep stages for stimulation, a clinical trial comparing the benefits of all night long NTM versus sleep-stage selective NTM should be tested. A comparison trial appears to be all the more important as sleep-stage selective NTM requires costly precise monitoring of sleep stages of patients through biosensors and automatic labelling of sleep stages in real time in order to infer decisions for masking sound volume. Contrastingly all-night long NTM stimulation can be performed with much more minimal, and thus economical, equipment.

Indeed, future research should test for longitudinal sleep-stage dependent NTM stimulation to test for stronger and longer-lasting clinical benefits; the technical challenge of replicating our clinical setting at home will have to be addressed. Patients should be able to bring their equipment at home and use it in autonomy if they were to use the sleep-stage selective NTM stimulation procedure for several days or a week.

## 6 Conclusion

This study suggests that nocturnal masking sound stimulation during wake, NREM1, NREM2 and REM can be helpful to reduce tinnitus sound perception. A significative effect was highlighted after one night of stimulation on the minimum masking level between the morning before and the morning after the intervention and more generally between the mean minimum masking level the morning(s) before intervention and the morning after intervention. This pilot study has several limitations and could be refined through further research. Future protocols should carry on more longitudinal paradigms, with control groups and possible crossover and washout modalities. Methodological etiology selection refinements should also be considered for further experimental investigations.

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## Appendix 3 : testing SIT tinnitus rhythmicity

We recently launched a new pilot study investigating whether or not tinnitus loudness in SIT patients was chaotic or had an intrinsic rhythm. To achieve this purpose, we monitored tinnitus loudness of four SIT patients for a duration between 50 and 150 days. Participants filled a daily questionnaire in the morning shortly after awakening and in the evening shortly before going to bed, giving us two time points of measurements per day.

We present hereafter in figure A3.1 the time course their tinnitus loudness measured by MML. Please note that x-axis and y-axis scales for each plot are different.

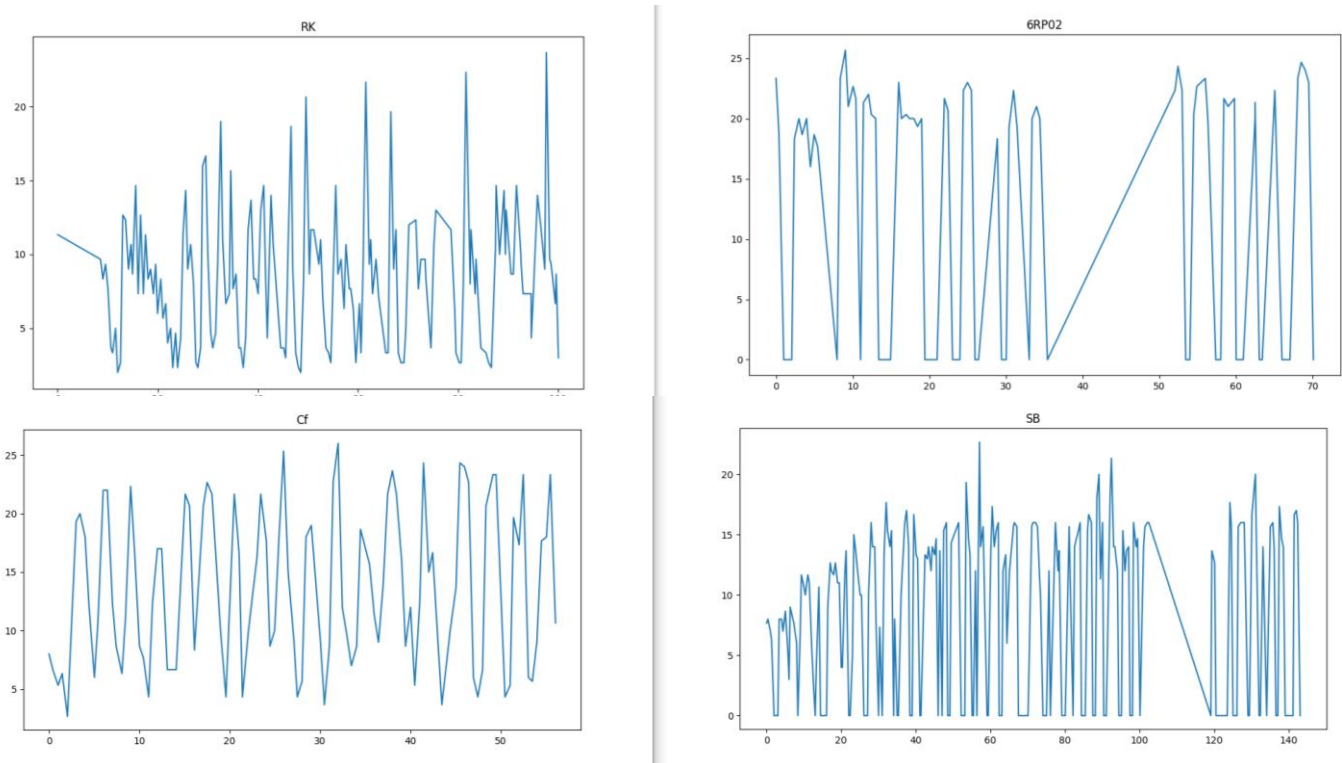


Figure A3.1 : Time course of tinnitus loudness measured by the MML of the four SIT

We applied a Cosinor test (Moškon, 2020; REFINETTI et al., 2007) to each of these time series to test if an oscillatory rhythm was present in these time series.

We were surprised to congruently observe significant similar rhythms in all these MML time series. Patient RK : period 2.9 days,  $p < 0.001$ . Patient 6RP02, period 3.1 days,  $p < 0.001$ . Patient Cf, period 2.9 days  $p < 0.001$ . Patient SB, period 2.9 days,  $p < 0.005$ . We are starting a larger scale observational protocol to try to confirm these preliminary results and try to correlate such tinnitus loudness oscillations with longitudinal sleep parameters of tinnitus patients.



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