

Multimodal investigation of the Parietal Operculum and its role in tinnitus perception.

Chloé Jaroszynski

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Présentée par

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préparée au sein du Laboratoire Grenoble Institut des Neurosciences dans l'École Doctorale Ingénierie pour la Santé la Cognition et l'Environnement

Exploration multimodale de l'Operculum Pariétal et de son rôle dans la perception d'acouphènes

Multimodal investigation of the Parietal Operculum and its role in tinnitus perception.

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Multimodal exploration of the Parietal Operculum and its role in tinnitus perception



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Abstract

Tinnitus, the subjective experience of sound outside any external auditory stimulus, is a recognised public health issue, with a 15% prevalence, a high diversity of causes and manifestations, and the potential for severe quality of life impairment. Neuroscientists and clinicians are faced with the challenge of distinguishing tinnitus perception from its associated distress, which is the main target of current treatment options. It is now well established that tinnitus perception involves dysfunctional cerebral activity patterns within and beyond the auditory pathway: tinnitus is increasingly viewed as a complex brain network disorder. Recent findings have linked tinnitus perception of acoustic trauma origin to middle ear dysfunction and identified the parietal operculum and, in particular, its third subdivision (OP3) as determined by cytoarchitectonic findings, as the central representation of this dysfunction. In this thesis, we question the role of OP3 as a potential key region in a cortical network underlying noiseinduced tinnitus. First, we explored non-invasive MRI connectivity measures, and then we strove to verify these findings using invasive high spatiotemporal resolution sEEG, and to obtain a direct signature of noise-induced tinnitus in OP3. To examine the role of OP3 as part of a functional brain network, while limiting the heterogeneity and distress-related biases, we focused specifically on a homogenous group of nonbothersome tinnitus participants and conducted a seed-based resting-state fMRI connectivity analysis. The results from this study highlighted a specific connection between OP3 and a dorsal prefrontal region, suggesting the involvement of top-down cognitive control mechanisms in tinnitus, as further discussed in an article published in Brain Connectivity. To establish the position of OP3 within a structural network, and the influence of tinnitus perception on it, we used diffusion MRI and tractography in a bundle-specific approach. We highlighted tinnitus-related differences in white matter tract density along the uncinate fascicle and the inferior fronto-occipital fascicle, evocative of both dorsal and ventral stream alterations, as documented in an article published in NeuroImage: Clinical. The second aim of this thesis was to obtain a form of ground truth evidence of tinnitus perception, thus moving to a higher spectro-temporal scale while preserving spatial resolution. This was provided by using intracranial recordings in three different frameworks. First, we examined the cortico-cortical connectivity of OP3 evoked by low-frequency stimulation as provided by the F-TRACT database. This analysis was published as part of a review article on OP3 with a focus on tinnitus, in Brain Sciences. Then, we questioned the specificities of erroneous sound perceptions separated into hallucinations, resembling

tinnitus, and illusions. Here, OP3 was found to be part of both an illusion and a hallucination network of high-frequency modulations, however, hallucinations were found to present a specific involvement of the limbic system. These results, interesting from the point of view of epilepsy, tinnitus, and schizophrenia which share fantom auditory percept semiology, were submitted as a publication in Neurology. Finally, we proposed a pseudo-tinnitus paradigm to provide verification of the main hypothesis of this thesis. Preliminary results provide evidence of the involvement of OP3 in the perception of the percussive stimulus, which is proposed to originate not from the sound processing stream, but from the somatosensory stream of the middle ear. This protocol is ongoing and has received support from the Fondation pour l'Audition to be continued for another year. Taken together, this thesis supports the view that OP3 plays a significant role in tinnitus as part of the network dealing with tinnitus-related somatosensory disturbances, and validates OP3 as a relevant neuromodulation target for tinnitus treatment.

Résumé

Les acouphènes sont une perception sonore fantôme, touchant 15% de la population avec des causes et des manifestations hautement variables. Les acouphènes sévères sont une grande source de détresse pour 0.5 à 2% de la population pour qui il n'existe pas à ce jour de traitement efficace : il s'agit donc d'un enjeu majeur de santé publique. Les études s'accordent sur le fait que les acouphènes résultent d'un dysfonctionnement complexe, impliquant des régions cérébrales au sein et en dehors de la voie auditive, organisées en réseau. Parmi les régions de ce réseau, l'operculum pariétal, et en particulier sa 3e division OP3, une région clé d'intégration de la voie somatosensorielle, a été trouvée impliquée dans les acouphènes survenant après un traumatisme sonore. L'objectif de cette thèse est de préciser le rôle de l'OP3 au sein d'un réseau cérébral des acouphènes liés au bruit, d'abord par des moyens non-invasifs en IRM, puis en exploration invasive par stéréo-encéphalographie. Afin d'examiner le réseau cérébral fonctionnel lié aux acouphènes et le rôle d'OP3 dans ce réseau, nous avons réalisé en IRMf de repos une analyse par région d'intérêts, en nous focalisant sur des acouphènes non-invalidants et de même étiologie, afin de limiter les biais liés à l'hétérogénéité des participants. Dans cette étude publiée dans Brain Connectivity, nous démontrons une connectivité spécifique des acouphènes entre OP3 et une région dorso-préfrontale, qui souligne une implication des régions de la voie auditive dorsale d'intégration multisensorielle et motrice. Dans un second temps, nous avons cherché à évaluer l'impact des acouphènes sur la connectivité structurelle du cerveau grâce à l'analyse d'images d'IRM de diffusion. Dans cette approche, nous avons comparé les faisceaux de fibres entre les acouphènes et contrôles. Nos résultats, publiés dans NeuroImage: Clinical, mettent en évidence une différence de densité dans le faisceau unciné, qui sous-tend la voie auditive ventrale, ainsi que dans le faisceau inferieur fronto-occipital, qui suggère, comme en IRMf, une implication de la voie dorsale. Afin de vérifier ces résultats tout en bénéficiant d'informations temporelles et spectrales, nous nous sommes intéressés à la connectivité intracorticale de l'OP3 issue des données de l'atlas F-TRACT obtenu par stimulation cérébrale à 1Hz chez des patients implantés pour le traitement de l'épilepsie. Cette analyse a été intégrée dans une revue de la littérature sur la caractérisation d'OP3 dans le cadre des acouphènes pour Brain Sciences. Par ailleurs, nous avons analysé chez 50 patients stimulés à 50Hz et présentant des symptômes auditifs induits, les réseaux cérébraux impliqués dans les hallucinations, ou des perceptions sans source extérieure, et les illusions, ou des perceptions déformées d'une source sonore existante. Cette

analyse, proposée comme publication dans Neurology, démontre l'implication d'OP3 dans ces deux perceptions auditives erronées, et met en évidence un rôle spécifique du système limbique dans les hallucinations. Enfin, dans une étude en cours ayant reçu le soutien de la Fondation pour l'Audition pour continuer encore une année, nous avons cherché à valider l'implication d'OP3 dans une perception de pseudoacouphène générée par des impulsions sonores répétées. Ce protocole nous permettra de préciser la signature neuronale liée aux acouphènes dans OP3. Les résultats préliminaires nous permettent déjà de constater une activation significative de OP3 durant l'écoute des stimuli, ce qui suggère une implication somatosensorielle dans l'écoute d'un signal rythmé, par la voie proprioceptive de l'oreille moyenne. Cette thèse nous a permis d'explorer OP3 sous des angles complémentaires, et d'atteindre la conclusion que cette région pourtant non-auditive, constitue une cible pertinente dans les approches de traitement par stimulation cérébrale.

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List of Abbreviations

| THI | Tinnitus Handicap Inventory |
|--|--|
| OP | Parietal Operculum (OP3 - third OP division) |
| A1 | Primary Auditory Cortex |
| MGB | Medial Geniculate Body |
| ROI | Region of Interest |
| fMRI | functional Magnetic Resonance Imaging |
| 2D, 3D | Two- or three-dimensional, referring in this thesis to spatial dimensions in an image. |
| DWI | Diffusion Weighted Imaging |
| EEG | Electroencephalography |
| SEEG | Stereo-Electroencephalography |
| MEG | Magnetoencephalography |
| BOLD | Blood Oxygen Level Dependant |
| HRF | Hemodynamic Response Function |
| $\mathbf{WM} \ \ldots \ \ldots \ \ldots$ | White Matter |
| $\mathbf{GM} \ldots \ldots .$ | Grey Matter |
| \mathbf{CSF} | Cerebrospinal Fluid |
| \mathbf{DMN} | Default Mode Network |
| CEN | Central Executive Network |
| MNI | Montreal Neurological Institute |
| $\mathbf{SPM}\ \ldots\ \ldots\ \ldots$ | Statistical Parametric Mapping |
| DARTEL | Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra |
| \mathbf{FSL} | FMRIB Software Library |
| $\mathbf{TR} \ldots \ldots \ldots$ | Repetition Time |
| ICA | Independant Component Analysis |
| GLM | General Linear Model |

FOD Fibre Orientation Distribution **DES** Direct Electrical Stimulation

Introduction

Contents

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1.1 Motivations for this thesis

Hearing related disorders are currently the fourth cause of disability among older adults, with long term implications extending beyond discomfort in everyday life: even mild hearing impairment has been shown to increase the risk of cognitive decline and dementia by up to over 40% [1, 2], and in the case of tinnitus, by up to over 60% [3]. The World Health organisation has estimated that 1 billion of young adults are currently at risk of developing permanent, avoidable hearing disorders due to unsafe listening practices [4]. Occupational noise exposure, found in domains such as the building industry, the military, or the music industry, as well as a wide range of leisure related noise exposure constitute a known risk of developing tinnitus. Certain medications, some of which have a highly democratised usage like aspirin, have documented ototoxic effects with tinnitus as a known consequence. Tinnitus of clinical significance has thus seen its incidence rate increase by close to 50% in England in the 2000-2010 decade [5]. In the past two years, the pandemic has been suggested to have further contributed to this increase, both due to the disease itself and to the stress and anxiety worsened by the exceptional societal circumstances [6]. With long term repercussions of tinnitus including social withdrawal and isolation, difficulties in everyday life with impacts on professional performance, and no adequate treatments, tinnitus constitutes a major burden on society and on the healthcare system [5]. There is thus a need to raise awareness on tinnitus and to educate people on safe listening practices, especially in higher risk populations chronically exposed to noise, as well as to support ongoing research on understanding its mechanisms, and providing therapeutic solutions.

Subjective tinnitus is defined as the conscious perception of sound despite no corresponding source [7]. It comes in different flavours of ringing, buzzing, whistling, rumbling, or sizzling in the ears or in the head, with intensities ranging from a gentle whisper in the ear, to the loud hissing a tea kettle or the full blast roaring of aeroplane engines at take-off. In the latter cases, tinnitus can hinder hearing performances by masking the acoustic sound environment, and this effect is further amplified when tinnitus co-exists alongside other auditory pathology such as sensorineural hearing loss or hyperacusis. Tinnitus may develop over time and become intermittently present in the conscious scene of an individual, or it may reveal itself suddenly, after a well identified event. Tinnitus can be or become bothersome and compromise a person's overall well being and performances, at which point it becomes a motive for medical consultation. While hearing loss can be mitigated using amplification devices to restore perception, there exists no 'Off' switch for tinnitus: current guidelines for treatment strategies mainly aim to manage the level of intrusiveness [8].

With all the weight of its 15% - and growing - prevalence in the adult population [7], tinnitus exposes a knowledge gap at the interface between clinical pathophysiology (driven by the urge to ease the suffering of patients worldwide), cognitive and philosophical considerations - what is a conscious perception, what is its likely neural substrate, and can perception, and consciousness of this perception occur sine materia? - as well as methodological challenges - how does one best make available for assessment something that remains inherently subjective? The current literature on the auditory system and on tinnitus does not provide a clear answer to these questions, but converges on one point: tinnitus is a highly heterogeneous condition, as acknowledged by a number of multidisciplinary consortia since 2006 [9]. Mirroring this heterogeneity, there is an agreement that tinnitus involves a wide diversity of anatomical structures in the auditory system from the sensory periphery to the cortex, as well as outside the auditory system, as will be addressed in chapter 2. Tinnitus seems to manifest differently depending on the etiology, underlying hearing loss or hyperacusis, age, but also on mood state, preexisting stress and anxiety levels [7]. These elements are not always taken into account in tinnitus exploration protocols, however there is a growing tendency for authors to advocate for bias mitigation through tinnitus subtyping, appropriate matching of control participants, and sample size increase in multi-site collaborations [10, 11. Furthermore, exploration methods are highly diverse, with their own specific methodological challenges. A high rate of non-reproduced results and the difficulty to compare findings even within one exploration approach - due to rapid evolution of aquisition, processing, and analysis techniques, and to sample size and statistical power issues - has motivated authors to acknowledge the need for standardisation and for sharing of datasets and processing pipelines [9].

By focusing on noise induced tinnitus, Job and colleagues have proposed an angle of approach to tinnitus which limits the heterogeneity related to the origin of tinnitus. In particular, the target population consisted of military participants, with higher prevalence of tinnitus but proportionally lower levels of related distress compared to the general population [12], thus enabling a control of tinnitus etiology, and at the same time providing, among the military who did not develop tinnitus, a control group with equal risk exposure. Repeated shooting during training sessions, even with standard ear protections, exposes the ear to intensities of over 120 dB that induce inner ear damage by metabolic hyperactivity at the cellular level [hearing]. However, what is less documented is that the mechanical pressure variations also cause damage to the middle ear structures, which include tendons and muscles which can be prone to stretching and injury. Evidence from middle-ear related tinnitus in cases of otosclerosis affecting the small bony structures of the middle ear, and following the surgical procedure to manage this condition [13], provides strong grounds for further investigation of the precise role of the middle ear in tinnitus.

1.2 Involvement of the middle ear in tinnitus

1.2.1 Where are middle ear movements represented in the brain ?



Figure 1.1: Top: topographic organisation in the motor (red overlay) and somatosensory (yellow overlay) cortices, obtained by Wilder Penfield [14] during the course of his work using direct electrical stimulation to the brain. In darker red, the region found as a likely correlate for the middle ear. Bottom: Brain mapping derived from post-mortem studies of cytoarchitecture by Korbinian Brodmann [15]. In addition to the motor and somatosensory areas, the primary and secondary auditory cortices are highlighted in blue, and in green the area number 43, found in Job and colleague's work on middle ear proprioception.

Tinnitus is an auditory perception, however its mechanisms are not fully supported by the structures of the auditory pathway, which poses a paradox. The lack of breakthrough in tinnitus research can thus be linked to an incomplete understanding of the auditory processes that are not strictly related to sound processing. One example of a missing connection relates to the information conveyed from the middle ear. While most of the body is, on the whole, well mapped on the somatosensory cortex, a representation known as the Penfield Homunculus (figure 1.1), the middle ear is mainly studied for its role in sound perception: the location of its somatosensory projections in the brain was thus missing, prior to Job and colleagues proposing an experiment to highlight it. By imposing movements on the middle ear structures, using slow patterns of pressure variation [16] that did not generate any sound, they specifically focused on the somatosensory and motor information originating from the middle ear.

The 1Hz pressure variations inside the ear canal triggered gentle deformations of the tympanic membrane, and via the direct connection of the latter to the middle ear ossicles, slow movements were applied to the middle ear. Simultaneously, functional MRI timecourses were recorded, allowing the visualisation of the neural correlates of these movements, which were found in a small area straddling the temporal and parietal lobes (figure 1.2). The parietal activation located in the operculum, in particular, was proposed as relating to oropharyngeal sensorimotor control in movements involved in swallowing, or gustation [17]. The temporal activation, on the other hand, in the auditory association cortex was interpreted as the correlate of a middle ear reflex that happens prior to self generated sounds such as vocalisations.



Figure 1.2: Functional MRI activations found by [16], bilaterally in BA43, on the group averaged anatomical image. In the right hemisphere, this activation was later identified as located in the parietal operculum 3.

1.2.2 Linking middle ear proprioception and tinnitus

Tinnitus heterogeneity has been identified as a major source of inconsistencies in the literature [9]. Focusing on specific characteristics of tinnitus thus constitutes the first step towards improving tinnitus research reproducibility and comparability, and subsequent design and patient-specific adaptation of treatment strategies [18].

The military provide an interesting study population subtype, since they constitute an exposed population, especially due to shooting training and artillery blasts, with a higher prevalence of tinnitus compared to the general population. And yet, among the higher risk population, the military have been shown to be less prone to tinnitus related comorbidities [12]. Intuitively, there thus seems to be an influence of psychological states, focus, and attention processes on the way tinnitus is perceived, and this is a source of bias if the aim of the study is to identify the correlates of tinnitus per se. Because the military rely heavily on sensory performances, crucial for understanding, anticipating, and reacting in potentially life threatening situations, their ability to shift their focus away from the phantom percept and on to relevant sensory cues may be enhanced compared to the general population.

In order to assess the impact of tinnitus on auditory discrimination performances, therefore on the capacity to extract and make sense of acoustic stimuli, Job and colleagues subjected a group of military participants with varying degrees of noiseinduced tinnitus, and healthy volunteers with no history of acoustic trauma, to an auditory oddball task monitored by functional MRI [19]. High frequency hearing loss was observed in the participants with acoustic trauma background, as well as different levels of tinnitus handicap and chronicity - ie whether the perception was recurrent, or occasional. The oddball task consisted in the detection of a target sound, presented infrequently and randomly, amidst a series of regular, non target.

An activation pattern was highlighted, in the target versus baseline condition and in the acoustic trauma participants > controls contrast, in the vicinity of the region previously found to be related to middle ear muscle movements. The intensity of the

1. Introduction



Figure 1.3: Reaction time, variability and rate of missed target detection between subjects with tinnitus following acoustic trauma (AAT) and control participants [19], assessed in the lab and in the MRI. Tinnitus subjects performed significantly worse than controls in the MRI.

fMRI signal in this region correlated significantly with tinnitus features of recurrence or chronicity, and handicap level. This result, in the light of new knowledge of the cortical representation of middle ear muscle movement, suggested that acoustic trauma was likely to have induced an altered sensitivity of the middle ear, and caused erroneous somatosensory information to be conveyed from the middle ear to the brain. This result, rather unexpected considering the initial aim of the study, prompted the authors to further discuss the role of both the middle ear and this cortical region in the mechanisms of tinnitus.



Figure 1.4: Functional MRI significant activation difference between participants with tinnitus and controls, comparing target versus baseline conditions, with effect sizes for controls, and for subtypes of tinnitus participants. There was a significant correlation between chronicity and handicap score values and the intensity of the fMRI activation. T+: occasional tinnitus; T++: frequent/permanent tinnitus; H-: low handicap scores; H+: high handicap scores.

An analogy was proposed with movement illusions issuing from skeletal muscles. Proprioception, or the awareness of the respective positions of our body parts, can be tricked into perceiving movement when none occurs, using muscle stimulation by vibration at specific rates in the 1-100Hz range [20], with the velocity of the perceived movement illusion depending on the frequency. A known example is the Pinocchio illusion: if a movement illusion is generated in the arm, while the hand is in contact with the nose, the subsequent interpretation is that the nose is getting longer, rather than acknowledging the false perception occurring in the muscles of the arm 1.5. Highly precise movement illusions have been documented, with more complex shapes than just the stretching of the arm [20], suggesting common mechanisms between kinesthetic illusions and motor imagery. Similarly to the response of skeletal muscles, the spindles of the muscles in the middle ear, too, can convey erroneous proprioceptive information, receiving strong validation from the brain where this information would signify the presence of sound travelling in the auditory system, when it is not the case. A model of tinnitus resulting from a proprioceptive illusion initiated in the middle ear was thus proposed.



Figure 1.5: Illustration taken from the thesis of Morgane Metral. Stimulation to the muscle of the arm generates the illusion of the nose getting longer due to the somatosensory perception issuing from the connection between the finger and the nose.

1.2.3 Proof of concept

This hypothesis was tested in a third study [21]. Following up on the analogy with kinesthetic illusion resulting from specific vibration rates, the auditory tinnitus illusion was hypothesised to emerge from mechanical stimulation, rather than sound. However, the middle ear is arguably less accessible to vibrating devices than the arm. Therefore, repetitive bursts at comfortable volume intensity, or click-train sounds were used, with the assumption that the auditory and proprioceptive mechanisms may be equally involved. Sure enough, although this had not been typically explored

in the literature, except for one other study [22], certain rates of click repetition were able to generate a transient perception of sound similar to tinnitus, which persisted for a short moment after listening to the stimulus. Different frequencies were tested and not all resulted in the described after-effect. Robustly, a 30 Hz repetition rate elicited a tinnitus-like after-effect in all participants, while the 8Hz repetition rate generated no such effect and was therefore used as a control condition. The experiment was repeated and fMRI timeseries were compared between conditions. An activation pattern was found, again, in the parietal operculum, and in particular in its third division (OP3), as the neural correlate of this tinnitus-like after-effect. Importantly, this demonstration was conducted in healthy participants, and was thus free of any tinnitus comorbidities.



Figure 1.6: A. Cortical representation of middle ear muscle movements highlighted in green [16] and results from the oddball paradigm, in red [19]. B-C. Activation patterns found during the tinnitus-like after effect generated in healthy volunteers [21].

1.3 Principal questions and thesis outline

These studies on the role of the middle ear in tinnitus have placed a new cortical region, OP3, in the focus of tinnitus research, particularly in the case of acoustic trauma tinnitus, and have contributed to shifting the attention away from the primary auditory cortex. As we will address in the following chapters, the auditory pathway contributions to tinnitus, although well documented in the literature, face some limitations in fully explaining the range of manifestations in tinnitus. Tinnitus perception requires input from brain regions outside the auditory system, mediating attention, emotions, and other sensory modalities such as somatosensation. Tinnitus is thus increasingly viewed as a brain network dysfunction, however, the precise role and organisation of the brain network of tinnitus beyond the auditory cortex remains an open question.

In this thesis, we question the role of OP3 as a potential key element in a cortical network underlying noise-induced tinnitus.

We addressed this question from different perspectives, drawing from complementary neuroexploration modalities.

In the second chapter of this thesis, we outline the broader scheme in which tinnitus research takes place, reviewing the state of the art on the human auditory perception system, on tinnitus as a disorder ranging beyond the auditory system, and on the methods of exploration relevant to tinnitus.

In the third chapter, we describe the methods used in this thesis to answer the specific question posed in each study, with an emphasis on how certain issues arose and were managed, at the level of participant recruitment, acquisitions, and processing.

In the fourth chapter, we adopt a non-invasive standpoint to investigate the functional and structural connections of OP3 using MRI-derived measures of connectivity targeting non-bothersome, acoustic trauma tinnitus participants and matched controls. In particular, we derived seed-based resting-state functional connectivity maps from BOLD fMRI to investigate the regions whose signals presented the strongest correlations with OP3 and with seed locations defined with respect to previous literature findings. Importantly, we used as little as possible spatial smoothing in the processing of fMRI images, and performed state of the art, diffeomorphic registration of subject data to standard space. As we will explain more in depth in chapter 3, this aspect of methodology is crucial for detecting anatomically localised effects. This study led to a publication in Brain Connectivity (10.1089/brain.2019.0712).

In addition, evidence of white matter connections being altered under the influence of stimulation or lack thereof [23, 24] justified the hypothesis that tinnitus, as an ongoing perception phenomenon, may induce a local increase in white matter density. From the perspective of tinnitus as an undue perception due to lack of inhibition, a decreased white matter density has also been proposed in the regions involved in gating mechanisms. However, the evidence to support the validation of these hypotheses is scarce: findings from structural imaging pertaining to tinnitus are, as we will review in the following chapter, highly diverse. Using constrained spherical deconvolution, we modelled the diffusion signal within tissuespecific compartments and worked in a bundle-specific framework using deep learning methods for segmentation and tractography. The results were subsequently published in NeuroImage: Clinical (10.1016/j.nicl.2021.102696). We further investigated white matter alterations using a Riemanian framework for anomaly detection by approximating the data in high dimension using graphs and projecting into a low dimensional space, preserving subject specific physiological variability and thus a potential to detect finer alterations with clinical relevance.

Both fMRI and diffusion-weighted MRI have high spatial resolutions, which prove useful in determining precise anatomical landmarks with clinical relevance. However, fMRI has a low temporal resolution and DWI has no temporal information at all.

In the fifth chapter of this thesis, we therefore adopt another standpoint to further investigate the neural correlates of tinnitus and to validate the role of OP3, we used intracortical electrophysiological recordings, as performed in the Epilepsy laboratory in patients with intractable epilepsy undergoing invasive exploration, providing high temporal resolution. The discrete spatial sampling trade-off due to the finite number of electrodes was not an issue in the present case, because we had formulated a local hypothesis about OP3. First, from an auditory sensation point of view, we performed a retrospective analysis of 50 drug-resistant epileptic patients undergoing pre-surgical intracranial exploration at the Epilepsy Exploration Laboratory in Grenoble, and having had 50Hz Direct Electrical Stimulation which elicited auditory symptoms. Distinguishing between hallucinations (no input to the auditory system) and illusions (modulation of an existing incoming sound stimulus), we analysed the distribution of the cortical regions having elicited each symptom, as well as the extent of the network of regions whose SEEG activity was found modulated by these induced perceptions. An article was submitted, describing this approach. Then, from a functional mapping perspective, we used the dataset from the FTRACT project directed by Olivier David (f-tract.eu), and based on the cortico-cortico evoked potentials from over 900 participants, to examine the connections of the parietal operculum and the periauditory regions with the rest of the brain. Finally, we conducted a pseudo-tinnitus induction protocol, adapted from the fMRI experiment by Job and colleagues [21], whereby a transitory phantom sound was robustly perceived by the patients after listening to recordings of clicks sounds at a rate of 30 clicks per second. A control condition was found for a rate of 8 clicks per second, with no after-effect perception. This allowed us to obtain a form of verifiable neural evidence of tinnitus perception, and provided the grounds for comparison with our work in the non invasive modalities.

Finally, in chapter 6 we discuss the results yielded by this research work, with respect to findings in the literature. We reflect on the perspectives that these results offer in terms of understanding tinnitus perception, and in terms of treatment opportunities.

2 State of the art

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In order to understand tinnitus perception as a disorder involving a complex network of auditory and non-auditory anatomical structures, we examine in this chapter the current state of the art on our knowledge of auditory structures and processes. After an anatomo-functional journey from periphery to cortex, we mention how the combined efforts of the elements encountered on the way may contribute to different models of auditory consciousness. Tinnitus, as a conscious auditory perception without sensation, or without a typical sensory input, illustrates the lack of a complete understanding of auditory perception processes. Research in neuroimaging and electrophysiology attempts to expose a consistent pattern of evidence to explain the mechanisms of tinnitus, with mixed results. A therapeutic breakthrough is hindered by the lack of agreement on a target region or a target network of regions, however, some options have provided encouraging results, which also informs on the mechanisms of tinnitus perception.

2.1 Auditory perception: anatomical and functional outlook

Prior to any considerations on tinnitus, all living organisms acquire information about their environment as they interact with it, through their sensory and perceptive systems. This process is key to their ability to react to the environmental cues, in other words to survive and thrive in this environment, and therefore its mechanisms are shaped by evolution. The nature and organisation of a given organism's sensory and perceptive systems is already the reflection both of the environment it is confronted to, and of the phylogenic history of its kind, or the series of adaptations to the external conditions imposed on it [25]. In humans, this acquisition of information contributes to the constitution of inner representations of the outside world, which in turn guide behavioural responses or psychological processes [26]. These representations have also been described in the Bayesian perception framework as inferences on the present state of the environment, based on prior knowledge of the environment, updated when compared with the input picked up by the senses [27]. The level of accuracy and detail of this representation is relative to the performances in terms of dynamic range and sensitivity of our sensory organs at the periphery, as well as that of the peripheral and central nervous systems. Each sensory modality developed in humans is sensitive to a specific range of physical properties, which may be both redundant in some aspects and incomplete in others. Incoming stimuli detected by the sensory organs are transformed into electrical messages conveyed up to the brain, following hierarchical and topological organisations with similarities and interactions existing across senses [28]. At the central level, the messages from the periphery are weighted by reliability rating mechanisms, or, in the Bayesian framework, weighted by precision [29]. In a context where one modality is hindered, due to disease, damage, or simply because of environmental noise, this rating allows the brain to set up a hierarchy between incoming inputs, that the inner representation will then be built upon. The trust that the perceptual system places onto the resulting filtered and weighted inputs is likely high, explaining how the brain can be tricked, why sensory illusions happen, and why they may persist despite the rational mind noticing the inconsistency.

The mechanisms of sensory information processing and subsequent inner representation have been examined in the field of cognitive psychology. Certain theories distinguish between sensation, relating to the physical process of stimulus detection and communication, and perception, referring to the way this information is organised, selected, and interpreted. Subsequent distinctions have been made between perception and conscious awareness of that perception, based on the evidence that one may respond to a stimulus without being aware of the stimulus [30] (figure 2.1). In this thesis, we adopt the view that the brain is actively making constant inferences about the environment, comparing these estimations through top-down pathways to the incoming bottom-up messages from the periphery, and aiming to minimise the error between the estimations - or predictions - and the sensory input. The probabilistic inference framework accommodates sensation, perception, consciousness, awareness, and subjectivity as processes that seek to minimise a prediction error at different scales and along different pathways [31–33]. This chapter will take us along a few of these pathways.



Figure 2.1: Illustration taken from [30], evidencing auditory cortex activity despite no behavioural evidence of perception, compared to perception with conscious awareness of that perception in which amplitude as well as spatial range are increased.

Auditory perception begins with the conversion of a mechanical sound wave into an electric signal occurring at the interface between the organ of hearing and the acoustic nerve. For this transduction process to take place, appropriate adjustment of the mechanical properties of the sound wave is performed in the outer and middle ear. The impedance difference at the interface between the air in the middle ear and the fluid filled inner ear is such that a total reflection of the incoming sound wave would occur, were it not for the actions of amplification and impedance adaptation performed by the outer and middle ear [34]. Together, the outer and middle ear contribute to increasing the transmission rate of the incoming sound wave from 2% to 35%.

2.1.1 Outer ear structures

The auricle, or pinna, constitutes the visible part of the outer ear, which also comprises the external ear canal, or acoustic meatus (figure 2.3), and the external surface of the eardrum. The cartilaginous structure of the pinna defines the unique shape of each individual's auricle, secured in place by tendons, muscles and fibrous tissue, and mainly innervated by the greater auricular nerve and the auriculotemporal nerve. Autonomous innervation from the vagus nerve is also found in the auricle, in the cartilageneous projection opposite the auricle above the ear canal opening known as the tragus, and in the ear canal itself, making the outer ear a window into vagus nerve stimulation for pathologies with autonomic dysregulation. While most mammals are able to orient their auricle in the direction of the incoming sound, this ability is vestigial in humans for whom the movement of the auricle is limited to slight vertical and lateral translations, [35]. Functionally, the auricle captures a multidimensional sound wave which it funnels into the auditory canal and to the

2.1.2 The eardrum

eardrum, turning it into a mostly one-dimensional wave.

Acting as the physical boundary between the outer ear and the tympanic cavity or middle ear, the eardrum converts the pressure variations of air molecules into vibrations. It is innervated on its external surface by the mandibular branch of the trigeminal nerve projecting to the trigeminal nuclei, and on its inner surface by the glossopharyngeal nerve, projecting general somatosensory information. The eardrum is a translucent cone-shaped membrane of 9 to 10 mm diameter and 0.1mm thickness, with two main distinct structures called the pars tensa, a more rigid structure which occupies most of the surface, and pars flaccida for the remaining area, with higher flexibility [36]. The specific functional contributions of pars tensa and pars flaccida are not altogether clear. The pars flaccida has been proposed to play a role in balancing out pressure variations in the middle ear [37] while it is suggested that the pars tensa be more involved in sound conduction, owing to its higher rigidity and the position of the components of the middle ear against it. Indeed, the handle of the malleus or hammer, the first ossicle of the middle ear, is inserted in the middle of the fibrous layer of the pars tensa. The vibrations of the tympanic membrane provoked by the incoming sound wave are thus efficiently transferred to the middle ear through movement of the malleus.

2.1.3 Middle ear structures and functions

The middle ear is in charge of efficient adaptation of the acoustic energy from upstream compression waves in air, into downstream fluid-membrane waves in the


Figure 2.2: Schematic view of the main structures of the outer ear (green dots), the middle ear (red dots), and inner ear (blue dot). The Eustachian tube, which is not further described in this thesis, connects to the nasal cavity and ensures pressure adaptation of the middle ear. Illustration based on Servier Medical Art (https://smart.servier.com/).

cochlea, by correcting the impedance mismatch at an air-fluid interface. This is for the most part the result of the size ratio between the area of the tympanic membrane at the outward interface, and the area of oval window at the entry to the inner ear. The connection, and thus the effective energy adaptation between these two surfaces is managed by three of the smallest bones of the body, the ossicles, located inside the tympanic cavity, and measuring between 1.5 and 9 mm (figure 5.1). In addition to the size ratio factor between eardrum and oval window, the pressure applied at the inner ear interface is again doubled due to the particular configuration of the ossicles. Furthermore, the proper functioning of the middle ear is ensured by the tendons and muscles present, by a pressure adaptation system, and by afferent as well as efferent messages conveyed through the different innervations.

2.1.3.1 The ossicles

Secured inside the tympanic cavity by three ligaments, the ossicular chain formed by the three ossicles (figure 5.1) displays a piston-like movement as the tympanic membrane vibrates [39]. The malleus or hammer mentionned previously is bound to the tympanic membrane. It forms a lever-like hinge with the incus, or anvil, in a joint with low mobility on the whole except at frequencies above 2kHz [40]. When the

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Figure 2.3: Schematic view of the main structures of the middle ear, modified from [38]. The 20mm long tensor tympani originates at the superior surface of the cartilage of the Eustachian tube, forms a right angle as it turns into tendon and attaches to the malleus, and is innervated by the tensor tympani nerve - a branch of the trigeminal nerve. The stapedian muscle emerges from the posterior surface of the tympanic cavity through a canal, together with the third branch of the facial nerve which innervates the stapedian, towards the posterior surface of the head of the stapes, where its tendon attaches. Its 6mm length makes it the smallest muscle in the human body.

tympanic membrane moves, malleus and incus rotate together. The incus is connected through a small knob at the end of its descending vertical branch to the head of stapes. This incudostapedial joint is a ball and socket type joint with high mobility, allowing the incus to rotate while pushing on the head of the stapes. In turn, the stapes or stirrup is secured to the entry of the inner ear by a ligament called the annular ligament ensures further transmission of its vibrations to the fluids of the inner ear.

2.1.3.2 The muscles of the middle ear

There is evidence for mainly three muscles acting on the middle ear. Two antagonist muscles work synergistically to adjust the sensitivity of the middle ear by actively regulating the rigidity of the ossicular chain and of the tympanic membrane: the stapedius and the tensor tympani. These muscles have been shown to contract involuntarily upon self generated sounds such as vocalisation or chewing , or during exposure to loud noises [41]. The main result is a protective mechanism of the inner ear, to prevent fatigue, interference or injury [38]. More specifically, when an incoming sound passes a certain threshold, the brainstem signals to the middle ear to trigger the acoustic reflex [42]. The tensor tympani then pulls the malleus inward, stretching the tympanic membrane and pushing the stapes into the oval window, while the stapedius pulls the stapes out and away from the oval window [43]. These two forces act in opposition, stiffening the ossicular chain, and thus hindering sound conduction. It is noteworthy that the middle ear muscles do not require sound to contract. Swallowing is one example where tensor tympani and a third muscle involved in middle ear function, the tensor veli palatini, contract and allow the eustachian tube to open. A dampening of self-generated sounds is thus achieved alongside pressure equilibrium. Furthermore, certain individuals are able to provoke and control middle ear muscle movements, suggesting a communication channel from cortical, as well as subcortical, motor structures. While voluntary and reflex contraction of the middle ear are triggered by descending signals to the middle ear, afferent sensorimotor messages from the middle ear are also conveyed.

2.1.3.3 Middle ear proprioceptive receptors



Figure 2.4: The mechanically sensitive spindle includes three types of intrafusal fibres, long bag1 and bag2 fibres as well as short chain fibres. Primary Ia afferent fibres make spiral terminations around all types of intrafusal fibres. Afferent secondary (group II) fibres supply bag 2 and chain fibres. Dynamic and static fusimotor fibres innervate different types of intrafusal fibres. Taken from [44].

The fact that proprioceptive receptors exist in the muscles of the middle ear is not a straightforward finding, because the size and location of the middle ear muscles make them difficult to examine in vivo. Little is known about their microscopic structures and mechanisms of action: they have mainly been investigated for their role in acoustic transmission, using impedance based methods. However, in a postmortem study, Kierner and colleagues demonstrated that the tensor tympani and stapedius contain several muscle spindles, although structurally different from skeletal muscle spindles, and one intrafusal muscle fibre. These muscles therefore possess the ability to communicate proprioceptive messages to the brain via the trigeminal and facial afferent nerve connections of the middle ear [45]. At the central level, the neural correlate of the proprioceptive information encoded by middle ear muscles has been evidenced in the parietal operculum, mainly the third division [16].

2.1.3.4 Innervation

The middle ear is connected to sensorimotor nerves and to the vagus nerve. The tympanic cavity is supplied by the 9thcranial nerve for general sensory information such as heat or pain, while autonomic innervation is provided by the caroticotympanic nerve. The stapedius receives sensorimotor innervation from the stapedial branch of the facial nerve, while tensor tympani and tensor veli palatini are supplied by the mandibular branch of the trigeminal nerve. The trigeminal nerve synapses within the trigeminal nucleus and from there, some projections arrive at the cochlear nuclei [46]. This fact supports a potential modulator role of the middle ear's sensorimotor activity on the acoustic processing happening in the non-primary cochlear nuclei.

2.1.3.5 Middle ear dysfunction

Middle ear structures, when exposed to high or sudden pressure variations, are prone to injury which may prevent the middle ear from functioning correctly. If the middle ear fails to adapt the impedance at the interface with the inner ear, sound waves are essentially reflected instead of transmitted, resulting in impaired hearing, even if the inner ear remains unharmed. In addition, the dampening mechanisms are hindered, resulting in an increased sensitivity to the sound that is transmitted, which can lead to discomfort or pain in normal acoustic environments known as hyperacusis. A dysfunctional middle ear may fail to protect the inner ear from damage: cochlear hair cell death and subsequent sensorineural hearing loss are likely to follow. This in turn has been correlated with increased risk of developing tinnitus: weak middle ear muscle reflex has been correlated to noise induced tinnitus, in participants with normal to near-normal hearing levels as assessed by current audiometric tests [47]. This result was interpreted as a possible marker for cochlear synaptopathy, or hidden hearing-loss. This finding also supports the hypothesis of somatosensory and proprioceptive tinnitus [21], deriving directly from middle ear muscle damage induced by disproportionate pressure variations. In addition to acoustic trauma, paralysis of the stapedius muscle has been documented in cases of injury to the facial nerve; middle ear muscle spasticity, as in the case of tonic tensor tympani syndrome, has been shown to result in both hyperacousis and in some cases, objective as well as subjective tinnitus [48]. Furthermore, a condition known as otosclerosis which causes abnormal bone growth on the footplate of the stapes, is a documented source of hearing-loss through reduced sound conduction, and of tinnitus [13]. The surgical treatment involves removal of the stapes and replacement by a metal or plastic prosthesis. Hearing has been found to be successfully restored in most cases, however tinnitus worsening has been highlighted as a possible side effect, likely caused by mechanical trauma during surgery, which further supports the importance of considering the middle ear when investigating tinnitus.

2.1.4 Inner ear structures relative to sound transduction

The inner ear is involved in both hearing and balance. The latter is the prerogative of the vestibular and semi circular canal system of the inner ear, which we will not develop here. The inner ear structure involved in the former is the cochlea, which hosts the Organ of Corti whose role it is to convert the mechanical energy it receives from the vibrating stapes into neuronal impulses (figure 2.5).

2.1.4.1 The cochlea

Three compartments spiralling alongside each other, inside a structure called the bony labyrinth, are the main components of the cochlea. The vestibular and tympanic ducts contain perilymph, and surround the cochlear duct filled with endolymph. The ionic content of these two types of fluids differ, allowing for electric potentials to occur. As the incoming mechanical vibration reaches the oval window through the connection with the footplate of the stapes, it propagates a wave in the perilymph of



Figure 2.5: Main anatomical structures of the inner ear responsible for sound transmission, from the oval window, communicating with the middle ear, to the first neurons conveying auditory action potentials (3D rendering based on Mozaik3D).

the vestibular duct, with high frequency sounds dissipating earlier than low frequency sounds, owing to the viscosity properties of the medium. As the wave progresses, the cochlear duct is compressed, inducing a displacement of the cells that line its inner surface and make up the organ of Corti.

2.1.4.2 The organ of Corti

Located inside the cochlear duct of the cochlea, the organ of Corti contains an average of 15000 mechanosensory cells known as hair cells, divided into outer and inner hair cells depending on their location on the membrane surface. The outer hair cells produce minute sounds in response to incoming stimulation, directed towards the outer ear, known as otoacoustic emissions, measurable using a device placed in the auditory canal. On top of the hair cells are tiny projections named stereocillia, organised by increasing size which allows a broadening of the tuning range of the auditory system. The outer hair cells possess the ability to stretch these sterocillia, known as motility, upon efferent input from the brainstem. As the perylymphatic wave compresses the cochlear duct, the endolymphatic fluid inside the cochlear duct is displaced and the stereocillia move with it, triggering depolarization of the inner hair cell, the release of neurotransmitters and in turn, the production of an action potential at the synapse of the cochlear nerve. The action potentials carry spectral information depending on where they are emitted from: there is a particular correlation pattern between the spatial organisation of the hair cells on the cochlea and their sensitivity to given frequencies, known as tonotopy. In addition to all frequencies not propagating evenly in the medium of the inner ear, each inner hair cell possesses a range of preferred frequencies, with in the order of a 0.2 percent difference between neighbouring cells, to which they react by firing an action potential.

2.1.5 Subcortical auditory pathways

Auditory information is conveyed through a pattern of fibres joining and diverging along the way (figure 2.6). This has been suggested as resulting from the constraints imposed on the auditory system by high temporal resolution picking up fluctuations on the scale of microseconds, happening alongside processes of filtering, inhibition or feature extraction belonging to the milliseconds scale. The apparent incompatibility between these types of analysis is mitigated by the complex configuration of parallel systems branching off to preserve the qualities required by each, and merging together again to integrate the result of the processing operations performed on either side [34]. Essentially these routes comprise the primary auditory or lemniscal pathway connecting to the primary auditory cortex, and the non-lemniscal pathway mediating unconscious components of attention, emotional response, and reflexes. Also described as driver and modulation pathways, the distinction stems from the macroscopic differences in fibre bundle trajectories, as well as in the microstructural morphological properties of the axons in each system [49].

2.1.5.1 The primary subcortical pathway

Connection to the cochlea

First order neurons are clustered together in the spiral ganglion, and receive their messages from the hair cells they connect to. They join with the neurons issuing from the vestibular component to form the vestibulocochlear nerve, preserving the

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Figure 2.6: A/ Main ascending connections in the auditory brainstem structures. The rainbow coloring indicates tonotopic organisation in the structures of the lemniscal pathway, while the blue areas and lines indicate the non-lemniscal pathway. The green arrows indicate input from the contralateral ear not represented in the figure. B/ Anatomical representation of the subcortical auditory structures, adapted from [50]. AVCN: Anterior Ventral Cochlear Nucleus; PVCN: Posterior Ventral Cochlear Nucleus; DCN: Dorsal Cochlear Nucleus; LSO: Lateral Superior Olive; MSO: Medial Superior Olive; IC: Inferior Colliculus; MGB: Medial Geniculate Body.

tonotopic organisation inherited from the cochlea. The nerve enters the brainstem and splits into two parts that project onto three regions of the cochlear nuclei. The anterior branch projects to the anterior cochlear nucleus, initiating the ventral auditory brainstem stream where, in particular sound localisation, processing takes place. The posterior branch innervates both the dorsal cochlear nucleus as well as the posteroventral cochlear nucleus, leading to the dorsal auditory brainstem stream involved in complex stimulus analysis and integration.

The cochlear nuclei

From the anterior ventral cochlear nucleus (AVCN), fibres project bilaterally to the medial superior olivary nuclei, which compares the timing of the stimuli originating from each ear, in order to determine the localisation of the incoming sound source. Additionally, the AVCN projects to the lateral superior olive, on the same side, only this time for intensity comparison of the input stimuli. The output fibres from the medial superior olive join with the output fibres from the contralateral lateral superior olive and ascend toward the inferior colliculus in a bundle known as the lateral lemniscus. This results in a summation of the timing and intensity-based processing

performed by each structure within the inferior colliculus. The posteroventral cochlear nucleus processes both time and frequency analyses and mainly projects to the contralateral side to join into the lemniscus pathway and up to the inferior colliculus.

To sum up, from the cochlear nuclei, three fibre tracts project, mainly switching over to the contralateral side of the brain, and for the most part ascending in the lateral lemniscus to the inferior colliculus. A smaller number of fibres from both cochlear nuclei stay on the same side, meaning that auditory information from both ears is conveyed to both sides of the brain from the cochlear nuclei onward. A nucleus of the lateral lemniscus is in charge of additional contrast management, accuracy and adjustment of the dynamic range, sending inhibitory messages to the inferior colliculus.

The inferior colliculus: a hub of integration

At the inferior colliculus, dorsal and ventral streams converge, and integration of sound pattern recognition and localisation amongst others takes place [51]. The inferior colliculus receives input from multiple sources, including but not limited to the auditory nuclei. It divides into the central inferior colliculus, which is the main component essentially in charge of the ascending stream and sensitive to frequency modulation, and its peripheral nuclei mainly receiving descending and multimodal or indirect inputs [52]. The inferior colliculus is thus a hub structure for ascending as well as descending information streams.

The medial geniculate body

In the medial geniculate body (MGB) of the thalamus, afferences arrive from the inferior colliculus and efferent signals are projected to multiple locations in the cerebral cortex. The MGB continues to integrate the spatial, temporal, and spectral components, already partially brought together in the lower brainstem nuclei. The primary auditory component of the MGB is its ventral nucleus, interacting bidirectionnally with the primary auditory cortex. Despite the complexity of the splitting and uniting of the auditory nervous pathway, the tonotopic organisation is preserved throughout and into the primary cortical auditory fields.

2.1.5.2 The non-lemniscal subcortical pathway

The non-lemniscal pathway is less documented in the literature than the primary auditory pathway. However, it has been clearly stated that those regions of a different cellular nature [49], where no tonotopic organisation is found, and where input comes from multiple sources, constitute a parallel but different stream of auditory processing to the brain.

The dorsal cochlear nucleus

The DCN has provided evidence of receiving multimodal input from the trigeminal nuclei of the somatosensory system and from the vestibular system in addition to the auditory, and being related to certain cases of tinnitus generation and modulation [53].

The inferior colliculus

In the inferior colliculus, somatosensory-auditory integration takes place. In particular, the external nucleus has been described as a relay of spatial reflex response, while the dorsal nucleus receives descending input from the non primary regions of the auditory cortex.

The medial geniculate body

The MGB also receives mixed somatosensory-auditory input in its dorsal and medial parts. The thalamocortical projections that follow are directed mainly towards the non-primary areas of the auditory cortex, as well as the limbic system, in particular the amygdala, thus introducing emotional context into the sound analysis process.

2.1.6 The auditory cortex

2.1.6.1 Evidence from animal models and controversy

The auditory cortex is the target of the ascending nervous pathways originating from the periphery and pertaining to auditory processing. In animal studies, a clear delineation of core regions surrounded by belt and parabelt areas exists based on anatomical and physiological analysis [54]. In terms of connections, for a region to be considered core, it must receive independent parallel projections from the

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ventral MGB at the end of the lemniscal pathway. Core regions are additionally highly interconnected with each other, each of the core regions possessing a particular tonotopic map. Surrounding regions that do not qualify as core, due to different cytoarchitecture and an absence of input from the ventral MGB, but that receive major input from the core regions and from the dorsal MGB belong to the belt area. Finally, a parabelt region is defined as the cortical area neighbouring the belt area, receiving input from the belt and the dorsal MGB but not the core. Functionally, the core regions correspond to the first stage of cortical auditory processing after the already substantial stages performed in the subcortical structures. The belt and parabelt are the likely substrates for higher order processes and integration.



Figure 2.7: Representation of high frequency (red) and low frequency (blue) sound processing areas in human and monkey models of the auditory cortex, as well as the orientation of the tonotopic gradients indicated by the green arrows. The solid green line indicates the limit between core and non-core areas, and the dashed green line the separation between areas within the core. A. Auditory cortex in the macaque monkey organised as three core areas including the primary auditory cortex A1, rostral area R, and rostrotemporal area RT. B. Human model derived from post-mortem analyses with only hA1 as human homolog of the monkey area A1. C. Model based on fMRI tonotopic mapping studies, and two homolog areas hR and hA1. D. Oblique model, attempting to integrate models B and C. Taken from [55].

This model has served as a basis for understanding the organisation of the human auditory cortex. In humans, there is a general agreement that the primary auditory cortex belongs to Heschl's gyrus [56], and that a core-belt-parabelt type hierarchy also exists (figure 2.7). However, this gyrus is not present in the monkey cortex, which hinders direct comparison with animal models [54], and it is highly variable across individuals, with frequent complete or partial duplication of the lobe [56, 57] adding to the difficulty of the task. There appears to be a debate on the precise functional and anatomical subdivisions, in terms of localisation and organisation of the auditory areas: evidence from cytoarchitectonic and multimodal functional mapping procedures seems to conflict [58]. Furthermore, while most descriptions use the terms primary auditory and core auditory interchangeably, the primary auditory cortex area classically referred to as A1 is only one of the core subdivisions: the overlap isn't complete [54].

In agreement with animal models, the primary auditory cortex in humans refers to the region of the cortex presenting high cellular density and myelination receiving point to point input from the ventral MGB, in charge of early auditory processing. It can therefore be examined at the microscopic scale using cellular evidence, at a mesoscopic and macroscopic scale using structural imaging, and functionally to check for early processing evidence using stimulation protocols or functional imaging.

2.1.6.2 Cytoarchitecture and myelination of the primary auditory cortex



Figure 2.8: Surface projection of the regions (left panel) determined by post-mortem analysis of brain slices (right panel); adapted from [59], with subdivisions of the primary auditory cortex from [58, 60].

The cytoarchitectonic segmentation of the primary auditory cortex presented in [60] proposes a division of the core auditory region into three areas, TE 1.0, 1.1, 1.2, along Heschl's gyrus (figure (2.8, 2.10). In contrast, multimodal evidence from [61] presents a single core region and follows the A1 - medial and lateral belt - parabelt nomenclature (figure 2.9, 2.10). The delineation of A1 per Glasser's multimodal atlas is mostly based on a thresholded map of myelination, to a lesser extent on its connectivity and activation profile, and on its relatively lower cortical thickness compared to its neighbours.



Figure 2.9: Bilateral quantitative maps used by Glasser and colleagues to build the parcellation of the superior temporal lobe early auditory regions. A: greyscale image highlighting the macroscopic folds on the surface of the brain, with orientations given for the left surface (A: anterior, P: posterior, M: medial, L: lateral - M and L are inversed for the right surface). B - C: myelin maps with different scaling obtained by MRI T1 and T2 weighting [62]; D: cortical thickness map; E: functional connectivity gradient; F: seed-based connectivity from the MGB; G: gradient of panel F; H: anatomical location of the thalamic seeds (M-LGB) projecting to the auditory cortex; I - J - K - L: activation fMRI maps in four different tasks. Data for this study are found at http://balsa.wustl.edu/RV3p; this figure is taken from the supplementary materials of Glasser et al., 2016 Nature paper [61]. MBelt: Medial Belt area; LBelt: Lateral Belt area; PBelt: Para-Belt area.

It seems noteworthy that the connectivity profile to the MGB does not unarguably support this particular delineation, in fact it seems that the area with highest connectivity should descend into the medial belt area, as would the TE1.0 and 1.2 regions. Glasser's multimodal atlas does not commit itself to a possible subdivision of the core auditory cortex, equating it with the primary auditory cortex. Furthermore, the belt regions seem to have non negligible connectivity with the MGN, although whether ventral or dorsal isn't documented. This may indicate that part of the belt regions from this parcellation share some properties of the auditory core. This does not appear to be in contradiction with the cytoarchitectonic evidence from [60]. More ambiguously however, core area TE1.2 which seems to extend into and past the medial belt area in the most lateral region, and has been proposed as an analog region for either core area RT or lateral belt in the monkey anatomical scheme [63].



Figure 2.10: The background image is the cytoarchitectonic atlas [64] on an inflated brain surface template, with a spotlight on the cortical regions involved in auditory processing, labelled in black. Overlaid in red contours is the multimodal parcellation [61], with regions labelled in white. A1: Primary auditory cortex, encompassing the primary core area of the cytoarchitectonic atlas (not represented here), a portion of core area TE1.1, and an incursion into core area 1.2; MBelt: Medial Belt area, overlapping areas TE1.1, 1.2 and 2.1; LBelt: Lateral Belt area, crossing over areas TE2.1 as well as core area TE1.1; PBelt: Para-Belt area, overlapping mainly with area TE2.2; A4 and A5 are associative auditory areas, aligned with area TE3.

2.1.6.3 Tonotopic mapping of the early auditory cortex

The spatial sensitivity to given frequencies, inherited from the cochlear frequency organisation, is expected to be specific to core regions and less present in the belt and parabelt. Therefore, the investigation of the central representation of auditory-tasks involving specific frequencies have been used to delineate the core auditory regions. Such investigations involve phase encoded stimuli as proposed in the Brewer et al. study of cortical field maps [65], based on a two dimensional mapping of the auditory cortex, with frequency gradients on one hand and temporal or periodotopic gradients on the other. Using only one dimension, [56] already highlighted two mirror tonotopic maps in analogy to the macaque A1 and R regions, and suggest

that the refinement of the tonotopic mapping may have constrained Heschl's gyrus into its particular shape during the course of evolution. [66] suggest instead two axes of frequency preference, not necessarily of periodotopy, and propose a different orientation running orthogonally to Heschl's gyrus. Schönwiesner and colleagues advocate for caution in the interpretation of tonotopic mapping when using BOLD fMRI and auditory stimulation: the spatial resolution may not be sufficient to reliably highlight a tonotopic gradient [67]. Evidence from direct electrophysiological recordings using the latency of auditory evoked potentials additionally have identified primary auditory regions as those answering with the shortest latencies, and agree with one or possibly two core auditory regions in Heschl's gyrus, the primary core located in the posteromedial part and a second core in the central part [68]. More recently, Besle and colleagues used functional activation MRI in response to sound stimuli, thus more specific than Glasser's study of the whole brain, and structural imaging to quantify myelin content to investigate different models of auditory cortex core region orientation and organisation. The results of the study argue against the monkey-model inspired alignment of the core with the tonotopic map, and the authors propose a different view with only two core regions, but which may remain

2.1.6.4 Secondary auditory areas

Within the superior temporal lobe, the non-primary areas, also described as associative areas, perform integration and modulation of the primary features received from upstream regions. Their input is both cortical, and subcortical from the non-lemniscal MGB and IC. There is evidence for a hierarchical organisation among these secondary auditory regions, reflecting a gradient of decreasing specialisation, going from belttype regions to non-specific regions of multisensory integration. In [59], a total of seven regions were identified based on cytoarchitecture around the three divisions of the core, spanning anteriorly and posteriorly as well as medially towards the insula, and laterally towards the superior temporal sulcus. In Glasser's atlas [61], the functional gradient view is backed by decreasing myelinisation, cortical thickness, and activation

compatible with the three-fold human cytoarchitectonic parcellation results [55].

profiles to stimuli including language and face recognition tasks. The multimodal atlas proposes three belt-parabelt regions of early non-primary processing, and 8 areas of auditory association in the superior temporal gyrus and superior temporal sulcus, activated by higher order tasks including language and mathematical tasks.

2.1.7 Higher order context-dependant pathways

In order for us to communicate, to enjoy music, or to react to an auditory cue signalling danger, the auditory information arriving at the auditory cortex requires integration with prior knowledge of the world stored in memory, with brain centres responsible for social interactions, emotional content, and motor coordination. Similarly to what has been described in the visual modality, building on animal studies, human neuroimaging, and lesion case reports, two major processing streams of auditory information have been identified, with anatomical and functional segregation [69] (figure 2.11). The bifurcation between the two pathways likely starts at the subcortical level, with the evidence of distinct lemniscal and non lemniscal routes [70]. In electrophysiology, a clear pattern of specific processing has been evidenced as early as within 100ms post stimulus [70]. At the cortical level, in continuation of the lemniscal pathway, the ventral stream mainly answers the 'What' question, referring to the intrinsic characteristics of sound and their integration into meaning, in music and language for example. The dorsal stream, receiving input from the non-lemniscal route, rather refers to the 'Where', allowing for sound source localisation, orientation, working memory evidenced by repetition tasks, motor coordination to react or act on the identified sound object, and speech production. This results, for example, in the understanding and production of speech to be distributed between these two pathways, with evidence from patients with lesions to the ventral stream areas, typically in the region historically referred to as Broca's area, unable to articulate words that they are otherwise able to understand, and conversely patients with lesions to the dorsal stream areas, in particular in the region known as Wernicke's area, who are able to imitate or repeat perfectly but are unable to recognise standard sounds or understand sentences.

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Figure 2.11: A. Meta-analysis results of studies exploring spatial (blue) and non-spatial (red) processing of sound using fMRI and PET, in [71], where the spatial stream appears also more medial than the non-spatial stream. B. Dorsal and ventral processing streams model proposed by [72] in which region BA44 of Broca's area constitutes the target region of the dorsal stream, and BA45 is the endpoint of the ventral stream, with both regions interacting through reciprocal connections. BA: Brodman area; CS: central sulcus; PMC (6, 8): premotor cortex; IPL: inferior parietal lobule (40); AC: auditory cortex (41, 42); IFC: inferior frontal cortex (44, 45); STS: superior temporal sulcus (22).

2.1.7.1 Ventral auditory processing

Originating in the anterolateral auditory cortex, auditory processing relative to spectro-temporal sound features has been shown to project ventrolaterally to the anterior temporal lobe, through the middle temporal regions and inferior temporal sulcus, where sounds are converted into semantic components [69]. Semantic information is then integrated into conceptual representations in the inferior temporal gyrus and ventrolateral prefrontal cortex [70], with additional evidence of simple memorisation processes [73]. Functional evidence from neuroimaging suggests that the ventral stream is essentially bilaterally activated for sound comprehension, with the main cortical hubs connected through the inferior fronto-occipital fascicle, and the uncinate fascicle [74]. However, a leftward preferential processing of language has long been established, and this was structurally supported by early studies providing evidence of greater axonal volume in left hemisphere [75]. Axons projecting to the left auditory cortex with thicker myelin sheaths occupy a larger volume and likely conduct information faster, consistent with rapid sensory signal processing as required

by language tasks. On another hand, spectral information modulation, prevalent in musical information, does not require such high dynamics for transmission, but finer specialisation to sounds of different frequencies. Electrophysiological findings have provided evidence that this is indeed the case [76]. However, cortical morphological differences between left and right hemispheres in post-mortem analyses were not highlighted as significant in the cytoarchitectonic study by [59]. MRI voxel-based morphometry performed in the subdivisions of the auditory cortex suggest that the asymmetry may be relative to the subregions targeted, and the measure of morphometry used [77]: the structural justification for the functional differences observed remains unclear at the cortical level.

In recent findings, spectral information of sound has been found to be preferentially processed in the right hemisphere and temporal features processing has been preferentially highlighted in the left [78, 79]. This was demonstrated by using an array of sounds with varying spectral and temporal modulations: the richer, but slower sounds were more musical, while the poorer but more rhythmic sounds resembled speech. This hemispheric segregation has been proposed as an optimisation through evolution of the auditory processing efficiency of the respective characteristics of two types of behaviourally relevant stimuli in humans: music and speech.

2.1.7.2 Dorsal auditory processing

Originating in the posterolateral auditory cortex, the process that integrates spatiotemporal properties of sounds projects in the posterior direction to the inferior parietal cortex and then to the prefrontal cortex, ending slightly posteriorly compared to the ventral stream [69]. The brain has typically been suggested to locate the origin of a sound source based on the differences between the information coming from each ear on intensity and timing of the stimuli [80]. Functional MRI studies, lesion studies, and stimulation studies have consistently provided evidence of posterior superior temporal and parietal cortex in spatial processing of sounds [80], as well as the dorsolateral prefrontal cortex [81]. The dorsal route supports a sensorimotor integration, for audiovisual processes as well as for articulation in speech [72], and of working memory required for complex tasks [82]. In terms of structural connectivity, the main white matter connections include the arcuate fascicle, and the superior longitudinal fascicle [74]. In terms of functional asymmetries, the dorsal auditory processing route seems to present a leftward attentional bias, as has also been documented in the visual system, evidenced by healthy participants mislocating centrally presented sound objects by 4.5° to the left [70].

2.1.7.3 Auditory emotional processing and gating mechanisms

Emotions are, as defined by Scherer, "episodes of massive, synchronised recruitment of mental and somatic resources allowing one to adapt to or cope with a stimulus event subjectively appraised as being highly pertinent to the needs, goals, and values of the individual" [83]. The ability to read the emotional content of acoustic input such as speech is crucial to navigating complex social interaction. Emotion is conveyed in several vocal features such as pitch, loudness, and rhythm, which are thus encoded in primary and associative auditory cortex and integrated in the ventral stream. In the dorsal stream, confirmation from visual information or from other sensory modalities can be integrated with the auditory emotion identified. A subjective judgement of the incoming sound, based on its characteristics, in the inferior frontal gyrus and orbitofrontal cortex, mostly in the right hemisphere [84]. At the cortical level, the superior temporal sulcus has been found to activate more strongly in response to speech with emotional content than in emotionally neutral speech [85, 86].

Emotional regulation refers to the process by which frontal brain regions including the orbitofrontal cortex, the ventrolateral prefrontal cortex, and the dorsolateral prefrontal cortex [88] exercise top-down modulation of subcortical, limbic circuits that mediate emotion. In particular, an orbito-frontal - amydala functional coupling has been found in decoding emotional prosody, in the form of oscillatory phase synchrony, and furthermore, this modulation was shown to be enhanced by attention [89].

It is noteworthy that impairment in the auditory processes that underlie emotion identification have been found impaired in patients with schizophrenia [90], for



Figure 2.12: A. In the case of emotion processing, bottom-up (white arrows) and top-down (black arrows) modulations are shown. Dashed lines indicate implicit processing, or task-independant activation patterns. STC: superior temporal cortex; MFC: medial frontal cortex; IFC: inferior frontal cortex. B. Crossmodal integration of auditory-visual in a 3-step approach. FFA: fusiform face area; OFC: orbitofrontal cortex. Taken from [87].

whom social withdrawal or feelings of inadequation is a major issue. In tinnitus, more specifically in tinnitus distress, dysfunction within this auditory emotional network could reasonably be hypothesised to dysfunction, and possibly correlating with levels of annoyance to the phantom perception.

In tinnitus, and later in schizophrenia as well, the involvement of limbic structures has also been reported in a different perspective, that of possibly dysfunctional gating mechanisms as we will discuss in the following section [91, 92].

2.2 Conscious auditory perception: insight from cognitive sciences

While all senses are constantly streaming information to the brain, not all sensations subsequently result in perception, typically during sleep, upon habituation to a stimulus, or when our focus is drawn elsewhere. Intuitively, we understand that conscious perception involves mechanisms of memorisation, attention, of gain adaptation and threshold adjustments, while emotional context may render a stimulus particularly salient, or dampened. Furthermore, evidence from patients with disorders of consciousness in vegetative states demonstrates that activity in the auditory cortex is necessary, but insufficient for conscious auditory perception [93]. In recent years, developments in cognitive neuroscience have proposed models of perception based on dynamic interactions, following bottom-up and top-down pathways, of brain regions distributed in a hierarchical organisation [94], in contrast to the historical more localisationist view segregating given functions to specific anatomical regions. Two main investigation trends are currently used to develop our understanding of auditory perception mechanisms. The first belongs to the domain of experimental psychology, focusing on the behavioural correlates of cognitive tasks. This perspective however lies beyond the scope of the present thesis. The second approach looks at the cortical structures and mechanisms that underlie perception, which we touched upon when we mentioned the non-lemniscal auditory pathway and higher order auditory processing, and falls within the scope of the question of the neural correlates of consciousness. This remains an open question today, since we do not have a direct access to bias-free objective evidence of conscious audition, for which several models have thus been proposed.

2.2.1 Auditory perception models

Because we do not have access to the ground truth of auditory perception mechanisms, we build models of what these may be, based upon evidence of what auditory perception involves, from simple sound detection to higher cognitive processes. Taken together, three major ideas are outlined in auditory perception models. First, the brain constitutes internal representations from sound features that are selected from the incoming stream of sensation. These features include simple auditory objects, perceptual collections of attributes grouped together such as pitch, loudness, spatial localisation and orientation. Auditory events refer rather to temporally salient changes in the acoustic environment, while cognitive attributes of auditory objects and events refer to the past experience of an individual with these objects or events, and to the way these objects and events are organised with respect to each other. The way that complex and mixed incoming environmental stimuli are separated and identified as distinct sources is the main focus of auditory scene analysis, which

2. State of the art

builds upon cognitive segregation of known auditory objects. The second main idea behind auditory perception is that the brain stores these elements, and the third idea poses that these stored elements are used to build subsequent representations.

As reviewed in [95], up to 10 auditory perception models, taken from more general models of consciousness and applied to the auditory modality, have been described in the literature and from which two main tendencies emerge. Although all models relate sensory cortices to higher order processing regions, the centre of gravity of this relationship can be either close to the sensory cortex, or delocalised. The models with a sensory-based focus include local recurrence models proposing strong interplay between early and higher order sensory regions, reverse hierarchy with a default form of representation hosted in higher order sensory regions, intermediate level models with representations featured somewhere in between early sensory and higher cognitive regions, and to a certain extent winning-coalition models where neural populations compete for their information to be featured on the scene of consciousness. The models requiring as a prerequisite the availability of brain areas distinct from any sensory modality include Global Workspace Theory and related models, positing that conscious perception necessarily involves the frontoparietal network, with additional conditions such as the unicity of the dominant object of consciousness, and the role of attention in order for sensory input to become conscious. Attention-schema theory, also connects higher order regions in the brain building a perceptual model of attention, but with a focus on the right superior temporal sulcus and right temporoparietal junction, rather than the frontoparietal areas. These areas are highly engaged during social interaction: the same mechanisms that attribute awareness to others are also responsible for attributing it to one's self. This is also supported by evidence from lesion studies in those areas reporting symptoms of neglect or failure to perceive objects.

2.2.2 Evidencing neural correlates of auditory consciousness

Several experimental setups have been developed in the attempt to validate the proposed models, supported by functional imaging such as electroencephalography or functional MRI.

2.2.2.1 Sound detection paradigms

In order to examine whether an auditory sensation reaches consciousness, sounds at the threshold of what an individual has reported to be able to distinguish are presented while recording brain activity. These paradigms include stimuli presented at the hearing threshold in a silent environment, or at comfortable hearing level but masked or rendered ambiguous by noise or competing stimuli. The electrophysiological correlates of the comparisons between accurate detection of the stimulus versus the non detection presents a typical negative peak around 100-200 ms, in non primary auditory areas associated with auditory awareness in the case of masker embedded target sounds, as well as a later positive peak around 300 ms, associated with context updating and conscious recognition of relevant target stimuli [96].

2.2.2.2 Oddball paradigms

Conscious auditory perception can be studied using change detection, whereby a target sound is presented randomly and infrequently, amongst a majority of non target sounds. In electrophysiology, using this study design, a negative peak arising from the auditory cortex around 130ms has been reliably elicited, labelled as mismatch negativity. The strength of the peak is found to be modulated by attention and perceptual organisation. There is evidence that clear suprathreshold changes may remain undetected in more complex settings, for example when missing objects are required to be detected, or conversely added objects, with a negative response between 100 and 200ms, and functional MRI evidence of frontoparietal, insular, and anterior cingulate activity. Mismatch negativity has also been proposed as a marker of auditory gating mechanisms, whereby a perception is blocked out from reaching perception [73], of transitions between sleep and wakefulness, and a predictor of recovery in patients with disorders of consciousness.

2.2.2.3 Bistable perception paradigms

The different perceptions arising from the same object are known as multistable perceptions. The most typical examples involve visual perceptions, with spontaneous switching between the possible perceptions. The classical auditory bi-stable paradigm involves alternating tones or noises such that either a single source is perceived, or two sources. The main results using this paradigm were found in the posterior auditory cortex and the intraparietal sulcus in the two streams > one stream contrast [95]. However, the extent to which these multistable illusions are able to represent neural correlates of consciousness, and not instead reflect automatic scene analysis remains a matter of debate.

2.2.2.4 Auditory experience in the absence of an external corresponding sound source

Vivid auditory experiences despite no sound stimuli provide evidence that primary auditory processing is not always necessary for sound perception. The most prevalent examples in pathological conditions of such experiences are found in schizophrenia and epilepsy, where they are typically referred to as hallucinations and auditory auras respectively. However, the most frequent manifestation on the whole happens in individuals with no particular underlying medical condition and is known as subjective tinnitus.

2.3 Tinnitus: sound perception beyond sensation

Tinnitus has recently been defined by an international research consortium, as "the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source", turning into tinnitus disorder "when associated with emotional distress, cognitive dysfunction, and/or autonomic arousal, leading to behavioural changes and functional disability" [10]. In this section, we will review the current epidemiological context of tinnitus research, as well as the main models developed in the literature to explain the occurrence and maintenance of tinnitus.

2.3.1 Tinnitus epidemiology

2.3.1.1 Prevalence of tinnitus

Most people experience the perception of a slight sound in a very quiet environment: this is considered physiological. In contrast, phantom perceptions of sound occurring in normal acoustic surroundings are considered abnormal [97]. However, the absence of a significant underlying medical condition generally prevents this condition from being considered pathological. Overall, tinnitus prevalence is estimated to reach between 10 and 15% of the adult population with around 0.5% of people prevented from leading a normal life due to tinnitus [7]. There is a general trend for bothersome tinnitus prevalence to increase with age, similarly in men and women [98].

2.3.1.2 Risk factors and main etiologies

The main risk factors for developing tinnitus involve damage to the auditory system and its vicinity, including noise exposure, ear infection, traumatic head or neck injury, orofacial disorders involving the temporomandibular joint, hypertension, emotional trauma or anxious and depressive states, and ototoxic medication [7]. Tinnitus is attributed to a specific cause in 40% of cases, the remaining 60% are unknown, and referred to as idiopathic. In 20% of cases, the identified cause of tinnitus is noise trauma. Injury to the head and neck occupy 9% of the known etiologies, ear infections and colds are estimated at 7%, medication 2%, and the remaining fraction is attributed to Menière's disease [99].

In the vast majority of cases, tinnitus co-occurs with hearing loss, which supports the historical view that similar mechanisms may be involved in both, starting at the periphery [100]. However, there is evidence of tinnitus in normal hearing individuals, and evidence of hearing-impaired individuals with no tinnitus, which has been put forth to advocate against a solely peripheral origin of tinnitus. The debate has been fueled by evidence from electrocochleography of hidden or subthreshold hearing-loss in tinnitus [101–103], suggesting that the correlate between tinnitus and hearing loss may be more prevalent than what is typically documented. Furthermore, the emotional state, such as preexisting anxiety or sudden stress, is a risk factor for developing tinnitus, as well as a typical comorbidity that can develop as a consequence of tinnitus perception. It has been highlighted in studies exploring the relationship at the cortical level between tinnitus perception and the limbic system, a network of structures involved in emotional processes in the brain [91].

The causal relationship between tinnitus and co-existing disorders, or comorbidities, is therefore not clear cut. Increasingly, the distinction is made between tinnitus perception, and tinnitus disorder referring to the entire picture of tinnitus and its emotional load and behavioural traits [10]. This has been found relevant in the investigation of tinnitus, which can otherwise be masked by its comorbidities in studies comparing healthy, normal hearing controls to individuals with tinnitus, a certain degree of hearing loss, insomnia and anxiety.

2.3.1.3 Clinical assessment

On one hand, we observe that mild forms of tinnitus do not usually motivate medical consultation, and on the other hand, that tinnitus does not justify, from a clinical point of view when a patient seeks medical advice, extensive exploration. There seems to be a gap in the clinical management and societal awareness on this subject [8]. Once any possible underlying conditions have been ruled out, there is no objective test for subjective tinnitus, which is mainly assessed using the patient's history, risk factors, and the detailed characteristics of the symptom. Present guidelines encourage questioning the nature of the perception, its laterality, the nature of its onset, and the level of impact on everyday life [104]. The characteristics of tinnitus can be further assessed using standardised questionnaires, which are useful for initial assessment as well as for following up on changes if a treatment option is set up. The tinnitus handicap inventory is one such example, yielding a score out of 100 which can help classify the severity of the symptom, from mild to severe [105].

2.3.1.4 Current treatment options

Tinnitus patients today are mainly offered solutions that aim to help them manage their condition and improve their quality of life. A major aspect of tinnitus management involves patient education on the natural history of the symptom, and the likelihood that acute tinnitus may spontaneously evolve with decreasing intensity [8]. More extensively, cognitive behavioural therapies and tinnitus retraining therapy (i.e. CBT with sound stimulation) [106] have been designed to help develop symptom management strategies and coping mechanisms to lead to habituation and therefore a decreased subjective perception of tinnitus. General psychological intervention has proven successful in helping to manage the comorbidities of tinnitus. In a comparison of cognitive behavioural therapy with no treatment or with an active control group performing relaxation, no differences in tinnitus loudness compared to baseline was found in any case; however, significant improvement of depression scores and quality of life was observed in the cognitive therapy group compared with the other groups. Medication options for tinnitus treatment have been tested, ranging from antidepressant to antiepileptic and anesthetic drugs [107]. These drugs have not proven particularly effective for tinnitus per se or for tinnitus management [108]. Restoring a proper sound environment through hearing aid, combined with white noise or music stimulation, will likely mask the tinnitus perception, building upon the hypothesis that it will help reverse the central auditory gain maladaptive changes by increasing neural activity in central auditory structures [109]. Yet existing treatment options are inadequate in acute cases, where tinnitus is least understood and most heavily loaded with comorbidities. However, the progress made in recent years in tinnitus research has supported neuromodulation-based management techniques which have yielded some promising preliminary results so far [110].

2.3.2 Contribution of the auditory pathway

Tinnitus has long been considered the symptom, or manifestation of a dysfunction triggered along the auditory processing stream. Historically, given the auditory nature of tinnitus perception, its frequent co-occurrence with hearing loss [111], and typical ear-related etiology, tinnitus was explained as a peripheral dysfunction. However, some compelling evidence showed the limits of this model, as it was observed that paradoxically, injury or complete resection of the acoustic nerve was able to both exacerbate and alleviate tinnitus [112]. As an alternative, emphasis was put

on the central mechanisms likely to explain tinnitus. Based on the current available evidence, it seems that initiation and maintenance may be supported by different mechanisms, and that regions outside the auditory pathway may be involved.

Here, we review the elements pertaining to peripheral and central dysfunction in the auditory pathway, which have been proposed to contribute to tinnitus.

2.3.2.1 Peripheral dysfunction

Injury to the inner hair cells of the cochlea can lead to aberrant neural firing patterns issuing from the cochlea, or in the case of hair cell death, to loss of input for some fibres of the auditory nerve, also referred to as deafferentation. This triggers a cascade of bottom-up and top-down events and adaptations, likely due to an imbalance in inhibitory and excitatory inputs, in the brainstem and in the auditory cortex, resulting in a range of symptoms, among which figure tinnitus, hearing loss, and hyperacusis [113–117]. The exact contribution of these adaptations to tinnitus perception, and the causal relationship between these events and all symptoms involved is an ongoing subject of debate. However, there is an undeniable correlation between deafferentation mechanisms initiated at the periphery, and the occurrence of tinnitus [118].

Animal models using salycilate or noise exposure to induce tinnitus provide evidence that tinnitus correlates with both increased and decreased spontaneous firing rates, referring to neural activity that is not driven by outer stimuli. Increased, hyper-synchronous spontaneous firing is documented along the non-lemniscal pathway in the dorsal cochlear nucleus [53, 119], the external nucleus of the inferior colliculus [120], and secondary auditory cortex [99, 121]. On the contrary, in the subcortical lemniscal pathway, there is evidence that spontaneous activity is reduced [99, 122]. Additional evidence from human neuroimaging comparing tinnitus and control groups have found elevated responses to sound using functional MRI in the inferior colliculus in tinnitus subjects [123].

Building on this evidence, some brainstem models of tinnitus suggest that there exists a dysfunction of subcortical gain control mechanisms [124], whereby high gains are attributed in the brainstem to irrelevant noise in the auditory pathway, and therefore pass the perception threshold when they should have been filtered out. Others propose in contrast that it is the gating mechanism of the frontostriatal system [92] that is impaired in tinnitus, and that the threshold has been lowered resulting in noise-like input to be considered significant. In both cases, tinnitus results from a compensation mechanism that amplifies otherwise unnoticed neural noise. It has also been proposed that both cases occur together, where spontaneous activity in the auditory pathway is interpreted as relevant sound input due to the alteration of neurotransmission mechanisms inducing simultaneous decrease in inhibition and increase in excitation [125]. However, these models do not account for the alleviation/exacerbation paradox upon auditory nerve section.

Another approach considers tinnitus to result from an alteration in the transmission at the interface between brainstem and cortex in the thalamus, described as thalamocortical dysrythmia [126], occurring as a reaction to deafferentation, in the form of increased gamma band activity and a slowing down of alpha-theta activity. This is proposed to support a mechanism of information retrieval by the brain, either in the neighbouring auditory cortical regions, or in memory circuits in the hippocampus. By focusing on deafferentation as the main cause of tinnitus, this model does not explain tinnitus without hearing loss - except perhaps in cases of hidden hearing loss, or deafferentation without loss of measurable auditory performances [124]. It does not explain either how tinnitus alleviation through auditory nerve section might occur.

In a different perspective, somatosensory-auditory interactions have been shown to occur in the brainstem in animal models [46, 127], with trigeminal innervation of the auditory brainstem. This is supported by behavioural evidence linking the somatosensory and the auditory systems in approximately two thirds of tinnitus patients: tinnitus perception can be modulated by somatosensory stimuli such as head movements, or tactile stimulation. In this case, tinnitus is proposed to result from an erroneous cross-talk, by means of neural plasticity, between the somatosensory and auditory modalities. While this does not necessarily apply to all forms of tinnitus, it sets a foot outside the auditory system for new hypotheses to build upon, and accommodates tinnitus occurring without hearing loss.

Together, these subcortical models provide insight into a part of the mechanisms at play in tinnitus. However, they do not settle the paradox of positive as well as negative tinnitus modulation by damage to the auditory nerve. Additional mechanisms at the cortical level are thus required to fully explain tinnitus.

2.3.2.2 Central auditory correlates of tinnitus

In the auditory cortex, the changes following the onset of the tinnitus-inducing event reflect the changes found in subcortical structures.

Thus, auditory synchrony models [128], in the form of excessive local synchronisation of neural firing in the auditory cortex have been observed mainly in animal models, as a result of deafferentation [99]. In humans, this has been proposed to translate into specific cortical oscillation patterns in the 30-60 Hz frequency band measurable using EEG or MEG [102].

Reorganisation of the primary auditory areas has further been highlighted following deafferentation, affecting the cortical tonotopic map. It is proposed to result in tinnitus from increased representation of edge frequencies [99, 129]. The cortical regions connected to injured cochlear areas are suggested to become responsive to the frequencies from adjacent regions. This builds on evidence of tinnitus perception concurring with the frequencies of hearing loss, thus relying on tinnitus and hearing loss co-occurring, and on decreased input from subcortical structures, however the evidence essentially highlights increased spontaneous activity, and recently tonotopic map reorganisation has been shown to predominate in hearing loss rather than in tinnitus [130].

Furthermore, elevated cortical activity in the primary auditory cortex [131] has been found for both tinnitus and hyperacusis, controlling for levels of hearing loss. While for hyperacusis this likely results from a lowering of the perception threshold, for tinnitus this was proposed to result from enhanced attention drawn to the auditory modality, thus involving extra-auditory brain regions. Nonetheless, this study points out that differentiating tinnitus perception from related disorders such as hearing loss and hyperacusis constitutes a challenge.

To sum up, damage to the auditory periphery triggers an imbalance in inhibitory and excitatory mechanisms, driving altered spontaneous activity in the auditory brainstem and cortex, increased synchrony and neural plasticity as reflected in tonotopic map reorganisation. We have seen how these elements explain a large extent of tinnitus. Yet, some issues do not find their answers in the auditory pathway: the possibility that tinnitus may occur without cochlear deafferentation, in certain cases of idiopathic tinnitus; the contribution of emotional states as an aggravating factor [7]; the modulation of tinnitus perception due to a shift in attention; the dispersion in onset delays of tinnitus, which can be either immediate or progressive; the fact that no objective difference is observed in most cases between controls and tinnitus participants [132]. With the contribution of neuroimaging, evidence outside the auditory pathway has increasingly been put forth. Recently, the emphasis has been set on the top-down mechanisms mediating chronic manifestation of tinnitus rather than on the discussion about the relevant bottom-up mechanisms leading to initial or occasional perception of tinnitus [133].

2.3.3 Contributions outside the auditory pathway

Tinnitus can be discussed as a dysfunction of brain networks, involving regions spanning the attentional, memory, and emotional network, in addition to the auditory cortex. Indeed, tinnitus has been shown to correlate with altered selective attention and working memory [134–136], with evidence of abnormal activity in the limbic system relating to emotional aspects.

2.3.3.1 Limbic system involvement

Based on the results of neuroimaging studies [66, 137, 138], the limbic system has repeatedly been proposed as an active component of tinnitus perception [91, 139]. Two major aspects of the limbic system have been documented in tinnitus. First, tinnitus perception bears an important emotional aspect, as it has been shown that levels of preexisting anxiety and depression predict more severe tinnitus, that emotional state modulates tinnitus perception, and that tinnitus loudness and level of annoyance are not always related [7, 8]. In particular, the amygdala has been found to be involved in the subjective appreciation of tinnitus perception, and thus in the level of tinnitus distress [140], or, as it has recently been defined, tinnitus disorder [10].

Secondly, the limbic system has been suggested to play a role in the feedback connections for filtering of irrelevant percepts such as tinnitus, in combination with frontostriatal regions [141]. In response to sounds with emotional content, and during a study evaluating the impact of physical activity on tinnitus outcomes, high distress tinnitus participants were found to activate the amygdala and parahippocampus more strongly than low distress tinnitus participants. Conversely, low distress participants were found to activate frontal regions, as well as insular more strongly than high distress participants [142]. This suggests a possible successful adaptation of low distress participants, with better top-down control, in this case through attention, on the negative emotions pertaining to tinnitus. However, in this study, low distress participants may have been better able to fully engage in the physical activities proposed, and that this may have resulted in increased frontal activation. Recent research has further highlighted the role of auditory-visual cross-modal modulation of attention and salience brain networks while listening to music. However, it remains unclear whether the impact of hearing loss may not have rather supported these results, since there are reasonable grounds for believing that decreased auditory modality performances may be compensated by increased activity of the visual modality.

2.3.3.2 Attentional network involvement

The attentional network is classically believed to include higher order brain regions of the frontal and prefrontal cortices, of the posterior parietal cortex, and the anterior cingulate involved in emotional valence [143]. Attention can be investigated using detection or discrimination paradigms, where tinnitus patients have been reported to perform more slowly than controls, particularly in discrimination tasks involving rapid choice making [134]. Based on additional evidence from activation and resting state neuroimaging, as well as structural evidence involving the attentional network regions, tinnitus has thus been depicted as a constant additional cognitive load, with increased vigilance to the tinnitus instead of the task at hand, resulting in reduced behavioural performances [133, 134]. It has also been proposed as a self sustaining paradoxical attention to an otherwise irrelevant percept, preventing habituation [144].

Increased activity in response to sound as well as structural differences in the ventro-medial prefrontal cortex (vmPFC) has been evidenced in tinnitus subjects compared to controls [145, 146]. Differences were also found in the orbitofrontal cortex, additionally correlating with levels of tinnitus distress [147]. Functional correlations patterns from the precuneus to the dorsal attentional network regions have been found altered in tinnitus compared to controls [146], which were suggested as a potential marker of long term tinnitus.

These elements support the claim that attention modulates tinnitus perception, and may influence whether tinnitus develops into a chronic condition, or subsides. In line with this, tinnitus distress has been shown to correlate with the neural activity of memory-related brain regions, suggesting a reinforcement mechanism possibly underlying long term tinnitus maintenance [118, 148, 149].

2.3.3.3 Proprioceptive contribution

The proprioceptive hypothesis presented in the introduction is specific to tinnitus of acoustic trauma origin. It stems from the findings that we mentioned, locating the cortical representation of the middle ear within the parietal operculum (OP3) [16, 19, 21]. Acoustic trauma is likely to cause damage not only to the hair cells in the cochlea, but also to the structures of the middle ear. Classically, injury to the middle ear results in hearing loss and increased risk of further damage to the inner ear, as mentioned previously. Spasticity of the middle ear muscles, due to excessive stretching is also a documented dysfunction of the middle ear, which can result in objective clicking sound perception. The muscles and tendons of the middle ear are subject, like any other muscle in the body, to tension, cramps, or elongation and rupture due to physical solicitations beyond their range of mobility. Disturbance to the muscle spindles is proposed to trigger phantom sound perception, due to hyperactivity in the somatosensory pathway, through the trigeminal innervations, up to the cortex in OP3. Hyperactivity in the somatosensory pathway is suggested to be further upregulated by the autonomous system through the sympathetic innervation.



Figure 2.13: Illustration adapted from [21], highlighting the role of middle ear proprioceptors found in the middle ear muscles and tympanic membrane. Neuronal excitability is modulated by autonomic input, innervating the intrafusal fibres of middle ear muscles, while excitability of the neurons in the auditory pathway is modulated through somatosensory input in the cochlear nuclei. The dashed lines indicate structural connections, and the full arrows indicate the strength of the contribution to tinnitus

In line with auditory-somatosensory interactions in tinnitus [46, 127, 150], proprioception from the middle ear is conveyed through the trigeminal nerve, and is thus integrated with the auditory modality in the dorsal cochlear nucleus, as well as in further instances of the non-lemniscal pathway. Following acoustic trauma, damage to the cochlea is proposed to result mainly in hearing loss. It is the integration process between the erroneous proprioceptive information and the auditory input, in the brainstem as well as in parietal operculum, which is proposed to be responsible for tinnitus of acoustic trauma origin.

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2.3.3.4 Analogies with other sensory modalities

Tinnitus bears some resemblance to other phantom perceptions [151]. Phosphenes are the visual equivalent : they can be mechanically induced by applying pressure to the eye, or using electromagnetic stimulation [152] and are typically related to conditions such as migraines [153] or multiple sclerosis [154]. Phantom limb syndrome and kinesthetic illusions, which can also be simulated, may act as the proprioceptive counterpart to auditory phantom perception [20]. Phantom perception mechanisms in general, and the correspondences between them (as done in [19]) may provide promising paths to explore for new insights into the mechanisms of tinnitus.

2.4 Exploration of the neural correlates of tinnitus

The primary motivation for the exploration of the neural correlates of tinnitus is to objectively quantify the subjectivity of this perception. Initially, tinnitus research was built upon animal models, with tinnitus being induced either through noise exposure, or using medication known to produce reversible tinnitus in humans [149]. Specific behavioural training of the animals enables downstream evaluation of presence of tinnitus, and subsequent analysis of brain changes [46, 92, 155, 156]. Although animal models are also continuously improved to investigate additional behavioural elements, it remains difficult to assess with certainty the level of hearing loss versus tinnitus or hyperacusis, or the attentional load issues and the related levels of annoyance. With the development of neuroimaging, several findings determined in animal models were verified in humans, such as increased brainstem activity [123]. Different imaging modalities and different paradigms provide a range of resolutions and approaches to tackle tinnitus. For example, its impact on attention is highlighted using discrimination tasks during electrophysiological monitoring, taking advantage of the millisecond temporal resolution to establish neural correlates. Resting-state functional MRI, in contrast, provides high spatial resolution to locate the anatomical regions involved. The progress made in all fields of imaging - acquisition, processing, statistical inference - has therefore provided a large and somewhat mixed body of evidence relating to structural and functional brain alterations in tinnitus.

2.4.1 Functional neuroimaging

In functional neuroimaging techniques, the measured signal reflects the changes in brain metabolism, oxygenation, local blood volume or flow, in the distribution of a radioactive tracer, or in electric potential. These physiological changes act as measurable proxies for brain activity at rest, or during a given task. While certain techniques have achieved a high level of reliability in characterising a pathology, such as PET scan in Alzheimer's disease, the case of subjective tinnitus is rather less clear. In this section, we review the evidence provided by each functional imaging modality with respect to tinnitus.

2.4.1.1 Functional MRI

Functional MRI builds upon the existence of neurovascular coupling: when neural activity takes place in a region, blood flow to that region increases [157]. The Blood Oxygen Level Dependent (BOLD) signal in functional MRI captures these hemodynamic changes. More specifically, active neuronal populations consume more glucose, which is conveyed by the blood flow. This causes local changes in the concentration ratio between oxyhemoglobin and deoxyhemoglobin. Because deoxyhemoglobin has a positive magnetic moment, this imbalance generates local disturbances in the magnetic field of the MRI. These mechanisms are typically modelled using the hemodynamic response function, which may vary across brain regions and individuals [158]. fMRI has a typical capacity to discriminate regions in the millimetre to centimetre range, depending on sequence parameters. Images of the brain are taken at a given sampling time, generally between 1 and 3 seconds, thus establishing a time course in each brain voxel. fMRI is therefore particularly indicated for processes that take several seconds, and to relate precise anatomical landmarks to functional properties: the brain has thus been extensively mapped using task activation fMRI.

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Figure 2.14: Image drawn from [159], highlighting activity in the visual cortex, upon opening and closing ones eyes. Spontaneous activity is also visible in the BOLD timecourse.

Spontaneous fluctuations in the BOLD signal, or noise, are independent of the task or stimulus temporality, but have nonetheless proven informative [159–161]. Provided the scanning sessions last long enough [162], the noise in the BOLD signal has been found to present synchronisation patterns between spatially distinct but functionally connected brain regions, consistent with known anatomical delineations. These patterns have been shown to correlate with fluctuations in high-frequency neuronal activity evidenced in electrophysiology, and to modulate behavioural responses. [159]. These observations have resulted in characterising the brain at rest as an organised system with multiple overlapping networks interacting dynamically with each other, with clinical relevance [163, 164]. The synchronisation can be assessed by computing pairwise correlations between voxel timeseries, where high correlation implies the existence of a functional connection between two voxels. Functional connectivity thus refers to the analysis of temporal correlations of the spontaneous BOLD signal fluctuations throughout the brain.

Resting-state functional connectivity specifically refers to the study of the brain at rest, whereby participants are instructed to lie still and to let their mind wonder. This simple paradigm has revealed several distinct brain networks, known as resting-state networks [163, 165]. Certain networks involve early sensory cortices, like the somato-motor, auditory, and visual networks. A coherent group of regions, in the medial prefrontal cortex, posterior cingulate cortex, precuneus, superior frontal gyri and inferior parietal lobules have been found to deactivate as tasks are performed,

and to activate during rest, introspection or day-dreaming: this network is known as the default mode network [166]. Areas otherwise involved in language processing, Broca and Wernicke's areas, have been found to constitute a synchronous network at rest. A dorsal attention-related network was identified, typically involved in goal directed tasks and including the frontal eye fields and the intraparietal sulci. An additional, ventral, attention network was found in the the ventral frontal cortices and the temporo-parietal junction, mainly involved in involuntary attention shifting [167]. A switch between these two attention networks is performed essentially by the saliency network, described as encompassing the inferior frontal gyri, the right middle frontal gyrus and right anterior insula.



Figure 2.15: Using data from over 200 subjects in the human connectome project and running an independent component analysis, the main resting-state networks were derived and provided in the Conn toolbox [whitfield-gabrieli]

Data-driven or hypothesis-driven techniques are the two main approaches for determining resting-state networks. In the former, independent component analysis (ICA) is the most prevalent method, taking whole brain activity and clustering highly correlated regions together, into a set number of components chosen *a priori*. Identification of the corresponding networks is performed visually, and the number of components may be adjusted to avoid splitting networks into sub-components. In the latter, one or multiple seed regions are chosen based on prior evidence and the correlation between the timeseries in this region and the timeseries in the rest of the brain is examined. This method is thus referred to as seed-based, or region-of-interest (ROI)-based functional connectivity. This approach allows one to investigate specific research questions, where the data-driven approach may not provide sufficient sensitivity.

The main findings regarding tinnitus using resting-state fMRI involve the auditory, default mode, attention, and emotion networks (table 2.1). An auditory limbic link, through positive correlation between the activation patterns of the parahippocampal regions and the auditory cortices has been documented, comparing tinnitus patients with varying levels of hearing loss and controls with or without hearing loss [168–170]. This is in line with the thalamocortical dysrythmia model and with the limbic gating mechanism described by [91], but has not been always reproduced in subsequent resting state fMRI studies [171, 172].

Cross-modal auditory visual interactions were highlighted, with a negative correlation between the activation patterns of the auditory cortex and the visual cortex regions [173], but the groups of participants were matched only in age, and not in hearing levels. In a later study targeting non-bothersome tinnitus only, matching participants for hearing loss, this result was not replicated [171].

Attention connectivity networks have been found altered due to tinnitus, in particular within the ventral network relating to involuntary attention shifting [173], and between the dorsal attention network and the parahippocampus [169]. This can be interpreted as tinnitus perception disrupting the normal course of attention processes, or the other way around, that tinnitus may be perceived due to attention network disruption [144].

In the default mode network, several studies have underlined group differences in functional activation patterns. Within the default mode network, decreased connectivity between regions and decreased coherency have been documented [66, 174], as well as decreased connectivity in particular with the precuneus [169]. This decreased precuneus connectivity has been associated with tinnitus duration and severity [175]. These findings of altered resting-state default mode network patterns have been interpreted as reflecting the difficulty for tinnitus participants to truly

| Study | Design | Nb Part. | Etiol. | Phen. | Results |
|---------------------|-----------------------------|-----------------------|--------|--------------------|---|
| Burton 2012 [173] | SB, 6mm GS, aff. reg. | 17T - 17C | ND | THI 38-76, unm. HL | Aud Vis. anticorr.; VAN alteration. |
| Maudoux 2012 [168] | ICA, 8mm GS, aff. reg. | 13T - 15C | Mixed | THI 16-84, unm. HL | Aud Limbic FC increase |
| Schmidt 2013 [169] | SB, ICA, 10mm GS, aff. reg. | 12T - 15+13C | ND | THI 0-22; m. HL | Aud Limbic FC increase; DMN FC decrease |
| Wineland 2012 [171] | SB, aff. reg. | 18T - 23C | ND | THI 4-14; unm. HL | No differences |
| Schmidt 2017 [146] | rs-FC, n.l. reg, 10mm GS | 13+12+17+15T - 15+13C | ND | Mild T; m. HL | DMN - DAN FC increase |
| Leaver 2016 [91] | ICA, 6mm GS, aff. reg. | 21T - 19C | ND | THI 0-88; m. HL | Aud limbic FC increase |
| Davies 2014 [172] | ICA, 4mm GS, aff. reg. | 12T - 11C | ND | THQ 18-68; m HL. | No difference in aud. FC. |

Table 2.1: Main functional connectivity results. SB: seed-based; GS: gaussian smoothing; aff. reg.: affine registration; T: tinnitus; C: controls; ND: non disclosed; THI: tinnitus handicap inventory; m.: matched; unm.: unmatched; HL: hearing loss; Etiol.: etiology; Phen.: phenotype; Nb Part.: number of participants; Aud.: auditory; Vis.: visual; VAN: ventral attention network; DAN: dorsal attention network; DMN: default mode network; FC: functional connectivity;

maintain a resting state, because of the ongoing tinnitus perception, which manifests itself more saliently during rest [8].

2.4.1.2 Electrophysiology

Vital functions are governed by changes in cellular electric properties throughout the body including the nervous system, the heart, the digestive system, or the sensory organs. In particular, neurons communicate with each other using electrical processes derived from differences in ionic concentrations, mainly sodium and potassium, between opposite sides of the cell membrane. At rest, there is a negative charge, or potential (V) of -60 to 70 mV across the membrane, due to differences in permeability of the membrane between sodium and potassium ions. The potassium ions are able to diffuse through the membrane through specialised channels: this movement of the ions across the membrane generates a measurable current (I), which is limited or facilitated by the number open channels and the gradient of concentration represented by a resistance parameter (R). Ohm's law can therefore describe the relationship between the physical properties in the neuron: V =I x R. Changes to this state of equilibrium may result in the opening of more ion gates and voltage changes. For example, upon stimulation, the cochlear hair cells release neurotransmitters that bind to receptors on the neurons of the acoustic nerve. This causes the current flow across the cell membrane to increase, and depending on the charge of the ions flowing across, for the membrane potential to become more positive, this is the depolarisation phenomenon, or to become more negative - to hyperpolarise. A local voltage change inducing depolarisation is therefore known as excitatory potential, while hyperpolarisation voltage changes are inhibitory potentials.

Localised potential changes can add in space and time resulting in an action potential if the summation reaches a threshold around -55 mV. An action potential is an all-or-none transient depolarisation of the membrane, through rapid influx of sodium ions bringing the membrane potential from a negative to a positive voltage. The strength of a stimulus is reflected not by the amplitude of the action potential, but by the frequency of action potential firing rates. The equilibrium state is then restored by the closing of the sodium gates and the opening of potassium channels. The action potential, or spike, then travels along the axon membrane, preserving the amplitude of the voltage change, and contributes to the extracellular electric field. At a given spatial location, the local electric field results from all electric currents, irrespective of their origins, but with the amplitude of each contribution scaling with the inverse of the distance between the source and the spatial location that is looked at.

There are thus different scales of investigation of the electrical mechanisms in the nervous system, depending on the hardware used and the level of invasiveness [176]. Implanted microelectrode devices, used for example in Brain Computer Interface research, can measure the firing patterns of action potentials from single neurons, or from small groups of neurons [177] in a discrete, point process approach. At the larger cell population level, local field potentials (LFP) refer to the continuous variations of electric field resulting from the summed activity generated by a population of neurons in the vicinity of the electrode [176]. In humans, such local activity recordings of single neurons or groups of neurons stem from medical procedures that include intracranial electrode insertion as part of the treatment or disease investigation procedure, for conditions such as epilepsy or Parkinson's disease. More frequently, extracellular potential variations, which can be decomposed into canonical oscillations, are measured non invasively from outside the brain, at the scalp level, using electroencephalography (EEG).



Figure 2.16: Example of brain oscillation patterns decomposed per frequency bands. Alpha activity (8-12Hz) is present during relaxed states and increases when eyes are closed. Delta waves have slow frequencies and reflect deep sleep (1-4 Hz). Beta waves (12-30 Hz) are present during active thinking, engaging in conversation or in a task. Theta waves (4-8Hz) reflect hypnotic states. Gamma waves (from 30 to 150Hz) have been shown to drive higher order cognitive processes, deep thought and highly focused attention [176]

EEG measures the electrical contributions of larger neural populations of several million neurons, which essentially renders a spatiotemporally smoothed version of the LFP oscillations. Due to the amount of soft and hard tissue the signal has to cross, via a volume conduction process, from the source of activity to the sensor placed on the scalp, the EEG signal is not directly reflective of neural firing patterns, however it does correlate with behavioural activity [178]. Magnetoencephalography (MEG) is another approach to human electrophysiology that uses superconducting quantum interference devices (SQUIDs) sensitive to the fT-range magnetic fields resulting from currents generated in the brain. While EEG reflects the activity of secondary, or volume currents, and is affected by the tissue between source and sensor, MEG measures fields generated by primary currents, or intracellular current generators, and is largely unaffected by skull, scalp, and other tissues. However, only current generators parallel to the scalp surface yield fields outside the head, therefore radial sources are not well detected by MEG. Furthermore, an MEG is

a highly expensive piece of equipment which is mainly used for research purposes. An intermediary approach relies on the measurement of potential variations from the cerebral cortex surface, known as electrocorticography (ECoG). However, this requires the removal of a large surface of scalp and skull, therefore remains invasive and limited to specific clinical frameworks.



Figure 2.17: a. Recordings from depth electrodes, cortical grid electrodes, and scalp EEG, showing the greater resolution of high-frequency patterns at the intracranial level. b. Scalp EEG (Cz, red) and LFP from the supplementary motor area (SM), entorhinal cortex (EC), hippocampus (HC) and amygdala (Am), as well as multiple unit activity (green) and single unit spikes (black tics). c. Simultaneous MEG (black) and depth EEG (red) recordings, with absence of phase delay between timecourses. d. LFP timecourses from different cortical depths, as well as intracellular recording from a layer 5 pyramidal neuron showing patterns of hyperpolarisation and depolarisation in an anesthesized cat. [176]

In tinnitus, the main electrophysiological findings derive from non-invasive

measurements (table 2.2). Analyses typically include a time-frequency decomposition of the electrophysiological signal to identify the contribution of the different frequencies of brain oscillations to tinnitus. A pattern of enhanced delta (0.5 - 4 Hz) and gamma (35 - 80 Hz) frequencies as well as decreased alpha (8.5 - 12 Hz) frequencies in the temporal areas was identified [102, 103, 179, 180]. These findings were interpreted as a resulting from an imbalance between inhibition and excitation in the thalamocortical circuits due to loss of sensory input, in a thalamocortical dysrythmia model. In particular, the delta rhythms were related to the deafferentation, while the alpha desynchronisations were proposed to reflect the downregulation of inhibitory mechanisms, and the delta oscillations the increased spontaneous firing. This pattern was proposed as a neural signature of tinnitus, and has served as a basis for neuromodulation techniques such as neurofeedback mentioned in the next section. However, this pattern has not been systematically reproduced in later studies [11], meaning that the underlying electrophysiological mechanisms of tinnitus, and the contributions of tinnitus versus tinnitus distress, remain an open question.

Electrophysiological networks have been further described, in a way similar to how functional connectivity was previously defined. Synchronisation between timeseries of neural activity derived from electrophysiological recordings has been observed in relationship to tinnitus beyond the auditory cortex, in particular in the gamma frequency range [181]. Core regions were identified in the prefrontal, orbitofrontal, as well as some parietal and occipital areas. This has since been divided between a network of tinnitus perception per se, a tinnitus distress network, and a tinnitus modulating network [182].

2.4.2 Structural neuroimaging

Structural methods investigate the impact of tinnitus on the organisation and characteristics of the brain's hard-wiring at multiple scales. The cellular changes due to adaptation, to new stimuli or following injury or disease, in terms of size and density of neuron populations or synaptic connections, translate into larger scale brain volume or tissue density. Morphometric approaches such as voxel-based

| Study | Design | Nb. Part. | Etiol. | Phen. | Results |
|-----------------------|-----------------|-------------|--------|------------------------|--|
| Kahlbrock 2008[179] | MEG, RI | 8T | Mixed | THI 11-63, unm. HL | Slow wave spontaneous activity decreased in RI vs control. |
| Lorenz 2009 [180] | rs-MEG | 26T - 21C | ND | THQ 27+/-3.5, unm. HL | Steeper slope in the α - γ power in T vs C. |
| Weisz 2005 [103] | rs-MEG | 17T - 16C | Mixed | THQ 9-68; unm. HL | α power $\downarrow - \delta$ power \uparrow in T in temp. lobe. |
| Schoisswohl 2021 [11] | EEG, RI | 45 T | ND | THI 4-80; | No corr. btw. T charact. and EEG; |
| | | | | | T suppr.: $\uparrow \alpha$ and $\downarrow \gamma$ in the right inf. temp. gyrus. |
| Schlee 2009 [181] | rs-MEG, bf | 23T - 24C | Mixed | THQ 3 - 59; unm. HL | Cortical network: change in γ in PFC, OFC, and POC. |
| Vanneste 2016 [118] | rs-EEG; sLORETA | 129T - 129C | ND | THI: 36+/-17, unm. HL. | Effect of tinnitus in left mid-temporal gyrus: $\gamma \uparrow$; |
| | | | | ¢ * | effect of HL in parahippocampus: $\gamma \downarrow, \theta \uparrow$. |

Table 2.2: Findings from electrophysiology, see [183] for an exhaustive review. Nb. Part: number of participants; T: tinnitus; C: controls; ND: non-disclosed; THI: tinnitus handicap inventory; HL: hearing loss; unm.: unmatched; A1: auditory cortex; rs: resting-state; Etiol.: etiology; Phen.: phenotype; RI: residual inhibition; bf: beamforming; PFC: prefrontal cortex; OFC: orbitofrontal cortex; POC: parieto-occipital cortex

morphometry compare cortical thickness, surface area, or curvature. In diseases where a known cellular loss phenomenon occurs, these approaches are particularly relevant. The case of subjective tinnitus is less clear, and results from morphometric studies have been particularly diverse. Several types of structural changes have been hypothesised. Reinforcement mechanisms, due to constant perception could be hypothesised to increase grey matter volume in early sensory areas, while lack of inhibition, in disrupted gating circuits, would rather be reflected by atrophy in the relevant areas. Cortical changes, in turn, may drive structural plasticity in the white matter, for example in terms of axonal density or myelination.

2.4.2.1 VBM

VBM uses high resolution anatomical images of the brain to compare grey matter volume between individuals on a voxel-to-voxel basis [184]. Individual images are transformed into a common reference space for comparison, and tissue segmentation is performed to dissociate grey matter from white matter and cerebral spinal fluid.

In tinnitus, mixed results have been found using VBM [185]. Mülhau and colleagues [186] found grey matter volume reduction in the subcallosal areas in tinnitus participants compared to controls, but this result has not been replicated since. A decrease in grey matter volume was also highlighted by Leaver and colleagues, but in the vmPFC, which was related to a decreased inhibition, allowing hyperactivity and as a result, an impaired top-down gating mechanism facilitating tinnitus [141]. However, Landgrebe and colleagues [187] found no differences at all when controlling for hearing levels between the groups, while Melcher et al. revealed that grey matter

volume changes in the vmPFC correlated not with tinnitus but with hearing loss [188]. Changes due to hearing loss were further corroborated by Husain and colleagues [189]. In contrast, an absence of hearing-loss related differences was reported by Boyen and colleagues [190], who found instead an increase in grey matter volume in the left primary auditory cortex and a decrease of grey matter volume in the limbic system and inferior temporal gyrus due to tinnitus, aligning with the first studies. Furthermore, reduced grey matter in the auditory cortex was also found related to tinnitus distress [191]. The effect of duration of tinnitus and the level of associated distress were targeted specifically in a study by Schmidt and colleagues, suggesting that the neuroanatomy of mild recent-onset tinnitus participants is similar to that of controls. Changes, mainly found in the auditory and limbic systems, were more pronounced as duration increased, possibly indicating plasticity and habituation [192].

Arguing that small sample sizes are an important source of inconsistencies in VBM results, Vanneste and colleagues conducted a study in a larger cohort of 154 tinnitus patients using both VBM and a quantitative functional measure using EEG, [193] and found no structural changes in the cortex. They suggest that the functional changes in tinnitus are not likely reflected by co-occurring morphometric alterations, which may lack sensitivity to study tinnitus. Other authors have since further stressed the need for tinnitus sub-typing to increase the reproducibility of VBM studies [194, 195].

2.4.2.2 DWI - structural connectivity

Diffusion Weighted Imaging (DWI) makes use of the magnetic properties of water molecules [196]. In a series of T2-weighted images taken by applying opposite gradient pulses in different directions, if the water molecules are static, the signal is preserved in all directions. However, if the water molecules move in the direction of an applied gradient, this causes dephasing of the nuclear magnetic signal emitted from the water molecules and results in signal loss in the corresponding direction. Therefore, in brain regions where water molecules roam freely, the DWI signal is hypo-intense, while in regions where the diffusion of water molecules is constrained the signal is increased. In the white matter, the axons of neurons are bundled together, forcing the movement of water molecules to align with the direction of the white matter pathways. Measuring the level of constraint on the water molecules in the brain, one can infer the geometry of the white matter fibre bundles. In addition, the ability to distinguish between different orientations of fibre bundles within a given volume is directly correlated to the number of gradients applied in different directions. Typically, a minimum of 12 gradient directions is used, and 60 directions and beyond enable high angular resolution diffusion imaging (HARDI).

Diffusion Tensor Imaging (DTI), is a method developed to model the diffusion signal in each voxel [197] using a three by three symmetric matrix, where the diagonal elements are proportional to the diffusion displacement variances (also known as apparent diffusion coefficients, ADC) along the three directions of the scanner's coordinate system, and the off-diagonal elements are the covariances. By diagonalising this tensor, which allows to convert to a local coordinate system relevant to the local anatomy constraints, the eigenvalues are estimated and from them, quantitative parameters are derived. The fractional anisotropy (FA) corresponds to the normalised variance of the eigenvalues, and the mean diffusivity (MD) is the trace of the tensor. These values describe the local level of constraint exerted on the water molecules, and thus, a measure of density of the white matter. Damage to the white matter, due to injury or disease, induces a decrease in FA values, and an increase in MD in the lesion. DTI is thus effective to quantify stroke or trauma lesions. DTI has also been used to derive the main orientation of white matter fibre bundles in each voxel, supporting whole-brain tractography depicting large scale white matter organisation and structural connectivity.

White matter atlases have been proposed to describe the main fibre bundles of the brain [199, 200], based on diffusion imaging. Three major types of pathways are found in the brain. The first are the commissural pathways, connecting the two brain hemispheres. The largest bundle, often subdivided into up to 7 sections, is the corpus callosum, connecting bilateral frontal, parietal, and occipital regions. It therefore supports a wide range of functions. In contrast, the anterior commissure is

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Figure 2.18: 72 white matter fibre bundles obtained using a deep-learning algorithm [198], which we will describe in depth in chapter 3.

a small, difficult to tract, fibre bundle connecting the anterior ventral temporal lobes, and the amygdalae. Its functional role is poorly understood, although it has been suggested to play a role in pain sensation, memory, and emotion [201]. The second type of white matter pathways are known as projection tracks, linking subcortical structures to the cortex. In this category, the corticospinal tract (CST) consists of mainly motor axons travelling from the spinal chord and to the sensorimotor cortices. The thalamic radiations, on another hand, form a large fan of bidirectional fibres spanning the entire cortex [202], involved in sensory, motor, and higher cognitive functions. The fornix is another type of projection pathway, with a geometry that makes it difficult to trace reproducibly, playing an essential role in the limbic system [200]. The third type of bundles bind areas of the cortex together in associative pathways, involving long fibres as well as short, U-shaped fibres. One such example connects the areas of language processing, the arcuate fascicle, while the cingulum runs medially and supports the limbic system; the longitudinal fascicle connect the occipital cortex involved in visual function, to the temporal lobes and amygdala.

While DTI is the most prevalent method used to model the diffusion signal, its primary purpose was not to support whole brain tractography [203]. In particular,

when multiple fibre bundle directions exist in the same voxel, as in intersecting white matter pathways, it can not reliably establish those directions. This is problematic due to the large amount of overlap between the different pathways: it has been estimated that up to 90% of voxels host several fibre directions [204]. As we will develop in chapter 2, other methods have been proposed based on constrained spherical deconvolution approaches that are better able to address this issue, and may thus more reliably derive quantitative white matter connectivity measures [205–207].

In tinnitus research, the main findings derived from DWI use a tensor model (table 2.3). Reduced white matter integrity, reflected by decreased FA, was found in the left frontal and right parietal arcuate fascicle in tinnitus patients compared to controls but without controlling for hearing loss [208], as well as in auditorylimbic connections. Significant differences were found bilaterally in the connections between the auditory cortex and the amygdala [209], as well as between the left inferior colliculus and the amygdala, and between the right auditory and inferior colliculus. The left anterior thalamic radiation, superior and inferior longitudinal fascicles were found to present increased FA, thus a higher white matter density, in tinnitus participants [210]. However, some studies found no differences in white matter structure between tinnitus and control participants [189, 192].

Similarly to what has been observed in VBM, diverse results have been produced in tinnitus studies using DTI, some of which did not take hearing loss into account, and for the most part with small groups of participants, and therefore suffer from a lack of reproducibility.

2.4.3Conclusion on the neuroimaging exploration of tinnitus

Despite the wealth of studies conducted and methods used to explore tinnitus, there is a lack of convergence across the literature on tinnitus. Strikingly, we observe a lack of reproducibility of most results, across and within approach types. Each method has its specific challenges and limitations, which can be discussed and eventually addressed. We mentioned that sample sizes for example, depending on the modality,

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| Study | Design | Nb. Part. | Etiol. | Phen. | Results |
|-------------------------|------------------|--------------|--------|-------------------|---|
| Lee 2007 [208] | 24dir, DTI, FA | 28T - 12C | ND | THI ND, unm. HL | FA differences in right PAF, left FAF |
| Crippa 2010 [209] | 60dir, DTI, ROI | 10T - 15C | ND | THI ND, unm. HL | right IC-AM, right IC-AC, and bilat. AC-AM |
| | FA | | | | |
| Benson 2014 [210] | 20dir, DTI, TBSS | 13T - 13C | Noise | THQ >35 ; m. HL | Left FA increase in T in anterior TR, IFO, SLF |
| Schmidt 2018 [192] | 12-31dir, DTI, | 15+13+19+18T | ND | THI<18; | No differences in FA in any subgroup analysis. |
| | FA TBSS, | 13 + 15C | | THI>18; | |
| | subtype analysis | | | m. HL. | |
| Seydell-Greenwald [211] | 30dir, DTI, | 18T - 14C | ND | HL unm. | Corr.: age-MD, anti-corr. age-FA. in frontal areas; |
| 2014 | FA-MD TBSS | | | | Corr.: HL-FA, betw. left AC and CC. |
| | | | | | FA decrease in T in bilat. AC, IC. |
| | | | | | Corr: vmPFC FA-tinn loudness |

Table 2.3: Main structural findings using diffusion weighted MRI. Nb. part.: number of participants; Etiol.: etiology; Phen.: phenotype; dir.: directions; DTI: diffusion tensor imaging; FA: fractional anisotropy; MD: mean diffusivity; T: tinnitus; C: controls; TBSS: tract-based spatial statistics; ND: non disclosed; m.: matched; unm.: unmatched; THI/Q: tinnitus handicap inventory/questionaire; HL: hearing loss; PAF: parietal arcuate fascicle; FAF: frontal arcuate fascicle; IC: inferior colliculus; AM: amygdala; AC: auditory cortex; TR: thalamic radiations; IFO: inferior fronto-occipital tract; SLF: superior longitudinal fascicle; corr: correlation; bilat.: bilateral; vmPFC: ventro-medial prefrontal cortex.

are particularly critical for statistical power. Acquisition duration [212], amongst other parameters, and downstream processing pipelines, and registration strategies for example [213] also influence results significantly.

Beyond these specifics the reproducibility of tinnitus studies is also hindered by the heterogeneity of subjective tinnitus perception, by the difficulty of matching control participants for comparison, and by tinnitus comorbidities acting as confounding factors. Only a minority of studies provide comprehensive and explicit values of THI scores or equivalent, audiometric measures, and etiology. A recurrent observation in the last two decades of research on tinnitus was the attribution of an effect to tinnitus, and the subsequent discussion on possible confounding contribution of hearing loss, or of cochlear synaptopathy without hearing loss.

However, there is a general effort in the community to conduct studies with larger cohorts, targeting sub-types of tinnitus in terms of duration or etiology, and to standardise approaches to mitigate the remaining reproducibility issues in tinnitus research [10, 18].

2.5 Neuromodulation treatment perspectives and ongoing research

Alongside the development of exploration methods, passively measuring resting-state or task-based activity, another body of studies used neuromodulation approaches to investigate tinnitus treatment avenues.

Neuromodulation techniques aim to induce modifications to brain activity for clinical purposes using stimulation devices, starting with sensory stimuli with specific timing parameters, and ranging to invasive stimulation approaches such as deep brain stimulation (DBS). In tinnitus, the involvement of multiple cortical networks, and putative maladaptive plasticity mechanisms, although still incompletely understood, have led to the hypothesis that plastic changes driven by targeted stimulation may reverse some of the effects responsible for tinnitus. It also provides the opportunity to test the different models of tinnitus proposed in the literature.

2.5.1 Non-invasive approaches

2.5.1.1 Sensory stimulation

Sensory-based stimulation has been or is currently being conducted in tinnitus research, using mainly acoustic or tactile signals. Tinnitus retraining therapy and hearing aid combined with sound stimulation could be considered to belong to this category, but it remains unclear whether the tinnitus is being treated or simply masked. Acoustic coordinated reset neuromodulation (see [214] for a review), is a well tolerated approach that consists in transcranial sound stimulation at a frequency matching the tinnitus perception, expected to desynchronize tinnitus-related neural activity in the increased synchrony framework. Patients are required to listen to the tones for up to 6 hours a day during the protocol, in order to desynchronise the pathological firing pattern. The model was compared to two other similar approaches in [215] with EEG monitoring and while tinnitus was alleviated (decrease in Tinnitus Loudness and Tinnitus Annoyance scores) in all cases, there is evidence that the electrophysiological effects (decrease in delta and gamma power and increase of alpha power in the auditory cortex) and clinical relief duration were most significant

in the acoustic coordinated reset neuromodulation method. The drawbacks of the method are described in [214], pointing out that clinical implementation is not yet possible due to lack of strong evidence. Combined auditory and somatosensory (through electrodes placed on the skin) stimulation has shown tinnitus reduction in humans with a specific type of somatosensory tinnitus (that modulates with certain physical manipulations) [156]. [156] also describe a lack of influence of the sole use of auditory stimulation, and a duration of symptom relief that does not outlast the treatment period. Further bi-modal stimulation using tongue stimulation and listening to tones, with matching of frequencies, have produced significant results in after treatment compared to before-treatment tinnitus status [110]. However, there is a lack of across groups effects, meaning that the effect may be related to the natural average evolution of the symptom, or to a degree of placebo effect. Mielczarek and colleagues explored direct electrical stimulation of the ear, which seems to give good results in a subgroup of tinnitus patients [216].

2.5.1.2 Transcranial magnetic stimulation

In repetitive transcranial magnetic stimulation (rTMS), a coil is placed on the surface of the scalp in line with the cortical target of interest and delivers electromagnetic pulses to that target [217]. The depth of penetration largely depends on the geometry of the coil, and the observed effect depends on the frequency of pulse delivery. To date, the penetration depth is limited to 2-3cm, which leaves the auditory cortex essentially out of reach. Low-frequency rTMS has been shown to be inhibitory, and is therefore relevant with respect to the hypothesis of tinnitus as a symptom of cortical hyperactivity. Indeed, certain studies report tinnitus relief correlating with an rTMS-related increase in alpha power in the auditory cortex [218], in line with the electrophysiological correlates of tinnitus proposing alpha band desynchronisations. Several studies have shown a positive effect of rTMS on tinnitus perception by targeting the temporal lobe [219, 220]. Some clinical trials have proposed to target in addition to the temporo-parietal lobe a selection of frontal and prefrontal areas [221], with temporary tinnitus alleviation results.

2.5.1.3 Transcranial electrical stimulation

Similarly to rTMS, transcranial electric stimulation aims to modulate brain activity by applying current on the scalp surface. In this case, three options are available.

Direct current stimulation or tDCS consists in applying a weak constant current through electrodes placed on the scalp. Under the cathode, hyperpolarisation of neurons occurs, while under the anode, depolarisation takes place. These phenomena control the excitation or inhibition properties of the stimulation paradigm [222]. Tinnitus was successfully suppressed in up to 40% of participants by placing the anode over the temporoparietal area and the cathode over the dorsolateral prefrontal cortex [223, 224]. Again, although the alleviation was successful, it was transitory, and progress stagnated after 6 sessions.

Alternating current stimulation (tACS) acts similarly to tDCS, but using alternating current for which the frequency can be used as a parameter to optimise stimulation. Regarding tinnitus, the alpha, beta, and gamma bands were proposed to play a particular role and are thus relevant frequencies to test using tACS. However, no significant effect of tACS on tinnitus has been found to date [225].

Random noise stimulation (tRNS) in contrast to tACS uses random oscillations of the stimulation current, with the aim to disrupt increased synchrony in the auditory cortex as posited in certain models. Vanneste and colleagues [226] showed an increased effect on tinnitus loudness reduction of tRNS compared to tDCS, with electrodes placed bilaterally on the auditory cortices. Combining tRNS on the auditory cortex with tDCS in the frontal areas has shown further improvement of the effect [227]. Joos and colleagues showed an influence of the frequency bands used in the random noise spectrum on both tinnitus loudness reduction, and tinnitus distress reduction [228]. Further studies are investigating the pairing of tRNS with auditory stimulation (see for example, clinical trial NCT04551404).

2.5.1.4 Neurofeedback

Neurofeedback is based on a feedback through visual or auditory cues of the real time neural activity measured by fMRI or EEG to the participant, during task performance. The participant is required to fulfil the task, while controlling the levels of activity to the target cortical region. A reward is given if the cortical activity is changed as instructed, and penalised if unwanted changes occur. In tinnitus, an increase in alpha band oscillations only, as well as in alpha increase combined with delta decrease have correlated with tinnitus distress scores improvements [183, 229, 230]. Recently, an individualised neurofeedback protocol was able to maintain lowered levels of tinnitus related distress scores up to 6 months following the protocol. However, tinnitus loudness returned to baseline levels after the protocol was completed by the participants [183]. Using fMRI, while the protocol has been validated and holds promising perspectives, tinnitus perception alleviations have not yet been evidenced [231].

2.5.1.5 Vagus nerve stimulation

Vagus nerve stimulation (VNS) is a stimulation technique, whereby electrical impulses are delivered to the vagus nerve by a device implanted below the skin, or placed on the surface of the skin [232]. The vagus nerve is a major component of the autonomous nervous system and plays a role in maintaining metabolic homeostasis. Its main clinical indications today are epilepsy and depression, but positive outcomes have been found when using cross-modal stimulation. Pairing VNS with motor function has driven motor cortex modifications, and improves post-stroke recovery [233]. VNS paired with sensory stimuli helps restore function after injury [234] and has been shown to act on limbic and emotional pathways.

Effects of VNS on brain activity, and in particular in relationship to tinnitus, have been found using neuroimaging in the thalamus, hypothalamus, cerebellum, medulla, orbitofrontal cortex and limbic system. Deactivations of the auditory cortices and activations of somatosensory regions, possibly including OP3, were found [235], when comparing different locations on the external ear for transcutaneous VNS. This highlights an auditory - somatosensory integration process, which is disrupted during VNS, arguing in favour of the presence of a somatosensory-auditory integration process.

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This somatosensory-auditory integration process, as well as the contribution of the autonomous system, is a key element of the proprioceptive tinnitus illusion model. A dual VNS-auditory stimulation approach is thus of particular interest for future work within this framework.

2.5.2 Invasive approaches

Invasive stimulation in tinnitus is rare, because brain surgery is not usually approved for tinnitus. Most cases of invasive tinnitus exploration are thus coincidental, cooccurring with diseases that do require extensive, invasive exploration, such as Parkinson's disease or epilepsy. Brain surgery for electrode implantation to treat tinnitus has only been proposed for intractable tinnitus - both psychologically and audiologically - as a last resort for very few, highly distressed patients.

2.5.2.1 Intracranial stimulation

A few studies have published case reports of cortical stimulation targeting solely tinnitus. De Ridder and colleagues proposed the case of a single tinnitus patient suffering from sudden deafness following injury to the acoustic nerve due to surgical removal of a tumor. The tinnitus perception started some time after the surgery, and activity in the auditory cortex contralateral to the side of injury was evidenced using fMRI. The patient responded to a TMS protocol to the contralateral auditory cortex, and thus an electrode was implanted extradurally for additional direct stimulation of the auditory cortex, causing the tinnitus to disappear for three weeks. Due to plastic readaptation, the tinnitus reappeared after that period of time [236]. In a follow up study, the authors suggest that recent onset, pure tone, unilateral tinnitus are particularly relevant candidate profiles for surgery and electrode implantation. Subcutaneous stimulation in addition to cortical stimulation was proposed to mitigate the effect of plasticity, and ensure longer relief from tinnitus: this was the case for the reported patient, who had reduced tinnitus for at least five years [237]. The anterior cingulate, involved in tinnitus distress, was also targeted in two patients, using extradural implants. One patient sustained significant tinnitus loudness and

distress reduction for two years, while the other reported no improvement [238]. It was found that the responding patient had increased functional connectivity between the implanted area and the parahippocampus and the insula compared to the non-responding patient. This result further stresses the point that tinnitus, in all degrees, is highly heterogeneous and may require extensive functional examination, using fMRI combined with non-invasive stimulation, prior to stimulation protocols to establish whether a patient is likely to respond to invasive stimulation.

2.5.2.2 Deep brain stimulation

Deep brain stimulation refers to stimulation delivered directly to deep brain nuclei or cortical structures.

Retrospective analysis of DBS outcomes in patients with coincidental tinnitus was evaluated using a survey, whereby patients who had undergone DBS surgery and stimulation were asked if they had noticed an impact on their tinnitus perception, if applicable [239]. 443 questionnaires were returned, and a control group was defined by 61 matched participants who had tinnitus but did not undergo DBS treatment, to account for natural course of tinnitus symptom evolution. They compared different DBS targets, which were guided by a clinical interest independent of tinnitus. Only the subthalamic nucleus provided evidence of a possible beneficial effect on tinnitus.

Case studies of tinnitus alleviation occurring during DBS surgery have also been documented, and in particular the area LC, situated between the head and the body of the caudate nucleus, was found to alleviate tinnitus [240] and to trigger controllable auditory percepts, leading to a clinical trial targeting this area specifically in tinnitus [241]. To date, preliminary results have determined that out of five patients who underwent the full protocol, three responders were identified.

2.5.3 Conclusion on neuromodulation in tinnitus

Neuromodulation techniques provide a unique opportunity to test the hypotheses existing in the literature to explain tinnitus. There is evidence that in some cases, brain stimulation is an appropriate treatment option for tinnitus. However, the same protocols also provide the evidence that what might work in one case, proves ineffective in another case. This underlines the need for more precise sub-typing of tinnitus perception and subsequent individualised protocol parameters or target definition. Another difficulty which remains is to establish treatment outcomes based on the subjective evaluation of the patient. Additionally, due to the exploratory nature of most of these neuromodulation approaches, sample sizes are small, and results may prove difficult to reproduce later. In the designs, placebo controls are not always possible and therefore it becomes difficult to assess whether any effect is truly caused by the treatment. There is a need for double blind placebo controlled study designs to provide validation of the preliminary, promising results from the pilot studies.

2.6 Main research problem statement and work hypothesis

In line with current recommendations across all fields of tinnitus research, we chose to limit the scope of this thesis to noise-induced tinnitus of acoustic trauma origin, specifically targeting participants with levels of tinnitus qualifying as non-bothersome.

We hypothesise that somatosensory processes come into play in this particular tinnitus sub-type, and that OP3 mediates these processes by integrating proprioceptive information from the middle ear muscles and sound features originating from the primary auditory pathway.

From a non-invasive neuroimaging perspective, we will investigate this hypothesis under the angle of functional and structural connectivity, with an emphasis on OP3.

From the perspective of high frequency stimulation and intracranial recordings, we will compare different phantom auditory perceptions in a direct electrical stimulation protocol, which will inform us on the spatio-temporal dynamics in the nuances that distinguish auditory hallucinations from illusions, and examine the role of OP3 in each perception.

From the perspective of cortico-cortical evoked potentials, we will investigate the functional connectivity from OP3 derived, as provided by the fTRACT project.

2. State of the art

Finally, we propose to validate the role of OP3 in a pseudo-tinnitus illusion, by adapting the induction protocol for participants undergoing intracortical exploration, to gain some direct insight into electrophysiological correlates of tinnitus.

3 Methods

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As highlighted in the previous chapter, the exploration of tinnitus is a difficult task, and part of the inconsistencies in literature findings can be linked to methodological issues such as participant selection, study design, data acquisition, and processing. During this thesis, our research question was investigated through two main avenues of exploration, in neuroimaging and electrophysiology, each respectively divided into two and three studies with a specific goal. The aim of the non-invasive approach (chapter 4) was to determine a functional network and its structural underpinnings in chronic, non-bothersome, noise-induced tinnitus. To do so, we used resting-state BOLD fMRI and region-of-interest based pairwise signal correlations, and we quantified, using diffusion MRI, the ability of fibre bundles to convey information between these regions-of-interest. In the invasive section (chapter 5), we sought to establish the neural signature in the parietal operculum of auditory phantom perceptions analogous to tinnitus. First, we investigated the network of regions underlying auditory hallucinations and illusions evoked by direct electrical stimulation (DES). Then, we examined the connectivity of OP3 and surrounding regions elicited through cortico-cortical evoked potentials (CCEP) in response to low-frequency stimulation. Finally, in an unprecedented study, we explored the role of OP3 in a protocol using acoustic stimulation to induce a transient tinnitus-like perception.

Despite a different finality across studies, some challenges were common to all studies: in each case, a study design was constructed and study participants were recruited accordingly. In the non-invasive studies, the main challenge was (i) to ensure group homogeneity within tinnitus participants and matching between tinnitus and control participants, (ii) to optimise MRI acquisition parameters, and (iii) to avoid merging signals belonging to different spatial areas, in particular in close anatomical areas. In the invasive SEEG studies, group biases typically documented in tinnitus were not an issue since all perceptions were induced, using direct electrical stimulation or sound stimulation, in participants with no tinnitus. Instead, a major aspect to address was the intractable epilepsy that the participants were initially undertaking invasive recordings for. Methodological challenges arose in each case, at different levels, and were specific to each exploration method. Common too all, however, was the underlying requirement for high spatial resolution to investigate a region such as OP3, with a volume in the order of 2.5 cm³. Methodological choices and trade-offs were thus oriented with respect to these objectives.

3.1 Study participants

3.1.1 MRI studies

3.1.1.1 Ethical aspects and funding

The MRI studies presented in this thesis were conducted on data acquired over a two year period between 2014 and 2015 within the same protocol, which was approved by the Local Ethics Committee CPP Sud-est V, Ref: 10-CRSS-05 MS 14-52, and conducted in accordance with the Declaration of Helsinki. The use of the dataset was approved by the ethical committee and all the concerned participants signed the informed consent form. Funding for these studies was provided by French government grant number PDH1-SMO-3-0811 (Dr Agnès Job).

3.1.1.2 Tinnitus participants group homogeneity

Study participant characteristics are detailed in chapter 4 and in the corresponding article [242]. Here, additional justification is provided as to why this specific target population was chosen.

The study was specifically focused on tinnitus of acoustic trauma origin in military participants undertaking specific shooting training, for the reasons mentioned in the introduction and state of the art chapters. However, a risk of occupational bias was identified in the exclusive recruitment of tinnitus participants among the military. Thus, 7 out of 19 tinnitus participants were recruited based on tinnitus origin relating to noise trauma in the workplace other than military, and music related acoustic trauma, while one participant had suffered acoustic trauma following rifle use but was not a military professional. However, sub-typing according to etiology was not sufficient, since tinnitus comorbidities, such as anxiety and depression, rapidly develop if the coping mechanisms are overwhelmed and no longer enable good quality sleep, fulfilling social interactions or speech comprehension. The study population was thus further narrowed down to tinnitus of low intensity, assessed using the tinnitus handicap inventory (THI) (figure 3.1) [105].

THI scores between 0 and 16, or grade 1 tinnitus, correspond to *slight* tinnitus, where the perception is only present in a quiet environment, is easily masked and does not interfere with daily life or sleep. Between 18 and 36, or grade 2 tinnitus, the score is considered *mild*, meaning that it is easily masked by environmental sounds, and forgotten when not paid attention to. However, it may occasionally cause sleep difficulties. Between 38 and 56, grade 3 tinnitus is considered *moderate*, and is noticed even in presence of background noise but does not prevent daily activities. *Severe* tinnitus corresponds to THI scores between 58 and 76, or grade 4, when the perception is almost always present, rarely masked by sound environment, and daily life, especially quiet activities, is disturbed. Grade 5 tinnitus, or *catastrophic* tinnitus, causes sleep disruption, and significant daily life impairment.

In the present study participants, THI scores ranged from 4 to - in one case - 44, with an average score of 16.2 ± -10.5 . In other words, the tinnitus was slight to mild for all participants save one who had moderate tinnitus. All tinnitus participants described their tinnitus as high-pitched whistling, except for one who described a medium high-pitched sizzling. Tinnitus loudness was additionally scored on an analogue visual scale (mean 4.5 ± 1.6 ranging from 2 to 8, from a total possible range 0-10). Bilateral tinnitus represented 68% of the group, and the same amount of right and left tinnitus was observed. From the perspective of tinnitus etiology and intensity, the group was thus considered homogeneous.

TINNITUS HANDICAP INVENTORY

| Patier | t Name: | Dat | te: _ | | | |
|---------------------|--|-----------------|-----------------|-----------------------------|--------------|----------------------------|
| INSTI becau | CUCTIONS: The purpose of this questionnaire is to identify difficulties that y se of your tinnitus. Please answer every question. Please do not skip any qu | ou ma estion | y be s. | e expe | rier | ncing |
| 1. | Because of your tinnitus, is it difficult for you to concentrate? | Yes | So | metime | es | No |
| 2. | Does the loudness of your tinnitus make it difficult for you to hear people? | Yes | So | metime | es | No |
| 3. | Does your tinnitus make you angry? | Yes | So | metime | es | No |
| 4. | Does your tinnitus make you feel confused? | Yes | So | metime | es | No |
| 5. | Because of your tinnitus, do you feel desperate? | Yes | So | metime | es | No |
| 6. | Do you complain a great deal about your tinnitus? | Yes | So | metime | es | No |
| 7. | Because of your tinnitus, do you have trouble falling to sleep at night? | Yes | So | metime | es | No |
| 8. | Do you feel as though you cannot escape your tinnitus? | Yes | So | metime | es | No |
| 9. | Does your tinnitus interfere with your ability to enjoy your social activities (such as going out to dinner, to the movies)? | Yes | So | metime | ∋s | No |
| 10 | Because of your tinnitus, do you feel frustrated? | Yes | So | metime | ∋s | No |
| 11. | Because of your tinnitus, do you feel that you have a terrible disease? | Yes | So | metime | es | No |
| 12 | Does your tinnitus make it difficult for you to enjoy life? | Yes | So | metime | ∋s | No |
| 13. | Does your tinnitus interfere with your job or household responsibilities? | Yes | So | metime | es | No |
| 14 | Because of your tinnitus, do you find that you are often irritable? | Yes | So | metime | es | No |
| 15. | Because of your tinnitus, is it difficult for you to read? | Yes | So | metime | es | No |
| 16 | Does your tinnitus make you upset? | Yes | So | metime | es | No |
| 17. | Do you feel that your tinnitus problem has placed stress on your relationships with members of your family and friends? | Yes | So | metime | ∋s | No |
| 18. | Do you find it difficult to focus your attention away from your tinnitus and on other things? | Yes | So | metime | es | No |
| 19. | Do you feel that you have no control over your tinnitus? | Yes | So | metime | ∋s | No |
| 20 | Because of your tinnitus, do you often feel tired? | Yes | So | metime | es | No |
| 21 | Because of your tinnitus, do you feel depressed? | Yes | So | metime | es | No |
| 22 | Does your tinnitus make you feel anxious? | Yes | So | metime | es | No |
| 23 | Do you feel that you can no longer cope with your tinnitus? | Yes | So | metime | es | No |
| 24 | Does your tinnitus get worse when you are under stress? | Yes | So | metime | es | No |
| 25 | Does your tinnitus make you feel insecure? | Yes | So | metime | es | No |
| | | FOR | CLIN | | JSE | ONLY |
| | Total Per Column | | | | | |
| | | x4 | | x2 | | x0 |
| | Total Score | | + | | + | |
| Newman, Handicap | C.W., Jacobson, G.P., Spitzer, J.B. (1996). Development of the Tinnitus Inventory. Arch Otolayngol Head Neck Surg. 122, 143-8. | To inter | pret tł Seve | ne score pl rity Scale s | ease howr | refer to th 1 on the re |

Figure 3.1

In addition, plasticity mechanisms have been suggested to operate at different time-scales starting from the onset of tinnitus [142, 175]. Acute phases, defined as the first 6 months of tinnitus perception [8], are hypothesised to be followed by habituation phenomena which may or may not revert to baseline, or absence of tinnitus. In chronic tinnitus, the habituation has generally contributed to diminishing the intensity of tinnitus compared to the acute phase. In order to avoid mixing phenomena pertaining to acute phases with those of habituation, inclusion criteria for the present studies thus explicitly required a minimum tinnitus duration of six months (mean 12.2 ± 7.3 years, range 0.5 to 25 years).

3.1.1.3 Matching of control participants

A recurrent issue in tinnitus literature relates to mismatched control participants, in particular in terms of hearing loss since this symptom often co-exists alongside tinnitus[243]. If no audiologic examination is conducted or if controls are not matched with tinnitus participants in levels of hearing loss, there is a risk that the results may reflect altered connectivity pertaining to hearing loss instead of tinnitus. In the present fMRI and DWI studies, as mentioned in the introduction, a control group could have been recruited among military participants without tinnitus. However, it was observed that military participants were less likely to inform on the presence of a slight tinnitus perception.

Thus, control participants were chosen in the non-military population, and were exactly matched in age (mean 42.5 ± -11.9) with the tinnitus group. Hearing levels were evaluated and were not different in the frequencies below 1kHz, however tinnitus participants presented significantly heavier hearing loss in the higher frequency range (Mann-Whitney test, p<0.05), as is typically observed in acoustic trauma (figure 3.2). This remaining difference is thus an identified source of bias, which was taken into account in the statistical analysis using regression models.



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Figure 3.2: Hearing loss in dB averaged in each group, with no significant differences in frequencies below 4kHz

It is noteworthy that at the frequency of the peak of the MRI scanner sequence noise in the acquisition sequences, no difference in hearing performance was found between the two groups, thus ruling out the possibility that differential structural or functional connectivity arose from differences in acoustic perception related to scanner noise (see figure 3.4, section 3.2.1).

3.1.2 Stereo-EEG studies

3.1.2.1 Ethical aspects and funding

All studies were conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of INSERM (protocols INSERM IRB 14-140, DRCI 1325: EPISTIM study, ID RCB: 2017-A03248-45: MAPCOG study).

For the intracranial functional connectivity of OP3 study, the research underlying the F-TRACT project received funding from the European Research Council under the European Union's Seventh Framework Programme (FP/2007-2013) ERC Grant Agreement no. 616268 F-TRACT, from the European Union's Horizon 2020 Framework Programme for Research and Innovation under Specific Grant Agreement No. 785907 and 945539 (Human Brain Project SGA2 and SGA3), and from a Grenoble-Alpes University Hospital grant.

The research underlying the tinnitus after-effect through acoustic stimulation study was supported by a grant from the Foundation pour l'Audition.

The funders had no role in the design of the studies; in the collection, analyses, or interpretation of data; in the writing of the manuscripts, or in the decision to publish the results.

3.1.2.2 Epileptic participants

The intracortical work described in this PhD was conducted in participants whose primary consultation motive was pharmacoresistant and focal epilepsy. The acquisitions for the 50 Hz DES study of auditory evoked responses, and the tinnitus-like after-effect acoustic stimulation study were performed at the Epilepsy Laboratory of the Grenoble University Hospital, where patients who suffer from drug resistant focal epilepsy are offered intracortical exploration prior to surgical removal of the brain region causing the emergence of the epileptic seizures. For the exploration of the intracortical functional connectivity of OP3, participants were included as part of the F-TRACT data collection consortium, a multicentric collaboration ranging across 25 epilepsy centres in France, Europe, North America and China (Appendix A).

Prior to surgery, an exploration is conducted to determine the location of the epileptogenic zone, based first on semiology, or patient history of the condition and symptoms, and on electroencephalographic monitoring. Then, in accordance with the major findings of this first stage exploration, electrodes are implanted stereotactically in the brain, monitoring with high temporal and spatial resolution the patient's cortical activity, for up to ten days maximum due to increased infection risks beyond this limit.

The intracortical exploration phase has two major objectives. On one hand, to monitor the onset and extent of spontaneous seizures during the patient's stay at the facility. Additionally, low frequency DES have been found to elicit epileptic activity when performed in epileptogenic areas: this approach has been found of clinical relevance to help mimic and map the patient's spontaneous seizures. The recordings of all attempts which did not yield seizure activity provide healthy brain function information, which the F-TRACT project has undertaken to gather (see chapter 5 and f-tract.eu).

On the other hand, high frequency DES has been found to elicit symptoms which can be used to determine functionally eloquent areas to be spared during surgery: this also informs on functional brain organisation, which is the core component of the 50 Hz DES evoked auditory responses study [244]. Functional mapping can also be achieved using intracranial monitoring during task completion, as we further describe in the third study targeting a tinnitus-like after-effect.

The intracranial framework for intractable epilepsy exploration thus provided us with three different angles to gain first hand insight into the functional properties of OP3. In the comparison study of hallucinations and illusions, 50 participants were retrospectively selected and included according to clinical needs of surgery due to intractable epilepsy, and for whom 50 Hz DES was found to elicit auditory symptoms. Symptoms were retrospectively established based on the video recordings of the stimulation sessions, where patients comment on their perceptions. A detailed summary of all participants, epileptic features, and evoked symptoms is documented as part of the article submitted, and presented in chapter 5.

The invasive connectivity study of OP3 builds upon an extensive body of prior analyses of multicentric recordings from over 1000 patients were gathered. All participants underwent low frequency stimulation protocols (<5 Hz) yielding corticocortico evoked potentials, and structural imaging to enable functional mapping on anatomical parcellations. Anonymised data were transferred to the F-TRACT database in accordance with the INSERM's international review board requirements. Additional information on participant data is available at f-tract.eu, and in Jean-Didier Lemaréchal's thesis work [245].

Finally, in the tinnitus-like perception study, inclusion criteria specified that participants present at least one electrode in the parietal operculum, or alternatively one electrode contact in the auditory cortex. 7 patients have been included thus far and have fully completed the experiment, with a total recruitment objective of 15 patients.

3.2 Data acquisitions

Detailed acquisition parameters are documented in the articles and sections of the following chapters. Here, we review some specific aspects of data acquisition, which were not mentioned in the articles, but contributed to the study design, limitations, or methodological choices.

3.2.1 MRI studies

3.2.1.1 MRI sequence optimisation: scanner noise management

In an exploration of individuals with chronic tinnitus as conducted in the present MRI studies, scanner noise management was a major issue, with a potential risk of tinnitus perception worsening after completion of MRI acquisitions. The duration of the exposure is another critical point, where a trade-off was required, especially for the BOLD fMRI sequence, where duration is a crucial parameter for reproducibility.

Noise levels in the scanner

Scanner noise in MRI studies, which originates mainly from dynamically created magnetic field gradients, is an issue when studying the auditory system in general, and increasingly so in the case of tinnitus, for two reasons. First, the noise exposure in participants with preexisting tinnitus is a risk of tinnitus aggravation. Secondly, in the case of mild tinnitus perception, the noise of the scanner may mask the tinnitus altogether. There was thus a need for evaluating and optimising the MRI sequences to make them comfortable and risk-free.



Figure 3.3: Gradient commutation illustration. The pulses of current in the gradient coils for the spatial encoding of the signal cause mechanical vibrations of the gradient coil surfaces and surrounding structures. The pressure variations in the centre of the MR scanner produces an acoustic pressure wave and sound. The sound intensity is directly related to rise and fall times, or rate of change. By decreasing the slope of the gradient commutation, the acoustic noise is reduced.

The two main leverage options, while maintaining sufficient acquisition quality, were to diminish the intensity of the peak of noise of the sequence, and to reduce the intensity of the high frequency harmonics, which are a major source of auditory discomfort. For the diffusion sequence, the peak noise intensity was already optimised, and the sequence was not further modified. For the BOLD fMRI sequence, several adjustments were implemented at the 3T IRMaGE facility in Grenoble. The main effect was obtained as described in figure 3.3, by lowering the slope of the gradient commutation, and smoothing the angles of the trapezoidal gradient waveform.

The evaluation of the observed noise levels could not be performed using regular microphone devices, because the intensities involved caused the devices to saturate. Therefore, the C.S.T.B (Centre Scientifique et Technique du Bâtiment) specialising in the characterisation of noisy environments of Grenoble was hired to evaluate the noise levels inside the scanner during acquisitions. It is noteworthy that in all cases, participants wore double ear protections (ear plugs and headphones).



Figure 3.4: Measured sound intensity variation with gradient frequencies per acquisition type. The peak intensity for DTI (yellow) and the optimised resting-state (orange) is lower and shifted compared to standard resting-state (blue) acquisitions.

For the standard BOLD fMRI sequence, a peak was measured at 116 dB for 1000 Hz, which roughly corresponds to the sound of industrial high power fire alarms, or certain rock concerts. At 20000 Hz, at the limit of the audible spectrum, the noise intensity remained at 75 dB, which is an extremely loud and high pitched noise. These elements quantify the level of auditory discomfort potentially experienced in the scanner during standard fMRI acquisitions.

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For the adjusted BOLD fMRI sequence, the peak level was found at 106 dB at 630 Hz, thus both lower in intensity and in frequency. Owing to the logarithmic scale, the noise level was thus divided by 8. Furthermore, the noise level dropped after the peak, and the sequence was silent in the 20000 Hz range.

For the diffusion weighted sequence, the peak was similar to that of the adjusted BOLD sequence, and although the high frequency noise was louder, the sequence was considered acceptable in terms of noise intensity by all participants. Additionally, ear protections consisting in ear plugs and headphones were worn by participants during all acquisitions.

3.2.1.2 MR sequence optimisation: scan duration

Scan duration is another factor contributing to noise exposure during an MRI sequence. In the case of BOLD fMRI, there exists a direct relationship between acquisition duration and robustness of downstream functional connectivity measurements. Since the signal in fMRI is largely dominated by physiological noise such as cardiac and respiratory activity, longer scan duration enables more comprehensive denoising of these components. Furthermore, the signal of interest in resting state fMRI, the low frequency spontaneous fluctuations, is located below 0.1 Hz, which can be captured over 10 seconds. Therefore, with a repetition time of 2 seconds, the question of how many timepoints are required to robustly capture physiologically significant correlations between these slow varying signals is relevant. In a study of several scan lengths between 5 and 20 minutes, Birn and colleagues demonstrated that test-retest reliability of fMRI functional connectivity was best at 13 minutes, and plateaued afterwards [162]. In a subsequent study, Termenon and colleagues further demonstrated the influence on test-retest reliability of both scan length and sample sizes, and highlighted that quantitative metrics derived from fMRI were most reliable with groups larger than 40 subjects and a scan duration in the order of 14 minutes. Here, scan duration was set at 13,5 minutes, and 38 participants were included.

In diffusion weighted MRI, scan length depends on the chosen number of gradient directions, which itself conditions the angular resolution of the acquisition. In the present case, the study aim was to investigate structural connections around OP3 and therefore perform tractography. Thus, an acquisition with 60 directions was chosen, yielding a scan duration of approximately 10 minutes.

3.2.1.3 MR Scanner upgrade and modification of DWI acquisitions

During the course of the MRI protocol acquisition period, the MRI scanner software was upgraded, which motivated some amendments to the diffusion sequence. In particular, the acquisition of a new fieldmap image was implemented, useful for geometric distortion correction of the spin-echo echo-planar images.

The geometric deformations in diffusion weighted imaging are due to susceptibility induced off-resonance fields, and the distortions manifest particularly in the phase encode direction of the image. This causes a mismatch between the diffusion image and the anatomical scan. In order to map the quantitative diffusion properties measured during the examination to the correct anatomical brain region, the correction of this geometric distortion is required. In addition, state of the art tractography methods require the knowledge of the white-matter to grey-matter interface, to constrain the location of fibre tracts beginning and end regions. This step can only be performed if the anatomical and diffusion images are correctly aligned. The correction of the distortion due to the off-resonance fields involves the estimation of a deformation field, or warp, which is applied to the diffusion-weighted images and yields unwarped images, which are back in alignment with the anatomy of the subject.

For the first fifteen participants, a single non-diffusion scan at b=0s/mm² was acquired, followed by 60 images taken with different gradient directions at b=1000 s/mm². An additional fieldmap image was acquired using two different echo times. For these acquisitions, the preferred method to estimate the voxel displacement map was to use the acquired fieldmap image, as available in the SPM FieldMap module. For the remaining participants, the same 60 directions were acquired, with additionally two b=0 s/mm² acquisitions with opposite phase-encode directions. In this case, the preferred method was to estimate a fieldmap using FSL's TOPUP tool,

3. Methods



Figure 3.5: DWI geometric distortion correction. Two b=0 images of the same subject (top), acquired with reversed phase encode directions, present different geometric distortions, compared to the subject's anatomy. The difference between the two distortion patterns is used to generate an estimated fieldmap in FSL, responsible for the deformation patterns during the acquisition (right). From this fieldmap, a deformation field is computed and applied to the remaining 60 volumes in the acquisition. Alternatively, the fieldmap can be acquired directly during the sequence, and used as input in phase and magnitude format in SPM's Fieldmap tool.

and to use this for subsequent warping of the distorted images. This was identified as a risk of introducing a processing bias due to different preprocessing methods applied within the study population, and we questioned the best way to limit this bias.

A workaround was found based on the generation using 3D U-Nets of an undistorted b=0s/mm² realigned with the anatomical image [246]. Thus, state of the art correction methods were subsequently applied homogeneously across the entire group, as is further detailed in paragraph 3.4.

3.2.2 Stereo-EEG Studies

As mentioned in the 'Participants' section, the SEEG data used and collected in this thesis belong to three different studies.
3.2.2.1 Brain mapping of DES-induced auditory hallucinations and illusions

Auditory symptoms are a prevalent effect of 50 Hz DES in a number of superior temporal regions, but as we further discuss in chapter 5, have occasionally been found elsewhere in the brain. In this study, the objective was to perform a precise brain mapping of all auditory symptoms elicited in a large cohort of 50 participants, and to investigate two major symptom categories. On one hand, illusions, or the modulation of an existing auditory input. On the other hand, hallucinations, or the perception of a sound without a corresponding source. Our major interest with respect to the present thesis was to investigate the role of OP3 in this functional mapping of auditory symptoms. Acquisitions are detailed in chapter 5. Briefly, a total of 141 stimulations were performed, across 50 individuals, with recordings from 2610 cortical sites. All implantations were guided by clinical needs, agnostic of any additional research question. Implantations were mainly unilateral (11 right-sided, 24 left-sided), and bilateral in 16 cases. MRI scans were performed prior to implantation, and following implantation, allowing precise registration of electrode contacts to anatomical regions. Signals, voltages measured between a target point and a reference contact, were referenced against a signal measured in the white matter. For analysis, however, a bipolar montage between adjacent contacts was chosen, since it improves sensitivity to local current generators. During acquisitions, patients were asked to describe any symptoms as soon as they arose, and were carefully examined by the observer.

3.2.2.2 Intracortical connectivity derived from CCEP

In this study, the main objective was to establish the electrophysiologic connectivity profile of OP3, and to compare it with literature findings, as well as our own findings in functional and structural MRI connectivity. This electrophysiologic connectivity is based on the CCEP recordings gathered within the scope of the F-TRACT project, performed at low frequency, with inclusion criteria specifying stimulation frequencies below 5 Hz (mainly 1 Hz). The F-TRACT project is an ongoing project, with regular updates of the atlas according to methodological implementations and data contributions.

In the work presented in this thesis, the version of the F-TRACT project used was based on a total of 32805 low frequency stimulations recorded, ranging across an average of 110 anatomical regions for each recording, resulting in a total amount short of 4 million cortico-cortical evoked potentials, with a near complete spatial coverage of the brain (figure 3.6). The inhomogeneous distribution of contacts and stimulations across the brain is the result of the clinical indication leading to these data, and of a higher representation of temporal lobe epilepsy for example.



Figure 3.6: Distribution of electrode contacts from all the recordings included in the F-Tract database, with stimulation contacts on one hand (A) and recording contacts on the other (B), taken from Jean-Didier Lemaréchal's thesis, completed in 2020. The two histograms highlight the right entorhinal cortex, presenting the highest contact density for stimulation (A), and recording (B). The most frequently explored regions are the hippocampus, lateral superior temporal lobe, and insula. [247]

With 1 Hz stimulations, cortical responses can be observed during a relatively long time interval in the range of a second, with the stimulation artefact usually visible for only a few miliseconds, allowing for the brain to resume baseline activity between pulses. The repetition of the pulses enables the functional mapping of regions involved in the epileptogenic zone and beyond.

3.2.2.3 Analysis of intracortical responses to a tinnitus-like perception

This study was designed in early 2020, and the first patient was included in October 2020. The rate of patient inclusions had been estimated at two per month, for a total aim of 15 patients for the exploration. However, all inclusions were interrupted during the pandemic, and therefore, inclusions for this study are still ongoing and at a slower frequency.

In this ongoing study, no electrical stimulations were performed. Instead, the protocol involved 6 repetitions of two 3 minute long listening tasks and a 30 second silent interstimulus interval where participants were asked to focus on any hearing experiences that might occur. Both stimuli were series of impulses, like clicks, at different rates. One stimulus presented a 30 Hz impulse rate, and was expected to generate an auditory after-effect, while the other, at 8 Hz, generated no after-effect and thus acted as a control stimulus. The design for this protocol was configured in EPRIME, with sound intensities for each stimulus set so as to ensure equal acoustic energy delivery, as documented in [21]. Stimuli are available for listening in the supplementary materials of [21]. During the acquisitions, a trigger was defined at the beginning and end of each listening task, at the end of the 30 seconds silent period, and a baseline trigger was defined for each stimulus. Thus, the labels corresponding to each event type were embedded in the recordings, and used in downstream analysis.

3.3 Data processing

3.3.1 MRI studies

3.3.1.1 fMRI processing

In this section, we emphasise two aspects of the pre-processing performed for the functional study [242], which were particularly relevant to the question at hand. We also underline the effort made in this study for the sake of reproducibility.



Figure 3.7: Organisation of the processing steps required for the processing of fMRI data. For each participant, the 3D anatomical image is segmented into cortex, white matter, cerebrospinal fluid and skull (respectively from left to right below 'Anatomical segmentation'), then white matter and grey matter are transformed to standard space using DARTEL diffeomorphic warps. The functional 3D images are taken throughout a 13 min long time-course and first need to be realigned with each other. Then, because each slice within the 3D volume is acquired at slightly different times, they need to be realigned too (slice timing correction). The corrected functional images were then realigned with the anatomical image in standard space, and smoothed to avoid gap formation in the transformed image. Further processing of noise components including cardiac, respiratory and subject movement were regressed, and the signal was bandpass filtered between 0.01 and 0.08 Hz prior to statistical analysis. Correlations were computed between pairs of regions, setting targets within specific brain networks as obtained using independant component analysis, and following a priori hypotheses on cortical landmarks in a ROI-based approach.

Data Normalisation

First, we hypothesised that imprecise normalisation, or transformation of subject anatomical images to standard MNI space (reference space based on the average anatomical image of 152 participants, adopted as a reference by the International Consortium of Brain Mapping (ICBM)), may misplace OP3 with respect to the primary auditory regions, leading to misattribution of results to one region instead of the other. We based the normalisation choice on a very thorough comparison performed across 14 deformation methods, including one linear method [213]. The comparison used 8 different error measures, 80 manually labelled brains, between which over 45000 normalisations were performed, and for which the ranking was established based on three independent analyses (permutation, analysis of variance, and indifference zone rankings). In terms of overlap of transformed regions compared to ground truth as a measure of performance, DARTEL - a diffeomorphic algorithm developed as part of the SPM toolbox (https://www.fil.ion.ucl.ac.uk/spm/) performed outstandingly, particularly in the perisylvian regions (figure 3.9), of interest in the present work, and was thus chosen for image normalisation.



Data Smoothing

The second aspect is linked to a typical preprocessing step which involves spatial smoothing of functional images, to improve signal to noise ratio. Typically, smoothing kernel size, in the framework of random Gaussian field theory, is linked to the expected effect size. Thus, in classical fMRI studies, isotropic smoothing kernels of full width at half maximum of 8 mm are often documented. Here, we hypothesised that the effect size may be comparable to previous fMRI activations of OP3 [16, 19, 21], therefore smoothing should not exceed 3 mm isotropic.

Furthermore, large smoothing kernel sizes introduce artificial local correlation patterns, and this may bias correlation based functional connectivity measures. In large smoothing computation, signals from neighbouring regions are merged which may reduce sensitivity of the analysis. Owing to the exploratory nature of the work, and the possibly small effect of the results, we chose to limit spatial smoothing. Here, we tested different smoothing parameters from 0 to 3 mm isotropic kernels. Below 1.5, the registration to template space yields poor results. However this was not the case for values above 1.5, and results were similar using 1.5 and 3 mm Gaussian kernels, therefore the smallest value was kept [242].

Data Organisation



Figure 3.9: The BIDS initiative to standardise the way data are organised, between raw acquisitions, and derivatives from multiple preprocessing and analysis steps. Taken from [248].

A major hindrance to reproducibility in tinnitus research is the lack of data availability and small sample sizes. In particular in resting-state paradigms, by

sharing anonymised preprocessed data, larger multicentric studies could be conducted in the future. We contributed to this general effort, and our functional and anatomical data, after anonymisation, were shared on the OpenNeuro platform in BIDS format [248], (dataset: doi:10.18112/openneuro.ds002896.v1.0.0).

3.3.1.2 Diffusion-Weighted MRI processing

In the diffusion MRI study, the main objective was to evaluate the influence of nonbothersome, chronic tinnitus on the microstructral properties of the white matter mapped onto the bundles of interest. In analogy with the fMRI study, effects were expected to be spatially localised and focal. Four major issues were faced in order to ensure the preservation of high spatial resolution, in the preprocessing, the diffusion signal modelling, and in two aspects of tractography. It is noteworthy that in the case of diffusion-weighted images, any normalisation step needs to take into account the gradient direction for each volume. Non-linear normalisation algorithms such as those used in fMRI have been found to induce a mismatch between registered images and the gradient direction in standard space. Therefore, only rigid body registration between images is possible, and DARTEL, despite its relevance described in the fMRI study, was not used here.

Preprocessing and handling of distortion correction

The standard preprocessing of diffusion-weighted images typically includes initial denoising, correction of Gibbs ringing artefacts, correction of geometric distortion due to local field inhomogeneity and patient movement, bias field correction, and intensity normalisation. In our study, most of the preprocessing was performed using MRtrix3 functions and scripts [249]. The denoising consisted in an implementation of random matrix theory, exploiting data redundancy properties in the PCA domain [250]. For Gibbs ringing artefacts correction, the method uses local subvoxel shifts, as developed by [251].

However, compared to the typical correction of geometric distortions induced by field inhomogeneities, we used the workaround step mentioned in the previous section,



Figure 3.10: The processing steps performed in MRtrix3 are displayed in grey boxes. The grey boxes with orange contour are from software outside MRtrix3 encapsulated in MRtrix3 scripts, and the orange box is the synthetic B0 image generation required for field inhomogeneity correction in FSL's TOPUP. At the end of the preprocessing, the signal $S(\theta, \phi)$ is equal to the convolution of the tissue's unitary response to the diffusion phenomenon $R(\theta)$ by a fibre orientation distribution (FOD) $F(\theta, \phi)$. Thus, the FOD can be obtained by deconvolution of the preprocessed signal by the response function estimated using tissue specific response functions [252].

to compensate for the different acquisitions between the participants. In the scanner, the presence of the patient locally modulates the static B0 field (of 3T strength in the present case), in the form of off-resonance fields distributed inside the subject, varying with subject movement. A second source of local off-resonance, current induced fields is due to gradient directions switching inducing eddy currents. These artefacts are dealt with by FSL's TOPUP and EDDY functions [253], provided reversed phase encoded acquisitions, at least of the minimally weighted b=0s/mm2̂, were performed. Here, as we mentioned, this was not the case for all participants. The deformation field to correct for geometric deformations was thus computed using a pre-trained, deep-learning model [246]. In brief, to estimate non-distorted, non diffusion-weighted b=0s/mm² images, Synb0-DisCo [246] uses a multi-slice, multi-band generative adversarial network, and training data taken from de-identified freely available datasets, with different signal to noise ratios, contrasts, and types of distorsions.

A test set of 100 subjects was taken randomly in the dataset, and the remaining 850 subjects were divided for 5-fold cross validation, into 680 testing sets and 170 validations sets for each fold. The performance of the network was evaluated in the withheld subjects of the 100 subjects test set. The undistorted $b=0s/mm^2$ image is obtained in MNI space, is warped back into subject space, and can then be used as second input for state of the art geometric distortion correction methods (figure 3.5).

Modelling the diffusion signal

The choice of the diffusion signal modelling defines the way the data may be subsequently analysed. Here, we wanted to preserve the spatial resolution (2mm thickness slices and in plane resolution of 1.67mm isotropic), but more specifically, we had an interest in certain white matter tracts with complex geometries. We hypothesise that the cortical area OP3 is connected to several white matter tracts with complex geometries, including long distance tracts such as the arcuate fascicle, which has known intersections with multiple other tracts, as well as multiple U-shaped, short-distance fibres. Therefore, there is a need for a method which handles crossing fibre pathways. In addition, we aimed to investigate the auditory radiations which begin in the middle geniculate body of the thalamus, end in core and surrounding regions of the auditory cortex, and are known for their difficulty to track [254], due to the angular geometry of the tract.

The DWI data were acquired with high angular resolution but only one shell or b-value other than 0 for diffusion weighting. In 2015 at the date of acquisition, tensor imaging was the predominant method in diffusion imaging analysis, and offered the possibility of retrieving orientation information of biological tissue in-vivo. However, the tensor model presented a number of shortcomings, mentioned in chapter 2. In up to 90% of brain voxels, different white matter pathways intersect, with different directions that the tensor cannot distinguish (figure 3.11) [255]. In line with this, the tensor model fails to correctly delineate a white matter pathway if it crosses through another dense pathway [255]. The metrics derived from the tensor may also fail to distinguish between fibre coherence and intrinsic white matter properties [255]. Loss of white matter integrity in pathological states as evidenced by decreased fractional anisotropy (FA) may thus be biased by crossing fibre pathway geometry. This problem of crossing fibre pathways modelling has been at the focus of active research, with progress made every year, along with increased caution in result interpretation of tensor derived results [256].



Figure 3.11: The corticospinal tract (CST), plotted from an example subject of our dataset, intersects with the fibres of the corpus callosum. At the voxel in the focus of the crosshairs, the local fibre orientation distribution (FOD) derived from a constrained spherical deconvolution approach allows one to clearly distinguish three peak directions, while the tensor does not allow for any clear identification of crossing directions.

Constrained spherical deconvolution has been proposed as a means to overcome the limitations of the tensor model, to estimate orientation distributions of fibre populations in a voxel. The main idea behind spherical deconvolution is that the diffusion signal measured for any fibre population is highly similar: the diffusion signal is typically low along the main axis of the fibres, while it does not decrease in general in the transverse direction, perpendicularly across fibres. Thus, an estimation of the diffusion signal for a canonical fibre population can serve as a basis for expressing the linear combination of signals originating from different fibre populations in a voxel.

The constrained spherical deconvolution approach thus uses a spherical harmonics basis to minimise the difference between the measured signal and the predicted signal. The predicted signal is estimated as the product of the spherical harmonic coefficient matrix along the sampled directions of the acquisition, and the matrix of response function coefficients (figure 3.12). Determining the response to the diffusion phenomenon of a canonical fibre population is thus a central prerequisite of this approach.



Figure 3.12: The signal measured in a voxel where two white matter pathways intersect results from the sum of the contribution from each fibre population. This can be equated to the convolution over the sphere of a canonical response function R with the fibre orientation distribution function fODF. Figure taken from [255]

In the present thesis, we made use of recent improvements establishing specific response functions in the white matter, grey matter, and CSF. Indeed, a recent branch of MRtrix3, MRtrix3tissue, allows for tissue specific estimation of response functions despite single shell data [252]. This approach uses a fully automated unsupervised algorithm which compares the diffusion properties of the different tissue types across shells, to establish the voxels from which best to derive the response functions [252], which in turn support the constrained spherical deconvolution modelling of the diffusion signal.

Analysis of tractography in a bundle specific approach

Diffusion-weighted imaging allows for quantitative characterisation of white matter structures in the brain. At the scale of the entire brain, tractography models are able to reconstruct estimations of millions of fibres in the white matter, and characterise microscopic properties [249], at the level of fibre bundle elements in a voxel, or fixels [206]. However, despite the best efforts in constraining the geometry of the fibres [256, 257], for example with the use of tissue-specific response functions, it has been shown that high amounts of false positives, or spurious fibres with no reasonable anatomical evidence, are yielded in the process.

In the diffusion study presented in chapter 4, we used a deep-learning based automatic bundle-specific tractography method [198, 258], in an attempt to mitigate the spurious fibres problem, and to increase sensitivity to group level tinnitusspecific differences. This approach builds upon the preprocessing steps mentionned previously, and uses as input the peak values of the first three components of the CSD-derived FOD. These peaks are fed to three deep neural networks previously trained on high amounts of data of mixed quality for sake of robustness. First, the algorithm establishes the beginning and ending regions of the set of fibre bundles it was trained to reconstruct. Then, it generates a mask of the entire fibre bundle. Finally, it provides a vector field, tract orientation map. These three outputs are then used in a probabilistic tractography algorithm to determine the trajectories of the fibres within each bundle.



Figure 3.13: Description of the deep-learning based algorithm used in the structural connectivity study, taken from [258]

The objective of this study was not only to provide the macroscopic geometry of fibre bundles for qualitative analysis of all participants. Here, the aim was to investigate quantitative changes in the white matter microstructure under the influence of chronic phantom sound perception. This was made possible by mapping quantitative metrics derived from the diffusion image onto the segmented fibre bundles in all participants, and to compare average metric profiles of variation along the major white matter pathways, between the tinnitus group and the control group.

Tensor and CSD metric comparison

Historically, quantitative metrics for white matter analysis were derived from the tensor model. Indeed, the tensor model is able to establish differences in degree of anisotropy in the grey matter (which is rather isotropic) and in the white matter (which is rather anisotropic), and Fractional Anisotropy (FA) [197] in particular has often been used as a measure of "white matter integrity". However, for the reasons mentioned earlier, changes in FA are often driven by different degrees of fibre coherence, which may not be related to relevant physiological changes [255]. Furthermore, in voxels with a multiple fibre configuration, FA is likely misestimated for both pathways and thus may present a bias in up to 90% of brain voxels.

The CSD model provides the framework to extract metrics which are rotationally invariant, and thus are not affected by a default in local fibre orientation estimation. Apparent Fibre Density (AFD) for example, used and described in chapter 4, is a documented measure of a fibre bundle's capacity to convey information [206]. AFD, in the present study, is a fibre specific measure, taken as the FOD lobe integral in the afdconnectivity function in MRtrix3 [206], thus quantifying the intra-axonal volume fraction. Nonetheless, because of the lack of direct comparability of our results using CSD-derived apparent fibre density (AFD) with tinnitus literature using diffusion imaging and tensor-derived metrics, we also mapped fractional anisotropy (FA) onto the bundles (chapter 4). Contrarily to AFD, FA is not fibre specific, since it averages information from multiple intersecting fibre populations, and suffers a lack of interpretability [205].

Briefly, the metric mapping procedure ran as follows (figure 3.14). After bundle tractography, a centroid fibre was defined as the fibre minimising the euclidean distance to all fibres in the bundle. All fibres were divided into 100 segments and for each segment, an index was chosen relative to the segment's distance to the corresponding centroid fibre segment [259]. Metrics were mapped onto the bundle and the average value was taken across all elements belonging to the same segment index, and projected onto the centroid fibre. Segment-wise statistics consisted in Student's 2 sample t-tests between tinnitus and controls, and metrics comparison using

Pearson's correlation. Permutation-based multiple bundles comparison correction was performed using 5000 permutations. The variation of the metrics with the position along each bundle was plotted as bundle specific profiles (chapter 4, section 4.3).



Figure 3.14: Comparison of z-scored metrics was performed once all bundles had been segmented in the CSD framework. SS3T: single shell, 3 tissue; RF: response function; WM, GM: white, grey matter; CSF: cerebrospinal fluid; AFD: apparent fibre density; FA: fractional anisotropy.

A this point, the tensor was not used for determining the trajectories of the fibres, since this was performed using the CSD model. We expected nonetheless to find differences in tract profiles between the mapped FA and CSD-derived AFD, in particular in the regions of complex fibre configurations.

Acoustic radiations tractography

The acoustic radiations were of interest to compare with literature findings of white matter density modifications in tinnitus, using different methods, as seen in the previous chapter. However, the acoustic radiations were not part of the reference bundles provided in the standard bundle-specific tractography algorithm, TractSeg [258]. An alternative version was provided, based on bundle segmentation masks from the X-Tract framework [260], but this did not allow for tract orientation mapping. Thus, the tractography for the acoustic radiations was performed with IFOD2 probabilistic tractography algorithm from MRtrix, instead of TractSeg's custom algorithm, but still using the automatic bundle mask segmentations as input. The beginning and end regions were derived from the intersection of the automatically obtained bundle mask and the grey and white matter interface for the auditory cortex, and from manual segmentation of patient specific MGB at the subcortical level.

TractLearn: preserving individual physiology to detect relevant pathological outliers

Building on the bundle-specific approach, we performed an analysis of the data in a different framework, with higher specificity potential. The following approach was presented at OHBM and SFRMBM in 2021. Tractlearn is based on TractSeg's bundle segmentation process as well as on the manifold approximation algorithm UMAP. The topological characterisation performed by UMAP offers a different statistical framework to detect anomalies between two groups of participants. The overall process for single subject anomaly detection is described in 3.15. This process is repeated for each tinnitus subject and the resulting anomaly maps are averaged.



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Figure 3.15: Illustration of the processing conducted in TractLearn [261], presented as an oral communication at the SFRMBM 2021 conference. After bundle-specific tractography (1), density maps and binary masks are derived (2). In all subjects, a graph of the topological properties of each fibre bundle is computed (3). Then, a low dimensional space is computed using only control data all subjects save one (4). The anomaly detection relies on 4 subsequent stages: first, project the patient data onto the previously defined subspace, as well as the left out control subject (5); then, estimate the mean of the three closest neighbours to the projected data (6); this latent space interpolated point is back-projected in high dimension (7) and compared to the initially projected patient and control bundle. Significant differences are determined where anomalies are found in the tinnitus bundle and not in the left out control bundle.

3.3.2 Stereo-EEG studies

3.3.2.1 Brain mapping of DES-induced auditory hallucinations and illusions

The objective of this study was to determine the extent to which auditory hallucinations and illusions were supported by different cortical regions and networks.

Hallucinations are typically considered an early sensory process, since they are interpreted as an original perception by the brain [262]. The input from prior knowledge of the environmental context, and the identification of no existing source for this sensory perception, is what enables the labelling of this perception as a hallucination. Here, hallucinations are thus expected to be generated by stimulation to early sensory cortices, yielding high frequency patterns in associative cortices and integration cortices, as well as frontal cortices of top down, context informative areas. This is of interest for the study of tinnitus, since tinnitus, as a phantom sound perception, qualifies technically as an auditory hallucination.

Illusions, on the other hand, are a modulatory perception of an existing sensory input, which makes them a more likely non-primary phenomenon [262]. They are thus expected to be obtained from stimulation to non-primary regions. Here, too, there is a realisation that the modulation is not due to environmental conditions, therefore context dependant pathways are likely involved in informing on the erroneous nature of this perception. The extent to which this network differs from that of hallucinations is an open question, which we aim to answer by looking into the HFA modulations underlying each perception.

The analysis consisted in a two-step approach. First, we mapped the location of the

electrode contacts generating auditory symptoms to corresponding anatomical areas. Then we examined the network of regions presenting high frequency modulations during stimulation and we contrasted these networks with respect to symptom type. The appropriate correspondence between the subject electrodes and anatomy was thus crucial, and was verified as part of the data preprocessing. Furthermore, the exact nature of all symptoms needed to be precisely established. Then the attribution of these symptoms and modulation patterns to anatomical landmarks poses the question of which reference parcellation of the brain, or which scale, is most relevant for the question at hand. Finally, while the symptom to ROI mapping is self-explanatory, and the details given in chapter 5 will suffice, we provide some additional details on the analysis of high-frequency brain activity modulations during stimulation.

Data curation and preprocessing

In this study, the recordings were taken from acquisitions previously performed between 2009 and 2015. In order to analyse these data as part of this thesis, anatomical labels attributed to the electrode contacts investigated first needed to be visually verified and re-positioned if needed.

First, anatomical images and corresponding electrode contacts were visualised, by overlaying on the T1-weighted MR image, a rigidly co-registered post-operative CT image. Images were manually loaded in IntrAnat software [263] and electrode contact positions were thus verified for all patients and amended accordingly. Patient symptoms, when highlighted as ambiguous by the neurologist due to some ambiguities in the patient documentation, were checked based on video recordings visualisation.

Then, all SEEG recordings were visually inspected and stimulation onset, stimulation cessation, and symptom onset were labelled. In addition, presence of postdischarge activity was evaluated by the expert neurologist involved in the project, and by verifying the patient file reports for all stimulation trials. It was thus established that in the order of 30% of the recordings presented post-discharge activity, with a post-stimulus onset. It was decided to conduct the analysis during the stimulation, where most symptoms were documented to have started, and where post-discharge

activity was not an issue. Bad channels were automatically detected and excluded from analysis [264], and a bipolar montage was applied.

Brain parcellation for auditory symptom analysis

In this study, because we aimed to investigate the precise distribution of symptoms involving auditory perceptions, we questioned the way the level of complexity of the symptom may correlate with its localisation, and inform on brain organisation. Thus, we needed a brain parcellation with multiple subdivisions of the primary, secondary, and associative auditory, in order to visualise differences in hierarchical processing. Furthermore, we were interested in the way the opercular subdivisions may be specifically involved, and particularly OP3, therefore this question required a parcellation were OP3 was represented. To date, while there are several options for subdivisions of the auditory areas, only one atlas provides a subdivision of the parietal operculum featuring OP3: the Jülich cytoarchitectonic atlas [64] (figure 3.19). For sake of illustration, we provide a comparison of the distribution of auditory symptoms between AAL and Jülich atlases (figure 3.16), which highlights the necessity of high resolution parcellation in terms of symptom to ROI matching.



Figure 3.16: Example of two atlases for the symptom to ROI mapping. The AAL atlas (left column) is interesting because it is part of many processing toolboxes, and provides the segmentation of the cerebellum which many other atlases do not. The Jülich brain atlas (right column) provides high resolution features in the temporal, opercular, and insular regions, which are of particular interest in our analysis. Here, we can see that in the left hemisphere, AAL does not make any difference between hallucinations and illusions, and in the right hemisphere, illusions were more frequently evoked than hallucinations. In the Jülich parcellation, there are variations within the superior temporal lobe between hallucinations and illusions which were not visible in the AAL parcellation.

High frequency activity analysis

High-frequency activity (HFA) patterns of brain activity have been proposed as a physiological indicator of perceptual and cognitive processes. HFA has been shown to correlate with fMRI BOLD signal, however it possesses vastly higher temporal and spatial resolution as well as spectral information, which provides a unique window onto the neural basis of perception and cognition. HFA is defined as a broadband energy modulation measured in the frequency range above 40 Hz, and is visible in raw SEEG recordings (figure 3.17) [265], but more clearly so in the time-frequency domain. The time-frequency decomposition of the measured signal enables the simultaneous visualisation of the experimental timecourse, with stimulation and symptom onset labels, as well as the changes in time of the energy per frequency band, which is what was performed in this study as described in chapter 5.



Figure 3.17: Example of an event related potential (ERP) in the fusiform area in response to visual stimulation, followed by high frequency activity (HFA). The signal is expressed in % of the maximum amplitude value. Figure taken from [265].

HFA has been proposed to emerge in any cortical region recruited during a specific task, making it a general signature of cortical processing, and a marker of network organisation in the brain [265, 266]. Thus, analysis of HFA modulations was

a relevant framework for investigating potentially subtle differences between induced auditory perceptions of different integrative levels in the sensory process.

The analysis, described in chapter 5, ran as follows. In all subjects, the target time-window was defined by stimulation onset and cessation during which symptoms emerge, as described by participants, while the target frequency window was taken in the 70-150 Hz range. This ensured that the signal is not contaminated by postdischarge activity, which occurs at a later time and in the 3-45 Hz frequency range. Baseline activity was taken in the [-30 -5] seconds interval prior to stimulation. Timefrequency decomposition was performed using a Hanning-tapered decomposition with a fixed window length of 1s and a 100ms step size. A notch filter was applied to remove harmonics of line noise between [98 102] Hz and [148 152] Hz, and Z-score normalisation was performed by dividing, for each channel and each trial, the difference between the time-frequency map and the mean baseline timefrequency sample (padded to match the size of the time-frequency map of the epoched trial) by the standard deviation of the baseline estimate (as expressed in the ImaGIN_NormaliseTF function from the ImaGIN2 suite, available at f-tract.eu). The stimulation artifacts were hyper-intense in the time-frequency maps, and were handled by removing z-score values above 10. Furthermore, for sake of caution, SEEG power matrix elements with a z-value above 10 in over 5% of channels were removed, including those for which the threshold was not reached. Then, the time frequency maps were spatially interpolated to produce images for statistical analysis: in standard space, the power values for each electrode contact were mapped to the corresponding electrode contact position. Spatial interpolation restricted voxels to the neocortex, the hippocampus, and the amygdala. For each contact, mesh vertices within a 1cm radius were detected and each vertex detected for at least one electrode is assigned the weighted average of the SEEG power values of all nearby electrodes, with weights chosen as the inverse of the distance between the vertex and the electrodes, the closest electrode thus receiving the highest weight. Gaussian smoothing was performed using a 3 mm isotropic kernel width, in the same order

of magnitude as the distance between contacts, for family-wise error rate control in the case of spatially correlated imaging data.

In each participant, and for each trial, the resulting interpolated maps of spectral power during symptom perception were compared to baseline using two-sample t-tests, with an FWE-corrected p < 0.05 threshold. Thus, the regions displaying significant HFA modulations during DES induced auditory symptoms were obtained for each trial. At the group level, the spatial distribution of recorded responses for each auditory symptom type evoked during DES was obtained. Briefly, analysis ran as follows: first, a binary mask was derived from the SEEG log power statistical maps previously obtained at a p=0.05 threshold. Voxels displaying significant SEEG power values during an auditory response were assigned to their corresponding atlas ROI. Each ROI containing at least one significant voxel was therefore considered active during the evoked symptom. The binary maps were averaged across trials to obtain group probability maps of symptom-related SEEG power modulation. For each symptom type, an additional threshold of minimum 10 recordings per ROI was applied for sake of reproducibility. The group probability maps, referred to as HFA maps, range from 0 (no significant HFA power increase in the ROI during any of the recordings) to 1 (systematic HFA increase during symptom perception).

3.3.2.2 Intracortical connectivity derived from CCEP

The F-TRACT project aims to provide a probabilistic anatomo-functional atlas of the healthy human brain. Due to the large amount of data collected, it is proposed that pathological brain states be averaged out compared to physiological processes. Furthermore, it has been demonstrated that over 80% of electrode contacts fall within healthy brain structures, while fewer than 20% of the remaining contacts are located in epileptic brain tissue [267]. This remaining risk of including pathological instead of physiological connectivity is mitigated through data examination, bad channels exclusion, a focus on early CCEPs rather than late ones [245], and detection of spiking activity which must be below 8 spikes per minute. Single pulse electrical stimulations at impulse rates of 1 Hz allow the brain to provide a transient response pattern with a return to equilibrium in between stimulations. The stimulation has been proposed to locally depolarise a neuronal population in the vicinity of the stimulating contact. This depolarisation is expected to travel along white matter fibres connecting cortical areas, and induce depolarisation of distant cortical sites. The existence of a connection between a target and distant cortical regions can thus be inferred from the measurement of all remote depolarisation patterns following stimulation in the target cortical site. A response to stimulation is considered significant if a measured variation of electric potential passes a certain threshold, expressed in terms of standard deviation. This response is averaged across all pulses performed at a 1 Hz repetition rate: this is known as a corticocortical evoked potential (CCEP).

Connectivity can thus be defined based on the features of the response, in terms of dynamic properties such as latency of the onset or of the peak of the response, or strength of the response based on the amplitude and integral of the first component of the response (figure 3.18). These features are then pooled by brain regions according to a brain parcellation and across all patients and stimulations, to yield an atlas of group representative connections between all pairs of cortical sites.

Data curation and Preprocessing

The data involved in the F-TRACT database were curated as part of the aforementioned international collaboration, and only the processed data were used in this thesis [245, 269]. Except for visual verification of electrode localisation and bad channel detection, all processing leading to the functional atlas is automated, and makes use of the SPM-compatible ImaGIN and Intranat suites developped for the F-TRACT project, available on the f-tract.eu website, and additional software tools for neuroimaging (FreeSurfer, BrainVisa). Further details on F-TRACT data processing are provided in [245, 268, 269].

On one hand, the anatomical data from the post-operative T1 MRI scans allow for electrode localisation. The post-operative scan is realigned with the



Figure 3.18: Example of a cortico-cortical evoked potential after z-transformation, with measures of onset and peak latencies, duration, amplitude, and integral as documented in the F-TRACT atlas. [268]

pre-operative MRI, which is parcellated according to 8 different atlases (AAL, AICHA, Brodmann, Freesurfer, Hammers, HCP-MMP1, Lausanne2008 - resolutions 33, 60, 125, 250, 500 - and MarsAtlas), providing different resolutions, for contact to region of interest mapping.

On the other hand, the functional data are first converted from raw data format to .mat format for SPM compatibility, then stimulation artefacts are detected using a thresholding of the abrupt gradient change at the onset of the event, as well as bad channels which are removed from analysis [264]. Then, a bipolar montage is defined, computed as the difference between pairs of adjacent contacts, enabling increased local response sensitivity and reducing the influence of distant sources. The stimulation artefact is subsequently corrected, to make sure that the measured responses are relative to brain physiology. This is based on a biophysical model of the interaction between electrode contact and brain tissue, which is added and then subtracted [269]. The data are filtered with a bandpass filter between 1 and 45Hz, thus removing the influence of both slow waves and fast oscillations, for improved evoked response detection. Each trial is baseline corrected using an averaged reference timewindow, and finally, each evoked response is z-scored using the same timewindow as the one used for baseline correction. A response is considered significant if it reaches the z=5 threshold within 200ms, in which case it corresponds to the N1 component, from which are derived metrics of peak latency, onset latency, duration, amplitude, and signal integral.

OP3 connectivity

In the present thesis, the main focus for the use of the F-TRACT atlas was set on the anatomical region OP3 and its neighbours, in adult participants. However, OP3 was not strictly present among the available parcellations part of the latest F-TRACT release. This can be explained by the fact that the Jülich cytoarchitectonic atlas, which provides the geometric definition of OP3, did not until recently provide a full cortical mapping. Recently, however, the atlas was completed, although roughly for several regions which have yet to be analysed in more detail ('GapMaps') [64], and was made available online as an interactive atlas tool as part of the Human Brain Project and EBRAINS suite. It is noteworthy that the F-TRACT anonymised CCEP data are also available on the EBRAINS website as part of the Human Brain Project.



Figure 3.19: Navigation interface dedicated to the Jülich cytoarchitectonic parcellation, centered on OP3 for the sake of this illustration. Available at https://interactive-viewer.apps.hbp.eu

The choice of a fine, high-resolution parcellation entails the risk that insufficient amounts of data may be present for each parcel for robust statistical analysis. However, in the case of the Jülich atlas which comprises 251 parcels, while the opercular, insular and superior temporal areas are very finely sub-divided, that is not the case for most of the remaining brain areas. Therefore, connections were able to be robustly elicited, despite a threshold of minimum 5 stimulations per parcel, and originating from at least 5 subjects. The atlas was generated as in [268], with a total of 942 patients. To obtain connection probabilities, the process ran as follows. In a given region, the maps of regions presenting a significant response (z-score above 5) upon each stimulation of that region are binarised, summed, and normalised which yields a probability between 0 and 1. The probability thus represents the likelihood that the region being stimulated may be connected to the regions presenting significant responses over multiple runs [268].

3.3.2.3 Analysis of intracortical responses to a tinnitus-like perception

The principal aim of this study is to verify the role of the parietal operculum in phantom sound perception, as previously highlighted in an fMRI paradigm. Here, in addition to simply investigating the activation of the parietal operculum, we were able to investigate precise brain oscillations, or large band frequency modulations, from the recorded signal during and after acoustic stimulation. In this study, a precise timelocking of the tinnitus-like perception is not possible: the perception is *induced*, rather than *evoked*, meaning that the brain activity of interest emerges with an unknown jitter between each trial and between subjects. Prior experience from the fMRI study informed us that the perception should be expected to emerge gradually with time, and persists after the end of the acoustic stimulus. Therefore, for the sake of exploring all possible characteristics in this unique experiment, in terms of latency as well as spectral content variations, a method that preserves both types of information was chosen: the time-frequency decomposition, based on the wavelet transform.

Anatomical processing

The functional processing is only relevant if recordings can be attributed an anatomical correspondence. In line with previously mentioned processing of DES and CCEP, electrode contacts were localised and anatomically labelled using IntrAnat Electrodes [263]. The process involves rigid-body co-registration, computed in SPM [270], of preoperative T1 anatomical image and postoperative MRI or CT scan, and initial segmentation of white and grey matter. Electrode contact positions were computed in both subject space and MNI space, and coordinates were then established for bipolar montage as the mean of the two contacts composing the bipole. Anatomical segmentation was performed in Freesurfer [271] according to the atlases used in the F-TRACT project. As mentioned previously, the Jülich parcellation was chosen for analysis since it provides a delineation of OP3, our main region of interest in this analysis, and was used to help narrow down the selection to the electrodes from which the recordings would be investigated in particular.

SEEG Preprocessing

Most of the preprocessing was performed using the ImaGIN toolbox of SPM (statistical parametric mapping) compatible functions, available at f-tract.eu.

First, SEEG recordings were converted from raw TRC data format to SPM compatible .mat format, and bad channels were detected and removed from analysis [264]. Recordings were re-referenced using a bipolar montage between adjacent contacts, which we mentioned enables increased sensitivity to local current generators by cancelling out the influence of distant sources which spread equally to both adjacent contacts due to volume conduction mechanisms. The events were checked visually, as defined by the triggers embedded in the recordings. Then, recordings were divided into time samples, or epochs, including for each listening task the three minutes of acoustic stimulation, 10 seconds prior to task onset, and 30 seconds post-listening task for after-effect analysis, thus a total of 220 seconds.

Time-frequency analyses

Time-frequency decomposition of epoched recordings was performed by convolving the signal with a continuous Morlet wavelet transform. In classical Fourier transform, the spectral information contained in a signal is retrieved, but the temporal component is lost. To preserve the information of *when* a given frequency is represented in a time-varying signal, a sliding-window adaptation of the Fourier transform

can be used. The wavelet transform is an extension of this framework, which adapts to multiple-scale data.

For a central frequency f_0 , and peristimulus time t, the Morlet wavelet kernel, a complex valued modulated Gaussian with parameter $\sigma_t = 1/2\pi\sigma_f$, is given by:

$$w(t, f_0) = A e^{-t^2/2\sigma_t^2} e^{2i\pi f_0 t}$$

where A is a normalisation factor and $(\sigma_t)^2$ is the temporal width of the kernel. Wavelets are normalised, meaning that the their total energy is equal to 1. A wavelet family is built by setting the f_0/σ_f ratio to a constant value, setting the trade-off between time and frequency resolution (MFact in figure 3.20), while f_0 ranges from 4 Hz to 120 Hz in steps of 1 Hz. At 10 Hz, this entails a wavelet duration of $2\sigma_t$ equal to 222 ms and a spectral bandwidth of $2\sigma_f$ equal to 2.85 Hz. At 30 Hz, the wavelet duration is equal to 74 ms for a spectral bandwidth of 8.5 Hz, and at a 100 Hz, the parameters are (22 ms, 28.6 Hz). Thus, the time resolution increases as the frequency increases, while the spectral resolution decreases. This property is interesting for analysing brain activity. For example, alpha band activity below 10 Hz requires one cycle per 100 ms: a temporal window in the order of 500 ms is necessary for robust estimation of transient alpha activity to allow a few cycles per observation. However, for gamma activity in the 60 Hz range, there would be 30 cycles per 500 ms, which can be considered overly generous. With a family or basis of wavelets, a mother wavelet at base frequency captures the low frequency signal, and the other wavelets scale appropriately in time to capture higher frequency signal.

In addition, a modulation factor for local bandpass filtering was tested (figure 3.20).

The transform of the signal into time-frequency domain is defined as the convolution of the kernel with the signal measured at a given voxel for a given trial, and the power is computed as the product of the transformed signal by its complex conjugate (or squared norm). In figure 3.20, we provide an illustration of time-frequency decomposition of the signal recorded in the auditory cortex in the [-4s 4s] interval at the end of the acoustic stimulation using 30 Hz clicks. Four sets of parameters are presented, among all incremental tests performed, and the result of the chosen trade-off between spatial resolution and computation time is shown.



Figure 3.20: Four sets of wavelet parameters of increasing factor of modulation for bandpass filtering and Morlet factor for time-frequency resolution trade-off adjustment. The 30 Hz harmonic is clearly visible, reflecting the response of the primary auditory area to the percussive sound stimulus. The frequency resolution enables the visualisation of the 60 Hz harmonic only when the number of cycles in the wavelet transform is high enough. A trade-off between frequency resolution and computing times was chosen, by using Mfact=7, and FactMod=15.

For normalisation, baseline activity was chosen in the 3 seconds interval at the end of the silent period, once participant tinnitus-like perception had subsided. After normalisation, time-frequency maps for each channel were saved in nifti format (img/hdr), for statistical analysis.

Within subject statistics were performed in each channel to compare brain activity patterns in the 30 Hz condition to the 8 Hz condition using a two sample t-test.

Non invasive exploration of chronic, non-bothersome tinnitus

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4.1 Introduction

Chronic tinnitus perception, as a hearing disorder, does not in general qualify for extensive exploration, let alone neuroimaging exploration. In the clinical setting, patients who seek medical treatment for tinnitus perception undergo comprehensive audiologic evaluation, mainly for hearing loss. If the physician finds that this evaluation suggests an underlying pathological condition, further tests may be performed such as otoacoustic emission tests or imaging such as an MRI or CT scan. Such additional exploration is thus typically not performed in subjective, nonpulsatile and lesion free tinnitus [8]. This implies that the data on tinnitus that go beyond epidemiological surveys are rare and strictly confined to research purposes, often with small sample sizes, with mixed tinnitus profiles, with comorbidities, and ill-matched control groups. Therefore, the literature on the neuroimaging exploration of tinnitus, as we reviewed in chapter 2, presents a high rate of diverse and nonreproduced results. One element which stands out from the literature review is the tendency for tinnitus perception to emerge as the result of a dysfunction of a network of brain regions involving non-auditory cortex. The chronic perception of sound is likely to relate to plastic mechanisms, both in the cortical structures and in the white matter. The causal relationship between tinnitus and brain plasticity is unclear, and multiple scenarii are possible. Tinnitus may result from plastic changes, as brain structures adapt to different sensory input, for example from new somatosensory information originating in the middle ear, or from decreased input from the cochlea. Conversely, the chronic perception of tinnitus may drive plasticity for example through reinforcement. The exploration of these changes, both in the cortex and in the white matter, is thus relevant.

Furthermore, the right parietal operculum has been found to be involved in noise induced tinnitus perception, and in tinnitus-like perception induced by specific acoustic stimulation in activation fMRI. These elements provide the grounds for further investigation into the role of the parietal operculum in tinnitus perception. In this chapter, we aim to determine the role of the parietal operculum in a network of functionally and structurally connected brain regions, relative to the plastic changes involved in tinnitus perception. The first part of this chapter presents a seedbased, resting-state functional connectivity study, examining the changes in cortical synchronisation due to tinnitus and published as an article in Brain Connectivity [242]. The second part of this chapter delves into the structural correlates of chronic tinnitus perception, using diffusion weighted imaging methods, and published as an article in NeuroImage: Clinical [272].

4.2 BOLD fMRI functional connectivity study

The main objective of this study was to determine how the parietal operculum engaged with other brain regions, and if these connections were different due to tinnitus perception. To achieve this, as previously mentioned in chapter 3, we focused specifically on a homogeneous group of non-bothersome tinnitus participants and matched controls, and used resting-state fMRI to examine spontaneous fluctuations of the BOLD signal, the gold standard for revealing the network organisation of the brain at rest [242].

My contributions to the study, which I joined after the acquisitions and preprocessing of the data had been performed, involved data processing, discussion of the results, figure generation, and manuscript writing, which justified my position as co-first author.

Functional Connectivity in Chronic Nonbothersome Tinnitus Following Acoustic Trauma: A Seed-Based Resting-State Functional Magnetic Resonance Imaging Study

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Abstract

Background: Tinnitus and its mechanisms are an ongoing subject of interrogation in the neuroscientific community. Although most current models agree that it encompasses multiple structures within and outside the auditory system, evidence provided in the literature suffers from a lack of convergence. To further our understanding of contributions to tinnitus lying outside the auditory system, we explored a new model based on a proprioceptive hypothesis specifically in subjects experiencing chronic nonbothersome tinnitus due to acoustic trauma. The present study addresses the role of the right operculum 3 (OP3) involved in this model. It also investigates classical models of tinnitus.

Methods: A seed-based resting-state magnetic resonance imaging study explored the functional connectivity in an acoustic trauma group presenting slight to mild nonbothersome chronic tinnitus and compared it with a control group. **Results:** Group differences were found with two networks: with the sensorimotor–auditory and the frontoparietal, but not with the default mode network nor the limbic regions. In the auditory pathway, the inferior colliculus displayed group differences in connectivity with the right superior parietal lobule. Exploratory analysis elicited a significant increase in connectivity between two seeds in the right OP3 and two mirror regions of the dorsal pre-frontal cortex, thought to correspond to the human homologue of the premotor ear–eye field bilaterally and the inferior parietal lobule involved in proprioception, in the tinnitus group.

Conclusions: These new findings support the view that acoustic trauma tinnitus could bear a proprioceptive contribution and that a permanent cognitive control is required to filter out this chronic phantom percept.

Keywords: acoustic trauma; chronic nonbothersome tinnitus; operculum 3; PEEF; resting-state networks

Impact Statement

Tinnitus studies are complicated by the large heterogeneity of etiologies in subjects that are recruited. Here, we included participants experiencing chronic non-bothersome tinnitus following acoustic trauma, thus having few comorbidities, to address the cerebral functional networks modifications induced by this percept. We found functional connectivity modifications in several networks, including in the auditory pathways supporting the idea that tinnitus is not a single auditory issue. In addition, a specific connectivity between the right OP3 region and bilateral superior frontal gyrus was found, in line with Job's recent hypothesis of an implication of the middle-ear pathway.

Introduction

TINNITUS (I.E., RINGING OR WHISTLING IN THE EARS) is a symptom that emerges with a variety of diseases (Baguley and McFerran, 2013), hence the definition of several types of tinnitus. Among those, acoustic trauma tinnitus has been considered as the direct result of cochlear injury and deafferentations, inducing maladaptive changes in the central nervous system. However, this generally accepted model has been contradicted by evidence of people having

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hearing loss without tinnitus and *vice versa*, whereas treatments based on this model to abolish tinnitus in humans have proved unsuccessful (Elgoyhen et al., 2015; Lehner et al., 2016; Vanneste et al., 2013).

Investigating tinnitus as a pathology of brain networks, many studies based on resting-state analysis of functional magnetic resonance imaging (fMRI), electroencephalography, or magnetoencephalography data were designed. They generated a large diversity of results showing the implication of regions extending far beyond the auditory network. Following alterations have been shown: in a network of the right parietofrontal and anterior cingulate cortex (Schlee et al., 2009); concomitant dysregulation of limbic and auditory networks (Chen et al., 2017; Leaver et al., 2016a); implication of the default mode network (DMN) as suggested through a review analysis (Elgoyhen et al., 2012); a reduced interhemispheric connectivity between auditory areas (Hofmeier et al., 2018); involvement of the right executive control network in tinnitus patients with distress (Kandeepan et al., 2019). Also, a decrease in information transfer between frontolimbic and medial temporal regions (Mohan et al., 2018); frontostriatal network dysfunction (Hullfish et al., 2019; Leaver et al., 2016b); modification of cortical and subcortical functional connectivity in tinnitus encompassing attentional, mnemonic, and emotional networks (Maudoux et al., 2012) and default mode, auditory, dorsal attention, and visual resting-state networks (Burton et al., 2012; Husain, 2014) were reported. The discrepancies in literature results may be partly due to the heterogeneity of the associated pathologies in the tinnitus population studied. Hence the importance highlighted by some authors of targeting homogeneous groups of subjects in tinnitus studies (Koops et al., 2019; Schmidt et al., 2017; Wineland et al., 2012). Focusing on the tinnitus percept while disregarding distress can be achieved by recruiting a subpopulation of chronic tinnitus subjects with similar etiology whose quality of life is not impacted. We aim to reinvestigate network-based functional connectivity in such a group.

Unlike current acoustic trauma tinnitus models, we showed in our previous fMRI studies that tinnitus may come, not from hearing loss itself, but from a somatosensory disturbance, most probably involving middle ear muscle proprioceptive dysfunction (Job et al., 2011, 2016b), leading to the erroneous integration of proprioceptive signals (i.e., illusory sound) in the brain. Indeed, our previous study aimed at stimulating the middle ear proprioceptors by applying specific click vibration rates to the ear (Job et al., 2016b), which resulted in a tinnituslike perception in healthy subjects at a particular frequency. Neural correlates of this stimulation were found in a small brain region in the right operculum 3 (OP3; Job et al., 2016b). This region had also been found hyperactivated in the fMRI study comparing sound detection in a tinnitus group with a control group (Job et al., 2012). We hypothesize that this region may have been overlooked in previous fMRI studies due to merging with neighboring regions when performing spatial smoothing with large kernel sizes.

It has been shown that disturbed muscle proprioceptive inputs using mechanical vibration send erroneous messages to the brain as a form of perception illusion (Kavounoudias et al., 2008; Roll et al., 2004). Similarly, auditory perception illusions could occur in the auditory system as long as such proprioceptors are present in the middle-ear muscles, a result that was demonstrated by Kierner et al. (1999). In acoustic trauma, the physical stress generated in the whole auditory system, including the middle ear, is extreme (Job et al., 2016a; Wojtczak et al., 2017) and could overwhelm physiological adaptations.

In this study, we focused on a homogeneous group of subjects presenting chronic nonbothersome acoustic trauma tinnitus, free of comorbidities such as anxiety or depression. In continuity with our previous study on this region in the right OP3, we wondered whether it could be involved in a network of tinnitus, or be part of an abnormal interplay between the main resting-state networks. Thus, we first investigated how the main resting-state networks described in the literature were affected by tinnitus in our study population. Second, we questioned the existence of a network specifically related to the tinnitus percept by exploring the connectivity of this OP3 region in acoustic trauma tinnitus. We sought to achieve these objectives using a seed-based connectivity approach with resting-state functional magnetic resonance imaging (rs-fMRI), which allows for adjustment of the data to confounding factors. In this study, hearing loss was a confounding physiological factor and psychological disturbance related to tinnitus was a second confounding factor. Following our hypothesis, specific connectivity related to the percept of tinnitus per se should be observed since we are taking these factors into account.

We studied whole-brain functional connectivity differences between the tinnitus group and the control group using several seeds including regions documented as belonging to the main resting-state networks, those located at and around the previously determined region in the right OP3 (Job et al., 2016a), and those along the auditory pathway. The left OP3 seed, mirror of the right OP3 seed, and the extended cytoarchitectonically defined right OP3 were also investigated.

Materials and Methods

Participants

Nineteen male chronic tinnitus participants (mean age 42.5 ± 12 years old) and 19 male tinnitus-free age-matched controls (mean age 42.5 ± 11.9 years) were included. Inclusion criteria required nonbothersome tinnitus of acoustic trauma origin, with a duration ≥ 6 months (mean duration 12.2 ± 7.3 years, median = 13 years). Tinnitus participants were recruited through medical unit physicians in military regiments, through general announcements in the regiments and through the ear, nose, and throat department of military hospitals open to civilians. Controls were recruited through an announcement on a specialized callfor-volunteers website for scientific protocols and by word of mouth. Control participants were not to have reported frequent or permanent tinnitus but may have experienced it once or occasionally. All participants were different from those studied in our previous publications to avoid circular analysis.

The study was approved by the Local Ethics Committee CPP Sud-est V, Ref: 10-CRSS-05 MS 14–52, and conducted

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in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants.

Hearing levels, tinnitus description, and tinnitus handicap inventory

Both tinnitus participants and matched controls underwent audiograms. We assessed hearing performances by tonal audiometry at 0.25, 0.5, 1, 2, 4, and 8 kHz (Audioscan fx by Essilor[©]) on the day of the magnetic resonance imaging (MRI) acquisitions. Electroacoustic calibration of the audiometer equipped with Beyer dynamics DT48 earphones was performed per French AFNOR standard S3007. We used the automated Hughson-Westlake procedure, which assessed hearing thresholds by modifying sound intensity using 5 dB up and 10 dB down steps. Sound intensity levels were modified automatically according to the participant's responses. The threshold was defined as the lowest level at which at least two responses were obtained out of three presentations on an ascending run. Hearing loss levels were expressed in dB hearing levels.

Two questionnaires were completed by tinnitus participants. The first was an interview form that collected general information about the participant's tinnitus. The second was the French version of the tinnitus handicap inventory (THI), used internationally to robustly assess the intensity/ intrusiveness of tinnitus and its associated handicap (Newman et al., 1996). THI scores are divided into severity grades (i.e., slight [THI 0-16], mild [THI 18-36], moderate [THI 38-56], severe [THI 58-76], and catastrophic [THI 78-100]; McCombe et al., 2001). According to this grading, the participants' tinnitus ranged from slight to moderate (Table 1).

Autonomic status

Tinnitus ID

T1

T3

Since chronic tinnitus is known to affect autonomic conditions with sympathetic overactivity (Choi et al., 2013),

Ear

R&L

R&L

Age

56

43

we wanted to make sure that group differences would not be attributed to an imbalance in autonomic nervous functions. To verify this, we measured the heart rate variability (HRV) in all subjects before, during, and after the MRI experiment. In the scanner, during the resting-state acquisition (13 min long), the finger photoplethysmography device of the scanner, sensitive to the hemodynamic pulse at fingertip, was registered at 100 Hz using the hardware delivered with the magnetic resonance (MR) system. The peaks were automatically detected and recorded with the data file for further analysis. These peaks are fully correlated with the R-peaks from electrocardiogram ($r^2 > 0.99$) but delayed in mean by 620 ms (Rubio et al., 2015). For all the data, HRV analysis was performed with the dedicated software, Kubios[®]. Time domain, frequency domain, as well as nonlinear analyses were applied on interbeats intervals measured between consecutive peaks. Standard autonomic parameters were computed and statistical comparison between groups was performed in SPSS using nonparametric Mann-Whitney U tests.

MRI data acquisition

A rs-fMRI study was performed in the search for a potential functional network specific to tinnitus perception per se. Scanning was conducted on a 3T Philips Achieva-TX scanner (Best, The Netherlands) at the Grenoble MRI facility-IRMaGe, equipped with a 32 channel-head coil. The protocol included a long rs-fMRI sequence (longer than current sequences used in tinnitus research investigations) for which participants were instructed to lie with their eyes open and let their minds wander without focusing their thoughts on anything in particular while a gray background image with a small white cross in the center was displayed. A highresolution structural T1-weighted image was also acquired. The parameters of the gradient echo echo planar imaging sequence were adjusted to lower the scanner noise, thus

Loss R

2 - 8

Loss L

0.25 - 8

0.5

and 8

| T4 | 38 | R&L | 15 | 26 | AR | 4–8 | 4–8 |
|-----|----|-----|-----|----|------|-------------|-----------|
| T5 | 59 | R&L | 25 | 22 | AR | 4-8 | 4-8 |
| T6 | 28 | R&L | 10 | 8 | М | _ | |
| T7 | 42 | R&L | 2 | 14 | AR | 0.5–1 and 8 | 8 |
| T8 | 43 | R&L | 14 | 32 | AR | 8 | 8 |
| T10 | 42 | R&L | 18 | 24 | M&AR | 0.25-4 | 2-8 |
| T11 | 51 | L | 10 | 44 | AR | 0.25-8 | 0.25-8 |
| T12 | 40 | R | 16 | 18 | AR | _ | |
| T16 | 26 | L | 1 | 12 | AR | _ | 4-8 |
| T17 | 60 | R&L | 17 | 12 | AR | 0.25-0.5 | 0.25-8 |
| T18 | 24 | R&L | 1 | 26 | Μ | — | |
| T19 | 25 | R&L | 16 | 4 | Μ | — | |
| T24 | 41 | R | 2 | 12 | М | 4-8 | 0.5 and 8 |
| T28 | 49 | R | 0.5 | 12 | AR | 4-8 | 8 |
| T30 | 57 | R&L | 10 | 6 | W | 4-8 | 4-8 |
| T35 | 51 | L | 10 | 16 | М | _ | |
| T37 | 33 | R&L | 15 | 6 | AR | _ | 0.25-0.5 |

TABLE 1. TINNITUS PARTICIPANTS' CHARACTERISTICS

THI

6

8

Noise

W

AR

Duration

12

25

Age (in years), ear: side of the tinnitus percept, duration: tinnitus duration (in years), THI score: from the tinnitus handicap inventory questionnaire. Origin of the acoustic trauma: M, AR, W. Hearing loss: frequency range (in kHz) where hearing loss >25 dB HL (hearing thresholds ≤25 dB HL in frequencies tested are denoted [--]).

AR, army riffles; HLs, hearing levels; M, music; THI, tinnitus handicap inventory; W, noisy workplace.


FIG. 1. Frequency spectrum of the low noise rs-fMRI sequence used in this study $(-\Box)$ as compared with the frequency spectrum usually used with this scanner $(-\diamond)$. The low noise sequence was adjusted to limit high frequencies for all participants, with a mean attenuation of 13 dB sound pressure level >1 kHz. rs-fMRI, resting-state functional magnetic resonance imaging.

limiting the acoustic dose received by the participants. This was achieved by decreasing the slope of the commutation gradients (i.e., SoftTone=yes). The frequency spectrum of the acquisition sequence presented a peak at a lower frequency (630 Hz) and a 10 dB reduction compared with standard sequences. High frequencies, above or equal to 1 kHz, presented an average reduction of 13 dB when compared with the standard sequence used in fMRI on this MR scanner (Fig. 1). This sequence was reported as acoustically comfortable by the participants. Other main parameters were 32 slices, 3.5 mm thick, acquired with a multiband factor of 2, in-plane voxel size = $3 \times 3 \text{ mm}^2$, repetition time (TR)= 2000 ms, echo time (TE) = 32 ms, flip angle = 75° , SENSE factor=3, 5 dummy volumes, and 400 volumes. This long acquisition duration (13'20") was chosen since it is directly related to the reliability of rs-fMRI connectivity estimates (Birn et al., 2013; Termenon et al., 2016). The T1-weighted structural image acquisition had the following parameters: 3D Magnetization Prepared Rapid Acquisition GRE, $0.9 \times 0.9 \times 1.2 \text{ mm}^3$, inversion time = 800 ms, TR = 25 ms, TE = 3.9 ms, flip = 15°, SENSE factor = 2.2.

MRI data preprocessing

As the seed of interest in the right OP3 is precisely localized within the brain, we designed the analysis pipeline to preserve spatial accuracy as much as possible. We preprocessed the fMRI data using Statistical Parametric Mapping 12 software. Preprocessing of fMRI data included motion correction, slice-timing, and coregistration of functional images on the individual structural image. We further realigned all individual anatomical and functional images to a common referential using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) elastic registration algorithm (Ashburner, 2007) that allows accurate interindividual brain realignment in particular around the main sulci (Klein et al., 2009). To do this, we first segmented each structural image to extract the gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) images. We then calculated the deformation field that transforms the individual GM images to a highly resolved GM template compatible with the standard Montreal Neurological Institute (MNI) coordinates system. We chose the template provided with the Computational Anatomy Toolbox for sake of spatial accuracy. The deformation field image of each participant was further applied to the structural GM, WM, and CSF images. The mean structural image of all participants was computed for display purposes so that our results precisely matched the anatomy. The deformation field was also applied to the functional individual images with a small smoothing kernel size $(1.5 \text{ mm}^3 \text{ isotropic})$ to limit blurring of the functional images. In an additional analysis, to better fit standard connectivity analyses, larger spatial smoothing (one with a kernel of [3 mm]³ and one with [5 mm]³) was applied to check whether the results found in the seed-based analysis with 1.5 mm smoothing were robust. All individual images were then in the same template space with the same spatial resolution (isotropic 1.5 mm) for further analysis.

Denoising was performed in all individual time series in template space within the connectivity (CONN) toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012; version 18.a). Outliers in functional time series were derived from the art toolbox, whereas physiological and noise sources were regressed from WM and CSF using CompCor (Behzadi et al., 2007). Six realignment parameters and their first-order temporal derivatives were also regressed at this point, but no global signal regression was performed since it can affect correlation patterns and introduce bias in group analysis (Saad et al., 2012). Before denoising, the histogram of voxel-tovoxel connectivity values varies between subjects and was shifted to the right. After linear regression of the confounds, the distribution of correlation values was centered around zero, with standard deviations across subjects ranging from 0.11 to 0.16 for 107 degrees of freedom, indicating good data quality. The results of the denoising step were visually inspected in each participant. Finally, band-pass filtering was applied within 0.008 to 0.08 Hz to all time series, to select the data matching the resting-state frequency band.

Seed definition for functional networks analysis

The network-based analysis included the DMN, first described by Fox et al. (2005) and six networks derived from the independant components analysis decomposition of resting-state data set of 497 individuals recruited in the Human Connectome Project. These networks correspond to the visual, the sensorimotor–auditory, the saliency, the language, the frontoparietal, and the dorsal attentional networks. A seed was defined at each node of the networks.

Definition of exploratory seed regions

We included as our main region of interest (ROI) the tinnitus-related region in the right OP3 derived from our previous study (Job et al., 2016a). This ROI and its spatial equivalent on the left hemisphere (as control) were boxes $(9 \times 4 \times 4 \text{ mm}^3)$ built with Marsbar, centered at MNI: ±40–13 17, corresponding to the location previously found. For a more extensive exploration of the right OP3, we created two additional equal-sized boxes just anterior and posterior to the first ROI, respectively, centered at MNI: ±40–9 17 and ±42–17 17 (Fig. 2). We also defined an ROI that encompassed the whole right OP3 with the help of the Anatomy toolbox.



FIG. 2. Seeds from the OP3 region used in this connectivity study: the tinnitus-related seed (in red; centered at MNI coordinates ± 40 , -13, and 17) and the seeds from the anteroposterior gradient: the anterior seed (in green) and the posterior seed (in yellow). Localizations are superimposed on the mean anatomical images of our group of 38 subjects. MNI, Montreal Neurological Institute; OP3, operculum 3. Color images are available online.

To address the connectivity of the auditory areas said to be involved in tinnitus perception, six other regions were chosen bilaterally along the auditory pathway. These seeds were defined based on the anatomy in the inferior colliculus (4 mm sphere centered at ± 4 , -36, and -10), the medial geniculate bodies (5 mm sphere centered at ± 17 , -24, and -10), and based on the Anatomy toolbox for Heschl's gyri by combining the Te1.0, Te1.1, and Te1.2.

Statistical analysis of functional connectivity networks

All connectivity analyses were performed using the CONN toolbox (v. 18a).

For each subject and each network, a seed-to-voxel connectivity map was computed from each seed of the network using Pearson's correlation. Individual maps were converted to *z*-maps using Fisher's transform to ensure data normality. In the network-based analysis, an *F*-test was performed across all seed maps and subjects in each group (within-group analysis), introducing THI and hearing loss as covariates of no interest. For within-group analysis, whole-brain false discovery rate (FDR), FDR-corrected threshold of p < 0.05 was retained for statistical significance. Differential functional connectivity (between-group analysis) is performed by weighing the *F*-test with a [1–1] contrast. For between-group analysis, p < 0.0001 and a cluster-size p-FDR corrected <0.05 were retained for statistical significance.

Statistical analysis of seed-based functional connectivity

For each subject and each seed, a seed-to-voxel connectivity map was computed using Pearson's correlation and converted to z-maps using Fisher's transform. For within-group analysis, a one-sample *t*-test was performed while regressing THI and hearing loss, considered as covariates of no interest. An FDR-corrected threshold of p < 0.05 was retained to assess statistical significance. In the between-group analysis, differential connectivity was calculated using a two-sample *t*-test with the contrasts [1–1] testing for stronger connectivity in tinnitus compared with controls and [–1 1] testing for weaker connectivity in tinnitus compared with controls. For exploratory analysis, we chose a statistical threshold (p < 0.0001, cluster-size p-FDR corrected <0.05) to elicit significant differential connectivity.

Results

Participants' characteristics

In tinnitus participants, the mean hearing threshold was significantly different from that of the control group, for frequencies ranging from 1 to 8 kHz (Mann-Whitney test, p < 0.05), with marked hearing loss at frequencies >4 kHz (Mann-Whitney test, p < 0.001), as usually observed with acoustic traumas (Fig. 3). At the frequency of the peak of noise in the acquisition sequence, no difference in hearing performance was found between the two groups, thus ruling out the possibility that differential connectivity arose from differences in acoustic perception related to scanner noise. All tinnitus participants described their tinnitus as highpitched whistling, except for one participant who described a medium high-pitched sizzling. Tinnitus loudness was scored on an analog visual scale (mean 4.5±standard deviation 1.6 ranging from 2 to 8, from a total possible range 0-10). Bilateral tinnitus represented 68% of our population.



FIG. 3. Audiograms of acoustic trauma tinnitus participants and control groups (mean $\pm 95\%$ CI) for both ears showing the hearing loss at high frequencies for the tinnitus group. Mann–Whitney tests results in the comparison of hearing thresholds (*p < 0.05, **p < 0.001) are displayed. CI, confidence interval.



FIG. 4. Between-group comparison of functional connectivity with the sensorimotor-auditory network (**A**) and with the frontoparietal network (**B**). From left to right: the network from the CONN toolbox atlas; surface rendering of the between-group differential connectivity with the network; MNI coordinates and sagittal, coronal, and axial views of the foci. Results are superimposed on the MNI template provided with CONN. CONN, connectivity. Color images are available online.

There was the same amount of right and left tinnitus. Tinnitus duration ranged from 6 months to 25 years (mean 12.2 ± 7.3 years).

THI scores described slight to mild tinnitus in all participants (mean 16.2 ± 10.5) except for one with moderate tinnitus (THI=44), reflecting a tinnitus population less impacted than in the current literature in the field.

Detailed results from audiometry and neuropsychological testing are presented in Table 1 for tinnitus participants.

No significant differences in autonomic status were found between our two groups during rs-fMRI acquisition.

Functional network-based connectivity results

Within-group network-based results were able to replicate typical patterns of connectivity in all networks.

At network level, between-group differences were found with the sensorimotor–auditory and with the frontoparietal networks (Fig. 4). With the sensorimotor–auditory network, we found differences in connectivity with the right paracingulate gyrus (5, 26, 41), the right middle temporal gyrus (63, -51, 04), and the right precentral gyrus (-50, 4, 15). In the connectivity with the frontoparietal network, differential connectivity between the two groups was found with the right medial frontal gyrus (40, 18, 34). Coordinates are reported in MNI system after DARTEL registration (Table 2).

No between-group differences were found in the connectivity with the DMN, visual, language, dorsal attentional, and saliency networks at the chosen statistical thresholds.

Functional connectivity with the auditory pathway seeds

Within-group analysis with Heschl's gyri showed bilateral connectivity with auditory regions, operculum, insula, dorsal anterior cingulate cortex, and the face representation of the sensorimotor cortex (Fig. 5).

 TABLE 2. SIGNIFICANT DIFFERENTIAL FUNCTIONAL CONNECTIVITY RESULTS

 FOR THE SENSORIMOTOR-AUDITORY AND FRONTOPARIETAL NETWORKS

| Two-sided networks of interest at $p < 10^{-4}$ | | | MNI coordinates | Statistical results | |
|---|--------------------------------|----|--------------------------------|---------------------|----------|
| Network seed Brain region | | BA | <i>x</i> , <i>y</i> , <i>z</i> | <i>F-value</i> | Extent |
| Sensorimotor-auditory | Right paracingulate gyrus | | 4, 26, 40 | 12.15 | 34 |
| network | Left inferior precentral gyrus | 6 | -50, 04, 15 | 10.03 | 21 19 |
| Frontoparietal network | Right middle frontal gyrus | 8 | 40, 18, 34 | 10.39 | 24 |

No other significant differential connectivity was found between both groups. Results were all obtained at height threshold p < 0.0001, extent threshold p-FDR corrected <0.05.

BA, Brodmann Area; FDR, false discovery rate.

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FIG. 5. Within-group connectivity with the right (A) and left (B) Heschl gyrus seeds for controls and tinnitus groups showing a common pattern between groups. Between-group differences reached significance for the single connectivity between left HG and the posterior cingulate cortex (right part of the figure). Results are overlaid on the MNI template provided with CONN. HG, Heschl gyrus. Color images are available online.

Between-group analysis with Heschl's gyri seeds elicited a single significant differential connectivity between left Heschl's gyrus and the bilateral posterior cingulate cortex (0, -46, 32; Table 3).

Between-group analysis with the inferior colliculus seeds elicited a difference in the right superior parietal lobule (38, -40, 39; Table 3). No differential connectivity was found from the medial geniculate body seeds at the defined statistical thresholds.

Functional connectivity with OP3 seeds

Within-group analysis of the right OP3 box at (40, -13, 17) in controls and tinnitus (Fig. 6A) revealed a main connectivity with the sensorimotor network (bilateral precentral gyri, bilateral postcentral gyri, bilateral central and parietal opercular cortices, and supplementary motor area), but also with the salience network (bilateral insular cortex and anterior cingulate gyrus) and the auditory network (bilateral planum temporale, and bilateral planum polare). Within-group analysis of the contralateral left

OP3 box in controls and tinnitus (Fig. 6B) provided a similar pattern as with the right OP3 box, reflecting a symmetrical pattern of connectivity. Within-group connectivity of the whole right OP3 region (Fig. 6C) presented a larger extent of connectivity than for the right OP3 box, justifying the precise localization of our seed.

Between-group comparison revealed a specific connectivity in the tinnitus group compared with controls with the right OP3 seed. Increased connectivity was found with a region in the right superior frontal gyrus at the border of Brodmann Area (BA) 6 and 8 (Fig. 7A), with a maximum at MNI coordinates (20, 11, 47; Table 4). We could not elicit any differential connectivity from the homologous left hemisphere OP3 box, even at a lower threshold. No significant reduced connectivity was found in the tinnitus group as compared with the control group. The additional analysis performed with a spatial smoothing of $3 \times 3 \times 3$ mm³ confirmed the finding in BA6/8 (same maximum location, T=6.17 and extent = 28 voxels). The additional analysis with a $5 \times 5 \times 5$ mm³ kernel provided no significant difference between groups, probably due to

 TABLE 3. SIGNIFICANT DIFFERENTIAL FUNCTIONAL CONNECTIVITY RESULTS

 FOR TINNITUS>CONTROLS GROUPS ALONG THE AUDITORY PATHWAY

| Tinnitus>control | | MNI coordinates | Statistical results | | |
|---|--|-----------------|--|-------------------------------|----------|
| Seed | Brain region | BA | <i>x</i> , <i>y</i> , <i>z</i> | T-value | Extent |
| Inferior colliculus (±4, -36, -10) Left Heschl gyrus | Right superior parietal lobule Posterior cingulate cortex | 40 23 | $\begin{array}{c} 38, -40, 40 \\ 0, -46, 32 \end{array}$ | 18.34 (<i>F</i> -value) 5.11 | 28 18 |

No other significant differential connectivity was found between both groups. Results were all obtained at height threshold p < 0.0001, extent threshold p-FDR corrected <0.05.





the mixing of signals originating from different regions (opercular, insular, and temporal regions) induced by spatial smoothing. These results confirm the need for a precise localization of the seeds.

The anterior and posterior seeds in the right OP3 gave different between-group differential connectivity results. The anterior seed did not show any significant differential connectivity, whereas the posterior right OP3 seed displayed an increased connectivity with a region contralateral to the frontal region elicited earlier with the original R-OP3 box and with the left inferior parietal lobule (IPL; Fig. 7B; Table 4). The seed comprising the whole OP3 displayed no between-group differences in connectivity. No decreased connectivity in the tinnitus group was found compared with the control group.

Discussion

The chronicity of tinnitus may induce particular connections within the brain, which could correspond to a "tinnitus network." Many investigations using fMRI were performed in an attempt to observe this phenomenon. However, facing the heterogeneity of literature results, the need for homogeneous groups of tinnitus participants has been recently pointed out. In this study, we conducted an fMRI study at rest with a group of subjects with nonbothersome chronic tinnitus of similar etiology, acoustic trauma, and compared resulting functional connectivity with a group of matched healthy subjects.

Differential connectivity with the main resting-state networks

Functional connectivity with the main resting-state networks revealed differences between our groups in two networks (Table 2). In the sensorimotor-auditory network, we found between-group differences in connectivity with the left inferior premotor area, the right associative auditory area, and the right paracingulate gyrus. The left inferior precentral gyrus is located within an area common to all kinds of motor illusions (Naito et al., 2017). This difference in connectivity in the tinnitus group reinforces our hypothesis that tinnitus could relate to a proprioceptive illusion linked to the middle ear muscles (Job et al., 2016b). The differential connectivity that we found with the right posterior middle temporal gyrus is associated with auditory processing, such as the detection and analysis of acoustic changes (Schönwiesner et al., 2007) or the tracking of sound in space (Da Costa et al., 2018). The paracingulate gyrus seems to be a key region for allocating cognitive resources to concurrent information (Gennari et al., 2018). This leads



FIG. 7. Between-group connectivity: (**A**) differential connectivity for the tinnitus group compared with the control group showing the increased connectivity of the right OP3 seed with the right superior frontal gyrus (R H-PEEF); (**B**) differential connectivity for the tinnitus group compared with the control group showing the increased connectivity of the right posterior OP3 seed with the left superior frontal gyrus (L H-PEEF) and left inferior parietal lobule. Results are overlaid on the MNI template provided with CONN. H-PEEF, human premotor ear–eye field. Color images are available online.

one to think that the chronic perception of phantom sounds must require a permanent allocation of cognitive resources to extract the relevant auditory input while minimizing the middle ear proprioceptive illusion corresponding to tinnitus. The frontoparietal network was also found to present a differential between-group connectivity with the right medial frontal gyrus, a core node for cognitive control. Interestingly, in this very region, the activity in response to a cognitively demanding task was found reduced in a group of chronic tinnitus subjects, suggesting a cognitive load permanently involved in maintaining tinnitus awareness (Trevis et al., 2017). Another explanation for this cognitive load could be the permanent filtering out of the tinnitus percept.

Unlike in previous studies, the lack of differences in other networks such as the DMN (Chen et al., 2018; Elgoyhen et al., 2012) or the attentional networks (Husain, 2014; Maudoux et al., 2012; Schmidt and Carpenter-Thompson, 2017) is notable here. In the DMN, this may be related to the lack of distress associated with tinnitus in the present participants. Indeed, the distress component of tinnitus has been shown to be associated with increased connectivity in the DMN (Chen et al., 2018) and between the limbic system and the auditory cortex (Chen et al., 2017; Leaver et al., 2016a). No difference in connectivity was found in our study with the dorsal attentional network, although Schmidt et al. (2017) found an increased connectivity of this network with the precuneus that correlated with tinnitus severity (Schmidt and Carpenter-Thompson, 2017). This discrepancy could be due to the low severity of tinnitus in our group of subjects compared with Schmidt's group.

 TABLE 4. SIGNIFICANT DIFFERENTIAL FUNCTIONAL CONNECTIVITY RESULTS

 FOR TINNITUS>CONTROLS GROUPS FOR THE RIGHT OPERCULUM 3 (OP3) SEED

 AND FOR THE RIGHT OP3 POSTERIOR SEED

| Tinnitus>control | | | MNI coordinates | Statistical results | |
|---|--|------------------|--|----------------------|----------------|
| Seed Brain region | | BA | <i>x</i> , <i>y</i> , <i>z</i> | T-value | Extent |
| Right OP3 box (40, -13, 17)Right superior frontal gyrusRight OP3 post box (42, -17, 17)Left superior frontal gyrusLeft inferior parietal lobule | | 6/8 6/8 40 | $20, 11, 47 \\ -21, 8, 44 \\ -42, -42, 48$ | 6.10 5.17 5.12 | 22 9* 18 |

No other significant differential connectivity was found between both groups. Results were all obtained at height threshold p < 0.0001, extent threshold p-FDR corrected <0.05. Seeds location can be seen in Figure 2.

*Region achieving above height threshold but only a tendency for statistical extent threshold.

OP3, operculum 3.

Differential connectivity along the auditory pathway

Along the auditory pathway, we found differences in connectivity between the inferior colliculus, known for its role in integrating multiple auditory signals that help filter out sounds from vocalizing, breathing, and chewing activities and focus on important sounds, and the right superior parietal lobule, which is involved once again in cognitive control. This suggests that early along the auditory pathway, different cognitive resources are required for the filtering out of tinnitus. Interestingly, in rats with noise-induced tinnitus, deep brain stimulation of the inferior colliculus suppresses behavioral evidence of tinnitus (Smit et al., 2016). Although Davies et al. (2014) displayed no group differences in the auditory cortex in their study of nonbothersome tinnitus, we found increased connectivity in the tinnitus group compared with controls, between the left Heschl's gyrus and the posterior cingulate cortex. The latter is a node of the DMN that is thought to play a central role in supporting internally directed cognition. For tinnitus treatment purposes, this region was targeted in a neurofeedback intervention and showed a reduction of tinnitus-related distress (Vanneste et al., 2016). In our case, as tinnitus subjects did not present such distress, this observation would not explain the increased connectivity. No other significant differential connectivity was found between our two groups, supporting the view that mild tinnitus after acoustic trauma is not directly related to modified connectivity with auditory regions. This is consistent with results from Langers et al. (2012) who found that macroscopic tonotopic reorganization in the auditory cortex is not required for the emergence of tinnitus, and that this reorganization relates to hearing loss.

Exploratory findings with OP3 and nonauditory hypothesis

When considering the seed of the right OP3 box derived from previous studies (Job et al., 2012, 2016b), withingroup connectivity was found to involve the somatosensory and the salience as well as the auditory networks. This suggests that our seed may play a pivotal role in the integration of somatosensory and auditory inputs presenting salient features. This result is in line with a recent functional connectivity study suggesting that the parietal operculum could be a connector hub linking auditory, somatosensory, and motor cortical areas (Tanaka, 2018). When checking for significant between-group differences, we found an increased connectivity between the tinnitus-related right OP3 seed and a region of the right superior frontal gyrus (at the limit between BA6/8). As this seed did not present any differential connectivity with sensorimotor-auditory networks, it seems to be a new connection. Furthermore, when testing the functional connectivity from the region just posterior to this seed, the increased connectivity found in the tinnitus group compared with controls in the left superior frontal gyrus mirrors that on the right (Table 4). This suggests the existence of a connectivity gradient within the right OP3. These bilateral regions are located anatomically just anterior to the bilateral frontal eye field. This seems to correspond to the region of the premotor ear-eye field (PEEF) documented in macaque monkeys (Lanzilotto et al., 2013), which is thought to play an important role in engaging the auditory spatial attention for the purpose of orienting eye and ear toward the sound source. The region found here could act as a human homologue of the PEEF, so a human PEEF (H-PEEF). In macaques, the PEEF involves auditory motor cells for both eye and ear movements (Hutchison et al., 2012; Lanzilotto et al., 2013; Lucchetti et al., 2008). The human homologue to the macaque PEEF (H-PEEF), for which the connectivity with the right OP3 is disturbed in participants with tinnitus, is a new finding. It is possible, although speculative, that similarly to the PEEF in macaques, the H-PEEF might play a premotor role in the control of coordinated ocular movements and tympano–middle-ear movements, pinna movements being vestigial in humans. If so, the oculomotor muscles' proprioceptive system responsible for eye coordination (Donaldson, 2000) would be disturbed by its potential coupling with an altered middle-ear system.

Interestingly, these results could shed light on unexplained observations of poor binocular coordination in subjects with tinnitus. Oculomotor performance during saccades (Lang et al., 2013), fixation, smooth pursuit, optokinetic nystagmus movements, and vergence was reduced in tinnitus participants Jozefowicz-Korczynska, 2002; Kapoula et al., 2010; Lockwood et al., 2001; Mezzalira et al., 2007; Yang et al., 2010); however, signs of vestibular dysfunction were absent. Furthermore, there is mention in the literature of tinnitus subjects capable of modulating their tinnitus with eye movements (Coad et al., 2001). These lower performances do not seem to be related to the severity of the handicap because they do not correlate with neuropsychological tests measuring the emotional/attentional status Jozefowicz-Korczynska, 2002). A cross-talk with the visual system could also provide some answers to another poorly understood condition, that of visual snow reported by 63% of subjects with bilateral tinnitus (Renze, 2017).

An alternative explanation could be that these bilateral areas in the superior frontal gyrus correspond to the 6 ma region described in the atlas derived from the data of the Human Connectome Project (Glasser et al., 2016). Interestingly, a study of the recently identified fiber pathway, the frontal aslant tract, describes the fine structural connections of this tract and shows the existence of a WM link between OP3 and the 6 ma region (Briggs et al., 2018). Its function is still not well documented but a report suggests the right frontal aslant tract may support executive function, namely inhibitory control and conflict monitoring for action (Dick et al., 2019). Whether this tract is different in subjects experiencing tinnitus remains to be studied and lies beyond the scope of this study.

In addition, in the right posterior seed, increased connectivity was observed with the IPL. The IPL is a vast region participating in the integration of sensory information. For instance, the left IPL is involved in proprioceptive illusion (Kavounoudias et al., 2008; Naito et al., 1999, 2017), tactile illusion (Kavounoudias et al., 2008), as well as auditory illusions (Brancucci et al., 2017). These new findings support the view that acoustic trauma tinnitus could bear a proprioceptive contribution.

Tinnitus group homogeneity

Tinnitus population homogeneity appears as a key parameter to help disentangle tinnitus percept *per se*, associated auditory dysfunctions such as hearing loss, psychological, and cognitive impacts of tinnitus, and resulting alterations of

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the quality of life. In this report, we studied a group of subjects experiencing chronic slight-to-mild tinnitus (mean THI 16.2), of moderate loudness (mean Visual Analogic Score 4.5 on a 0–10 scale), with greater hearing loss in the highfrequency range than in the control group, and duration >6 months, indicator of the chronicity of the percept. We regressed out the THI and the hearing loss to limit their contribution. The influence of duration was tested (not described here) but did not show any significant results, indicating that chronicity rather than duration is the important feature in these subjects. Moreover, to rule out the potential influence of the autonomic system to the functional connectivity, we measured the HRV in both groups, finding differences in neither the low-frequency range nor the high-frequency range related to respiration rythm. We thus believe that the results correspond to the percept per se, and that the regions highlighted are involved in the coping strategies for living with tinnitus without discomfort.

Methodological issues

Common to all tinnitus subjects are the phantom percept and the related coping mechanisms. However, the acquisition conditions, the analyses used in the field are heterogeneous and consensual results are difficult to provide. We thus believe that future studies would be able to replicate at least part of our findings when using the same kind of data and processing (long-acquisition duration, precise normalization using DARTEL, and small smoothing kernel). To allow future researchers to benefit from our results, we deposit our preprocessed, denoised, and filtered data on the OpenNeuro platform.

Conclusion

In this study, we compared the functional brain networks of a group of subjects with chronic slight to mild nonbothersome tinnitus of acoustic trauma origin with a group of control subjects. We found differences in connectivity in the main networks with regions involved in cognitive control and proprioception. In an exploratory analysis, we found that the subregion in the right OP3 already shown to be related to tinnitus (Job et al., 2012, 2016a) and its immediate posterior region are connected to two mirror areas located bilaterally in the superior frontal gyrus, just anterior to the bilateral frontal eye fields. This altered connectivity does not reflect an abnormal interplay between the main resting-state networks. Instead, it seems focal because when we further tested a larger seed involving the whole cytoarchitectonic right OP3, there no longer was any abnormal connectivity.

These new findings support the view that tinnitus could have a proprioceptive contribution in acoustic trauma and that a permanent cognitive control is required to filter out this chronic phantom percept.

Authors' Contributions

Experiment conception and design were carried out by A.J. and C.D.-M. Experiment execution was done by A.J. and C.D.-M. Data analysis was performed by A.J., C.D.-M., and C.J. Discussion of the study was carried out by A.J., A.J., A.K., C.J., and C.D.-M. Article writing was carried out by A.J., C.D.-M., A.J., A.K., and C.J.

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Author Disclosure Statement

The authors declare that no competing financial interests exist.

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4.3 Structural analysis with Diffusion Weighted Imaging

The second part of this chapter questions whether non-bothersome tinnitus of acoustic trauma origin may correlate with structural changes in the white matter. Because white matter changes have been shown to occur as a result of sensory stimulation, tinnitus as a constant ongoing perception may drive increased white matter density in fibre bundles connecting to regions involved in auditory perception. On the other hand, tinnitus may also occur as a result of disrupted inhibitory circuits, and thus be reflected by decreased white matter density. To examine these elements, we used diffusion-weighted imaging and state of the art models of the diffusion signal using tissue-specific constrained deconvolution, and a deep-learning based fibre bundle segmentation and tractography approach [272].

4.3.1 Tracking white-matter brain modifications in chronic non-bothersome acoustic trauma tinnitus

My contributions to the article included data preprocessing, analysis, results and figure generation and discussion, and manuscript writing, which justified my position as first author. NeuroImage: Clinical 31 (2021) 102696

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Tracking white-matter brain modifications in chronic non-bothersome acoustic trauma tinnitus



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ABSTRACT

Subjective tinnitus is a symptom characterized by the perception of sound with no external acoustic source, most often accompanied by co-morbidities. To date, the specific role of white matter abnormalities related to tinnitus reaches no consensus in the literature. The goal of this study was to explore the structural connectivity related to tinnitus percept per se, thus focusing on a specific population presenting chronic non-bothersome tinnitus of similar etiology (noise induced) without co-morbidities. We acquired diffusion-weighted images with high angular resolution in a homogeneous group of mildly impacted tinnitus participants (n = 19) and their matched controls (n = 19). We focused the study on two subsets of fiber bundles of interest: on one hand, we extracted the acoustic radiation and further included any intersecting fiber bundles; on the other hand, we explored the tracts related to the limbic system. We modeled the diffusion signal using constrained spherical deconvolution. We conducted a deep-learning based tractography segmentation and mapped Apparent Fiber Density (AFD) on the bundles of interest. C, as well as Fractional Anisotropy (FA) and FOD peak amplitude for comparison. Between group statistical comparison was performed along the 27 tracts of interest controlling for confounding hearing loss, tinnitus severity, and duration since onset. We tested a potential correlation with hearing loss, tinnitus duration and tinnitus handicap score along these tracts. In the tinnitus group, we observed increased AFD related to chronic tinnitus percept after acoustic trauma in two main white matter regions. First, in the right hemisphere, in the isthmus between inferior temporal and inferior frontal cortices, in the uncinate fasciculus (UF), and in the inferior fronto-occipital bundle (IFO). Second, in the left hemisphere, underneath the superior parietal region in the thalamo parietal tract and parieto-occipital pontine tract. Between-group differences in the acoustic radiations were not significant with AFD but were with FA. Furthermore, significant correlations with hearing loss were found in the left hemisphere in the inferior longitudinal fasciculus and in the fronto-pontine tract. No additional correlation was found with tinnitus duration nor with tinnitus handicap, as reflected by THI scores. The regions that displayed tinnitus related increased AFD also displayed increased FA. The isthmus of the UF and IFO in the right hemisphere appear to be involved with a number of neuropsychiatric and traumatic disorders confirming the involvement of the limbic system even in chronic non-bothersome tinnitus subjects, potentially suggesting a common pathway between these pathologies. White matter changes underneath the superior parietal cortex found here in tinnitus participants supports the implication of an auditory-somatosensory pathway in tinnitus perception.

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Abbreviations: AF, Arcuate Fascicle; AFD, Apparent Fiber Density; ATR, Anterior Thalamic Radiations; CA, Anterior Commissural bundle; CC6, Corpus Callosum, isthmus part; CG, Cingulum; CSD, Constrained Spherical Deconvolution; CST, Cortico-Spinal Tract; DTI, Diffusion Tensor Imaging; DWI, Diffusion Weighted Imaging; FA, Fractional Anisotropy; FOD, Fiber Orientation Distribution, also known as fODF, fiber Orientation Density Function; FPT, Fronto-Pontine Tract; FX, fornix; IFO, Inferior Fronto-Occipital fasciculus; ILF, Inferior Longitudinal Fasciculus; HCP, Human Connectome Project; HL, Hearing Loss; MNI, Montreal Neurological Institute.

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1. Introduction

Tinnitus consists in the conscious perception of sound in the absence of a corresponding source. It is an inherently complex condition to assess, since it cannot be characterized objectively (Jackson et al., 2019) and is symptomatic of a range of diseases (Baguley et al., 2013; Jastreboff, 1990; Møller, 2016). Its characterization mainly relies on the subject's description of their condition and its possible etiology (Crummer and Hassan, 2004; Heller, 2003), which is why understanding the underlying mechanisms responsible for this symptom remains a hot topic in neuroscientific research.

In the case of tinnitus following acoustic trauma, defined as an injury to the inner ear often caused by exposure to high decibel noise, it has been suggested that the symptom may originate from cochlear deafferentation (Eggermont and Roberts, 2015; Henry, 2016; Jastreboff, 1990; Lanting et al., 2009). Impacting the auditory pathway up to the cortex and leading to neural plasticity, this model is the historical view on tinnitus. It has been empirically contradicted as unique explanation by cases of tinnitus subsisting for instance after acoustic nerve section (House and Brackmann, 1981). In contrast with this hypothesis, some authors suggest that tinnitus persistence could also involve systems different from the auditory pathway. Reviews of neuroimaging studies have investigated grey-matter or connectivity modifications in tinnitus subjects and underline the role of the limbic system in tinnitus perception, at the level of tinnitus generation and maintenance (Adjamian et al., 2014; Simonetti and Oiticica, 2015). Further studies have shown the implication of the limbic system (Chen et al., 2017; Leaver et al., 2016), as well as the default mode network (Elgoyhen et al., 2012), the right executive control network (Kandeepan et al., 2019), but also the autonomic pathway (Vanneste et al., 2013) or a proprioceptive pathway involving the middle-ear (Job et al., 2016). In the latter, a model of tinnitus induced by acoustic trauma based on auditory, autonomic, limbic and middle ear proprioceptive pathways is proposed.

Yet, no clear picture emerges from these numerous studies. Why? The discrepancies found throughout the literature likely relate to comorbidities associated with tinnitus. Indeed, subjects included in most studies present various levels of hearing loss, distress, differences in etiology or differences in coping strategies to manage their symptom, to name a few. The lack of consensus due to these confounding factors has led some authors to advocate for more homogeneous groups of participants (Koops et al., 2019; Schmidt et al., 2018; Wineland et al., 2012). First, considering the chronicity of tinnitus helps categorize the percept. Tinnitus is considered chronic when it has been at a constant state for at least 6 months (Tunkel et al., 2014). Second, quantifying the subjective experience using a visual scale or a questionnaire makes it more observable and comparable. Moreover, the subjective characterization of tinnitus as bothersome seems to constitute a criterion for medical intervention. Tinnitus is considered bothersome when negatively affecting sleep, concentration, emotions, and social enjoyment (Bauer, 2018). For clinical studies, Bauer encourages clinicians to distinguish patients with bothersome tinnitus from patients with non-bothersome tinnitus. In the field of tinnitus research, in order to deepen the understanding of the neural correlates of tinnitus percept per se, targeting chronic tinnitus with a low impact on daily life as evaluated by the Tinnitus Handicap Inventory (THI) limits the occurrence of confounding factors related to the presence of co-morbidities. In addition, focusing on tinnitus of acoustic trauma origin further improves the homogeneity of the recruited subjects. Finally, remaining confounds such as degree of hearing loss or age that may still appear between tinnitus and control participants must also be accounted for using appropriate statistical methods

That said, the literature provides evidence that long term mechanisms come into play in the presence of chronic acoustic trauma tinnitus perception. It is now established that the central nervous system has a remarkable capacity for plastic change, even into adulthood, resulting from changes in input stimuli (Gage, 2004). The literature on structural plasticity suggests that white matter modifications, as measured with Magnetic Resonance diffusion weighted imaging (DWI), are reinforced by disease duration as in multiple sclerosis (Deppe et al., 2016), by chronicity of traumatic brain injury (Håberg et al., 2015) and psychological factors (Melloni et al., 2019), among others. The persistent subjective perception of a chronic sound, as experienced by tinnitus subjects after an acoustic trauma event, could also lead to structural as well as functional plasticity. Few studies have investigated the structural modifications of white matter fiber bundles in tinnitus subjects using DWI. One of the first studies to do so reported the involvement of auditory or auditory-limbic connectivity (Seydell-Greenwald et al., 2014). This is consistent with anatomical evidence of afferent and efferent connections between the auditory and the limbic system in the healthy brain (LeDoux, 2007; Sah et al., 2003; Weinberger, 2004; Winer and Lee, 2007) However, it was also found that changes in white matter were rather related to cofactors such as hearing loss, age, depression levels or to tinnitus loudness (Adjamian et al., 2014; Gunbey et al., 2017; Luan et al., 2019; Ryu et al., 2016; Seydell-Greenwald et al., 2014; Yoo et al., 2016). The question of the role of the limbic system specifically in non-bothersome tinnitus remains open. Other reports addressed WM connectivity alterations with matched groups, or while regressing confounding factors, and using Diffusion Tensor model (Benson et al., 2014a; Schmidt et al., 2018). Schmidt's subgroup study showed no differences with the control condition, supporting the idea again that homogeneous groups are needed for white matter differences to be elicited. Benson's matched hearing loss study of tinnitus provided evidence of Fractional Anisotropy (FA) increasing in the tinnitus group in the left thalamic, frontal and parietal white matter. In the present study, we aim to focus on the WM alterations related to the chronic tinnitus perception per se with a specific focus given to the auditory and to the limbic pathways, based on reviews of the literature and models of noise induced chronic tinnitus (Job et al., 2016; Kapolowicz and Thompson, 2020; Kraus and Canlon, 2012; Langguth et al., 2019; Leaver et al., 2016).

Finally, additional heterogeneity in DWI studies may pertain to methodological issues: rapid progress in the field of DWI inevitably makes results difficult to compare (Scott-Wittenborn et al., 2017). Indeed, DWI developments have come a long way since diffusion modeling by tensor as performed with diffusion tensor imaging (DTI) (Farquharson et al., 2013), a model that assumes a single fiber orientation per voxel. DTI prevailed in previous studies on tinnitus and may remain relevant in brain areas where simple fiber configurations exist but has proved to be particularly limited in regions of crossing fibers (Douaud et al., 2011; Pierpaoli et al., 2001; Wheeler-Kingshott and Cercignani, 2009), which is the case for most white matter voxels (Jeurissen et al., 2013). Both improvements in data acquisition (high angular diffusion directions, multiple b-values, among others) and in computational modeling of the signal using Orientation Distribution Function (ODF)-based models were developed to solve complex cases of crossing or kissing fibers (Tournier et al., 2011). In practice, for tractography related applications, spherical deconvolution and its constrained versions (CSD) using a spherical harmonics basis offers a good trade-off between clinical feasibility and the model's ability to accurately represent the underlying fiber populations (for a review, see (Dell'Acqua and Tournier, 2019)). Recent additional contributions of deep-learning methods for distortion correction and for fiber bundle segmentation have taken diffusion imaging processing a step beyond (Schilling et al., 2019; Wasserthal et al., 2019). These methods benefit from the increasing availability of large, standardized, high-quality datasets, such as provided by the Human Connectome Project (HCP), improving the robustness of fiber bundles delineation for use in neural network-based methods.

The aim of the present study was to investigate whether or not there may exist white matter modifications related to the chronic experience of tinnitus in a homogeneous group of participants with non-bothersome tinnitus induced by acoustic trauma. In this study, we took advantage of the latest methodological developments to revisit structural WM plasticity related to tinnitus.

2. Materials and methods

The study was approved by the Local Ethics Committee CPP Sud-est V, Ref: 10-CRSS-05 MS 14-52, and conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants.

2.1. Participants

In the chronic tinnitus group, nineteen male participants (mean age 42.5 \pm 12 years old, range 24 to 64 years) were included. Inclusion criteria were tinnitus of acoustic trauma origin, tinnitus duration of at least 6 months, tinnitus considered as non-bothersome by participants. Subjects having had ear surgery, or with objective tinnitus, neurological lesions or diseases, psychiatric disorders, or with MRI related contraindications were excluded. Tinnitus participants full description is given in Table 1A. Their tinnitus characteristics were: mean duration 11.6 \pm 7.6 years, median = 12 years, range 0.5–25 years; 68% of bilateral tinnitus, 16% right lateralized and 16% left-lateralized; loudness (mean 4.4, range 2–8) assessed on a visual analog scale from 0 to 10; medium high pitched sizzling (n = 1) and high pitched whistling (n = 18).

Table 1

Demographic data of the population investigated. A. Tinnitus participants description, including: laterality (B: bilateral ; L: Left-sided; R: Right-sided), duration of tinnitus since onset, THI: Tinnitus Handicap Inventory score, origin of tinnitus (W: Working environment; AR: Army Rifle; M: Music), HL: Hearing Loss in decibels. B. General characteristics for the entire study group.

| л | | | | | | | |
|---------|----------------|------------|---------------------|-----|-----------------|------------|--|
| Subject | Age (years) | Laterality | Duration (years) | THI | Origin of AT | HL (dB) | |
| T1 | 56 | В | 12 | 6 | W | 34 | |
| T3 | 43 | В | 25 | 8 | AR | 14 | |
| T4 | 38 | В | 15 | 26 | AR | 20 | |
| T5 | 59 | В | 25 | 22 | AR | 46 | |
| T6 | 28 | В | 10 | 8 | М | 8 | |
| T7 | 42 | В | 2 | 14 | AR | 18 | |
| T8 | 43 | В | 14 | 32 | AR | 18 | |
| T10 | 42 | В | 18 | 24 | M & AR | 25 | |
| T11 | 51 | L | 10 | 44 | AR | 31 | |
| T12 | 40 | R | 16 | 18 | AR | 10 | |
| T16 | 26 | L | 1 | 12 | AR | 25 | |
| T17 | 60 | В | 17 | 12 | AR | 23 | |
| T18 | 24 | В | 1 | 26 | М | 6 | |
| T19 | 25 | В | 16 | 4 | М | 12 | |
| T24 | 41 | R | 2 | 12 | М | 22 | |
| T28 | 49 | R | 0.5 | 12 | AR | 23 | |
| T30 | 57 | В | 10 | 6 | W | 29 | |
| T35 | 51 | L | 10 | 16 | М | 9 | |
| T37 | 33 | В | 15 | 6 | AR | 11 | |
| В | | | | | | | |

| | | Control Participants (n = 19) | Tinnitus Participants (n = 19) |
|----------------------|------------------------|----------------------------------|-----------------------------------|
| THI | Mean (std) | - | 16.2 (10.5) |
| Hearing Loss (dB) | Range Mean (std) | _ 13.2 (3.8) | 4–44 20.2 (10.3) |
| Age (years) | Range Mean (std) | 70 42.5 (11.9) | 6–46 42.5 (11.6) |
| Duration (years) | Range Mean (std) | 24–64 – | 24–60 11.6 (7.6) |
| - | Range | _ | 0.5–25 |

Etiology included acoustic trauma related to military and leisure activities (rifle noise, loud music). 9 participants were professional military and 9 had other backgrounds. They were offered to participate in the study by medical unit physicians in military regiments and by the Ear Nose and Throat department of military hospitals. Since most tinnitus subjects having experienced acoustic trauma were male and in order to avoid an odd male/female ratio, we chose to include only male participants, thus avoiding a gender bias factor in our study. In the control group, the 19 age and gender-matched participants were recruited by word of mouth and through a call for volunteers. They were allowed to have experienced tinnitus occasionally in the past. There were no military among the controls because there was a risk that hearing problems may not be mentioned by the participants out of concern for an impact on their careers.

Prior to MRI examinations, hearing levels were measured in all participants using tonal audiometry at 0.25, 0.5, 1, 2, 4, and 8 kHz (Audioscan fx, Essilor®) and electroacoustic calibration was performed in accordance with French AFNOR standard S3007. The audiometer was equipped with Beyer dynamics DT48 earphones. Hearing thresholds were established using the automatic Hughson-Westlake procedure and hearing loss was expressed in dB HL. As described in (Job et al., 2020), hearing thresholds for frequencies of 1 to 8 kHz were significantly different between the groups (Mann-Whitney test, p < 0.05), with increased hearing loss above 4 kHz in the tinnitus group, consistent with acoustic trauma sequelae (Fig. 2).

Tinnitus participants were asked to complete a form collecting general information about their tinnitus, and the Tinnitus Handicap Inventory (THI) questionnaire to assess the intrusiveness of the symptom on daily life (Newman et al., 1996). The THI was translated to French and yielded a score out of 100 reflecting tinnitus severity. THI scored slight to mild in all participants (mean 16.2 ± 10.5 , range 4–44) except for one participant with moderate tinnitus scoring THI = 44, reflecting the effort made in this study to constitute a homogeneous group of mildly impacted subjects.

Demographic data from the two groups of participants are reported in Table 1B. Noteworthy is the fact that tinnitus appears immediately after acoustic trauma, and therefore tinnitus duration is equal to the duration since the acoustic trauma event.

Autonomic status was assessed at rest in all participants by measuring heart rate variability before MRI acquisition using the signal from an ear photo-plethysmography (emWavePro, HeartMath ®) sensor. The signal was registered at 100 Hz sampling frequency and the peaks of the hemodynamic pulse were detected. The estimation of heart rate variability from these pulses are excellent at rest (Schäfer and Vagedes, 2013) allowing the analysis with Kubios software (https://www.kubios. com). Inter-peak intervals were further examined in time-domain, frequency-domain, and in nonlinear frameworks. Differences in autonomic status between the groups were tested using non-parametric Mann-Whitney U-tests in SPSS (IBM Corp. Released 2013). IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp®). No significant differences were found between the groups in the autonomic status during the course of the experiment.

2.2. MRI acquisitions

A 3 T Philips Achieva-TX system (Best, The Netherlands) from the IRMaGe MRI facility (Grenoble, France) with a 32-channel head coil was used for MRI scanning. The protocol included an anatomical T1-weighted sequence and a 15 min-long high angular resolution diffusion-weighted sequence.

The spin-echo diffusion-weighted sequence included 70 axial slices of 2 mm thickness with in-plane spatial resolution of 1.67 mm², and a SENSE factor 2 was applied in the antero-posterior direction. 60 diffusion images were acquired with different gradient orientations at b = 1000 s/mm^2 as well as one image at b = 0 s/mm². The repetition and echo times (TR/TE) were set to minimum with actual values 5500/72 ms. The total sequence duration was 15:08 min.

The 3D-T1 MPRAGE (Magnetization Prepared Rapid Acquisition Gradient Echo) anatomical acquisition was the same for all participants, with following parameters: 150 axial slices, voxel size = 0.9*0.9*1.2 mm³, TI = 800 ms, TR = 25 ms, TE = 3.9 ms, flip angle = 15° and acceleration factor = 2.2.

2.3. Preprocessing of diffusion images

After conversion from raw DWI Philips data (PAR-REC format) to nifti, we performed denoising (Veraart et al., 2016) and removal of Gibbs artifacts (Andersson and Sotiropoulos, 2016) using corresponding functions from the MRtrix3 package (Tournier et al., 2019), version 3.0 RC3. In order to correct susceptibility-induced EPI distortions, we used an approach based on a synthetic non-diffusion image derived from the T1 using deep learning (Schilling et al., 2019). The synthetic b = 0 image was subsequently used to correct the DWI volumes for eddy current distortions and susceptibility-induced EPI distortions using FSL's TOPUP and EDDY functions (Andersson et al., 2003; Graham et al., 2017). We ran a bias field correction with ANTs (Tustison et al., 2010), upsampled the images to a 1.3 mm isotropic resolution and proceeded with global intensity normalization (Raffelt et al., 2012). Finally, the individual DWI maps were rigidly registered to MNI space as advised for TractSeg use (Jenkinson et al., 2002; Wasserthal et al., 2019).

For each subject, the response to the diffusion phenomenon of single fiber white matter (WM), grey matter (GM) and CSF were obtained using an unsupervised method (Dhollander et al., 2019). These subject-specific responses were averaged across the group to obtain, for each tissue compartment, a unique group-specific response function. This ensures downstream comparability of the fiber orientation distribution (FOD) images and further computed metrics (Dell'Acqua et al., 2013; Raffelt et al., 2012).

We then modeled the diffusion signal voxel-wise using a single shell, three tissue type constrained spherical deconvolution (CSD) framework and estimated the FOD images as well as CSF and GM compartments with MRtrix3Tissue (https://3Tissue.github.io), a fork of MRtrix3 (Tournier et al., 2019). The peaks, or three largest maxima of the FOD expressed in a spherical harmonics' basis, were extracted and used as input for bundle-specific segmentation and tractography.

2.4. Fiber bundles of interest (FOIs)

The scope of the study was narrowed down according to a tinnitus related hypothesis. We focused on the acoustic radiations (AR), the tracts that were found to intersect with them, and those documented as part of the limbic system atlas (Mori et al., 2009). These criteria thus targeted the following 33 FOIs. Those from commissural bundles: the isthmus of the corpus callosum (CC6) and the anterior commissural bundle (CA). Those from association bundles: fornix (FX), bilateral cingulum (CG), inferior fronto-occipital fasciculus (IFO), uncinate fasciculus (UF), inferior longitudinal fasciculus (ILF) and arcuate fascice (AF). Those from projection bundles: acoustic radiation (AR), anterior thalamic radiations (ATR), superior thalamic radiations (STR), optic radiations (OR), fronto-pontine tract (FPT), parieto-occipital pontine (POPT), thalamo-parietal (T_PAR), thalamo-occipital bundle (T_OCC).

2.5. FOI tractography

The bundle specific tractography pipeline TractSeg that allows to compute the individual tractography based on deep neural networks was used (Wasserthal et al., 2019). Briefly, it runs as follows: the subject-specific peaks image is fed to a deep neural network (U-NET) that was trained on a dataset of 105 subjects from the Human Connectome Project (HCP). The pretrained UNET returns three output types per subject. First, the mask of the FOI. Then, the ROIs corresponding to the

beginning and end regions of each FOI. Finally, it returns the vector field representing the local fiber orientations, also known as tract orientation maps (Wasserthal et al., 2018). This in turn supports the probabilistic tracking of 10,000 fiber trajectories in each FOI and each subject.

Note that the acoustic radiations require a specific pipeline. As reported in the literature (Maffei et al., 2019), the acoustic radiations are notoriously difficult to segment and tract. Nonetheless, this was made possible using a different initial segmentation with Xtract (Warrington et al., 2020), which TractSeg was also trained upon. This was followed by a probabilistic tracking of 10,000 fiber trajectories in MRtrix3 using the segmentation results provided by Xtract.

As a quality control, a visual inspection of each FOI was performed for each subject. As the fornix and anterior commissure were not robustly reconstructed across all subjects, as expected with clinical data quality (Wasserthal et al., 2019), they were removed from further analysis.

2.6. Along FOI profiles of CSD and tensor derived metrics

In each bundle and each subject, the FOI profile was represented by the centroid fiber, estimated as the fiber minimizing the average distance to all fibers in the bundle (Garyfallidis et al., 2012; Yeatman et al., 2012). All fibers were divided into a fixed number of 100 segments. Fiber segments were then assigned the segment index of the closest centroid segment in an approach based on Bundle Analytics (Chandio et al., 2020). The metric values were evaluated along each segment of each streamline, and the average of these values was assigned to the corresponding centroid streamline segment.

The main metric used in this study was the Apparent Fiber Density (AFD), computed as the integral of the FOD lobe using afdconnectivity in MRtrix3 to access the results of FOD segmentation (Smith et al., 2020, 2013). As a complementary metric, we also used the FOD peak amplitudes and the tensor-derived fractional anisotropy (FA) for further comparison with previous literature.

Note that for ST-PAR and ST-OCC, the geometry of the bundles prevented this approach to find a clear segment assignment. These tracts were thus not included in the statistical analyses.

For sake of clarity, the overall pipeline is represented in Fig. 1

2.7. Statistical analysis

2.7.1. Between groups comparison

Age and hearing loss were reported to impact WM tractography (Yoo et al., 2016). Since both groups were matched in age, the co-factors that were retained in the analysis were the hearing loss, the THI and the tinnitus duration. In order to highlight any group differences related solely to tinnitus perception, we first linearly regressed all three confounds. Then we used a standard independent 2-sample t-test to compare metrics between tinnitus participants and controls, for each bundle and each position along the tract, using the additional statistical tools provided in TractSeg. Multiple comparison correction was performed (in TractSeg's tractometry scripts) using non-parametric permutation testing with 5000 permutations (Nichols and Holmes, 2002), for multiple bundles and multiple positions along tracts correction. The permutation-based correction algorithm returns a family wise error (FWE) corrected value ($p_{FWE}\,<\,0.05$), which provides the threshold below which the pvalue is considered significant. In addition, we considered a five neighboring segments cluster extent threshold for the discussion. For completeness, we provide the results obtained with 2 neighboring segments in the Supplementary Materials. The statistical threshold was again divided by three (additional Bonferroni correction for 3 metrics).

Results were plotted as tract profiles (Yeatman at al., 2012) displaying the evolution of the considered metric of interest for each group (mean and standard deviation) versus the position along the bundle. Overlaid are the statistically significant regions.



Fig. 1. Pipeline of the processing used.

In order to check for any remaining influence of tinnitus laterality, we also performed the aforementioned analysis on the subgroup of bilateral tinnitus participants (n = 13).

2.7.2. Correlation analysis

We investigated the potential influence of each cofactor on the metrics of interest using a correlation analysis. We estimated a linear

regression model and computed the correlation between the cofactor of interest and the target metric, while subtracting the terms corresponding to the other confounds weighted by their respective regression coefficients. For hearing loss, we computed Pearson's correlation with the metric values of the entire group, while for THI and tinnitus duration we used only the values from the tinnitus group. Permutation based correction for multiple comparisons was applied as described above.



Fig. 2. Frequency dependant levels of hearing loss in decibels in tinnitus and control participants.

Finally, we calculated the effect sizes (Cohen's d for group differences and f2 for correlation analyses) and evaluated *post hoc* statistical power of significant results.

3. Results

3.1. Between group differences along tracts

The results with corresponding p-values and calculated power are summarized in Table 2. The two-sample Student's *t*-test between both groups for all profiles revealed an AFD increase in the tinnitus group compared to controls in four FOIs: in the right uncinate fasciculus, the right inferior fronto-occipital bundle, the left thalamo-parietal bundle and in the left parieto-occipital pontine tract (Fig. 3 and Table 2A), after linear regression of all 3 cofactors. More specifically, in terms of locations along the FOIs, in the right UF (Fig. 3A), the significant area

Table 2

Between group differences along the tracts: (A) significant differences in AFD; largest differences along the acoustic radiations; (B) significant differences in FOD-peak-amplitudes; (C) significant differences in FA. * values uncorrected for multiple comparisons.

| Bundle names | Min p- value* | Segment number | T- value | Cohen's d | power |
|------------------|------------------|-------------------|-------------|--------------|-------|
| (A) AFD | | | | | |
| IFO_right | 6.70E-08 | 17 | -6.764 | 2.255 | 0.980 |
| POPT_left | 8.32E-07 | 10 | -5.942 | 1.981 | 0.907 |
| UF_right | 4.95E-09 | 62 | -7.632 | 2.544 | 0.998 |
| T_PAR_left | 1.63E-08 | 11 | -7.233 | 2.411 | 0.993 |
| AR_right | 4.70E-05 | 29 | 4.623 | 1.541 | 0.554 |
| AR_left | 0.00037 | 22 | -3.930 | 1.310 | 0.312 |
| (B) FOD-peak- | | | | | |
| amplitudes | | | | | |
| ATR_right | 4.48E-06 | 14 | 5.394 | 1.798 | 0.802 |
| IFO_right | 1.6E - 09 | 17 | -8.017 | 2.672 | 0.999 |
| UF_right | 8.02E - 08 | 57 | -6.705 | 2.235 | 0.979 |
| T_PAR_left | 2.23E-07 | 9 | -6.371 | 2.124 | 0.958 |
| (C) | | | | | |
| FA | | | | | |
| AR right | 1.30E-05 | 34 | 5.037 | 1.679 | 0.702 |
| IFO right | 1.64E-08 | 17 | -7.231 | 2.410 | 0.994 |
| OR left | 3.10E-08 | 51 | 7.018 | 2.339 | 0.990 |
| POPT_left | 2.22E-06 | 10 | -5.622 | 1.874 | 0.855 |
| STR_left | 9.53E-06 | 13 | -5.149 | 1.716 | 0.736 |
| UF_right | 1.86E-06 | 62 | -5.680 | 1.893 | 0.867 |
| T_PAR_left | 6.50E-08 | 9 | -6.775 | 2.258 | 0.982 |
| T_OCC_left | 2.44E-08 | 50 | 7.099 | 2.366 | 0.991 |

corresponds to the inferior part of the isthmus between the ventromedial prefrontal cortex and inferior temporal lobe. For the right IFO (Fig. 3B) the significant area was situated between the anterior insula and the ventromedial prefrontal lobe, in the superior part of the isthmus between frontal and temporal lobe. The left POPT (Fig. 3C) presented a significant increase in the fanning portion of the tract, close to the parietal cortex. For the left T-PAR (Fig. 3D), the significant increase in AFD in the tinnitus group is located in the fanning part of the parietal subdivision of the corona radiata close to the left POPT, while a significant decrease was observed in the region close to the thalamic seed (Fig. 3D).

When considering specifically the acoustic radiations, no statistically significant differences in AFD were found between both groups. None-theless, at a weaker threshold ($p_{uncorrected} < 0.0001$), a difference could be elicited in the right acoustic radiation that we report for future studies at a location that bends just above the posterior part of the ventricle (Table 2A; Supp. Mat. S1). The low power found for this result does not robustly argue in favor of the involvement of the acoustic radiation in this subjective phantom percept. Note that this result holds for the segment between the medial geniculate body and the temporal lobe but not between the inferior colliculus and the medial geniculate since the acoustic radiation pipeline used here doesn't allow the reconstruction in this portion of the tract.

Considering the FOD peak amplitudes metrics, differences between both groups were found significant in four bundles with increased FOD peak amplitudes for the tinnitus group in the right IFO, the right UF and left T-PAR (Supp. Mat. S3) in the same locations as with AFD and with decreased FOD peak amplitudes in the right ATR and another part in the left T-PAR (Table 2B). No significant difference was found in left POPT, the region found with AFD.

Finally, for sake of comparison with the previous literature, the results with the FA metric (Fig. 4 and Table 2C) presented increased values in the tinnitus group as compared to controls in the right UF, the right IFO, the left T_PAR, the left POPT and the left STR . The locations in these bundles (except left STR) are the same as those with the AFD. The left STR location was also found with the AFD but with a smaller extent threshold of two neighboring segments. The tinnitus participants also present decreased FA values in the right AR, the left OR and the left T_OCC bundles (see statistical values in Supp. Mat. Table 3). This pattern of decrease was not found with the AFD analysis. Conversely, the region where decreased AFD was found in the left T-PAR also presents a similar profile in the FA analysis but does not reach significance.

We also present the results obtained for group comparisons with a smaller segment extent ($n \ge 2$) for AFD (Supp. Mat. S1). Significant differences were then found in 12 additional fiber bundles: in the bilateral AF, the bilateral ATR, the right size of the isthmus of the CC (CC6), the left and right CG, the left FPT, the left part of the IFO, the right OR, the left UF and the left T_OCC. In these smaller segments, the Cohen's d were higher than 1.8 with power above 0.80 (see statistical values in Supp. Mat. Table 1).

Additionally, the analysis of AFD in the subgroup of bilateral tinnitus participants reproduced the results found with the whole group analysis. Following results were elicited: a decrease of AFD for tinnitus participants in the middle of the right AF, an increase of AFD in CC6, in the middle of the right IFO, at the beginning of the right ILF, in the left OR, in the left STR, and in the right T-PAR, in the mirror region of T-PAR left found for the whole group analysis. Two more results were found: in the right AR, at the cortical extremity (joining Heschl's gyrus), and in the left AR in the vicinity of the medial geniculate body, mirroring the result displayed in Supplementary Fig. S2.

3.2. Effect of hearing loss, THI and tinnitus duration

As expected, age and hearing loss were found to be significantly correlated, (r = 0.545, p = 0.0005) (Cardin, 2016; Yoo et al., 2016). No other significant correlation was found among cofactors.

The correlation analysis between AFD along the tracts and the three



Fig. 3. Statistically significant Apparent Fiber Density group differences.

cofactors (hearing loss, tinnitus duration since onset and THI scores), returned significant results only for hearing loss. A negative correlation was found in the left FPT and in the left ILF (Fig. 5). The more severe the hearing loss, the lower the AFD in these tracts. In the left ILF, the correlation with HL was found significant in the inferior lateral part of the temporal lobe (Fig. 5A), while in the left FPT, the correlation was found significant in the fanning part of the dorsal frontal lobe (Fig. 5B). For sake of completeness and further studies on tinnitus, we report the tendency results ($p_{FWE} < 0.1$): at this threshold, the right UF in the inferior part of the temporal lobe presents an additional negative correlation with hearing loss (Supp Mat S4). No tendency for a correlation with THI or with tinnitus duration was found.

The FOD peak amplitudes correlation analysis rendered a single correlation found with hearing loss in the left FPT, similar to the result found in the left FPT for AFD. (Supp Mat Fig. S5)

Finally, the correlation analysis with FA returned a negative correlation with HL in two tracts: the left FPT and the left ILF (Fig. 6), both in the same locations as with the AFD analysis. No significant correlation with THI nor with tinnitus duration was observed.

3.3. Metrics comparisons along FOIs

The previous literature mainly reports FA metric based on the tensor model that assumes a single main fiber per voxel, while in this study we derived AFD and FOD peak amplitude metrics derived from a model accepting multiple fiber directions per voxel. It appears thus interesting to document these different metrics along the FOIs, for further comparison with previous DTI studies. We thus displayed the profiles of AFD, peaks amplitude and FA metrics taken in the control group (Fig. 7) along the FOIs after Z-transforming within each bundle for comparison. We observed strong similarities between AFD, FOD peak amplitudes, and FA profiles in most tracts. Noticeable is the difference in the acoustic radiations in their middle parts with lower AFD than FA, located approximately in region ld1 of the right insula. Other minor differences are located at the extremities of tracts (AF, CG, POPT, UF) or in their middle parts (CC6, FPT, OR, T_OCC). Note that right AR presents a particular profile with a decrease in its center (see Supp. Mat. S3), that might come from the particular geometry of this bundle.

4. Discussion

4.1. Summary/overview

The present study mapped apparent fiber density (AFD) profiles along fiber bundles of interest in chronic non bothersome tinnitus participants and controls. Fiber density is a metric of connectivity, reflecting the capacity of a fiber bundle to transfer information (Raffelt et al., 2017). While decreased AFD could thus reflect white matter atrophy, increased AFD could reflect white matter plasticity mechanisms, as typically supporting learning or adaptation to new sensory input (Sampaio-Baptista and Johansen-Berg, 2017; Stampanoni Bassi et al., 2019). White matter maladaptive plasticity is an erroneous modification of brain circuitry causing unwanted side effects, such as phantom perceptions. Evidence of cortical plasticity occurring after noise trauma both in the auditory pathway (Langguth et al., 2019) and in the limbic structures (Kapolowicz and Thompson, 2020) support the hypothesis of a joint contribution of both pathways for tinnitus to be perceived.

Here, we observed increased AFD related to chronic tinnitus percept

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Fig. 4. Significant results in the Fractional Anisotropy profiles.

after acoustic trauma in two main WM regions. First, in the right hemisphere, in the isthmus between inferior temporal and inferior frontal cortex, in its inferior part, in the UF, and in its superior part, in the IFO. Secondly, in the left hemisphere, in the superior parietal region of fiber bundles T-PAR and POPT. No significant differences were found in the acoustic radiations for AFD. Furthermore, significant correlations with hearing loss were found in the left hemisphere in the ILF and FPT. No additional correlation was found with tinnitus duration or with tinnitus handicap reflected by THI scores. The regions that displayed tinnitus related increased AFD also displayed increased FA.

Considering that the tinnitus group was mildly impacted by the symptom, that they had similar etiologies for that symptom and that confounding factors and multiple comparisons were taken into account in the statistical analysis, we rest assured that these results relate to the perception of tinnitus *per se* and are not contaminated by co-morbidities.

4.2. Involvement of the isthmus between inferior temporal and frontal lobes

The major result of this study emerged in the isthmus between inferior temporal lobe and inferior frontal cortex of the right hemisphere within two fiber bundles, the uncinate fasciculus and the IFO.

So far, the function of the uncinate fasciculus remains poorly known.

It was recently described, with a virtual dissection study of a cohort of 60 participants (Hau et al., 2017) and using diffusion data of the Human Connectome Project (Briggs et al., 2018). It has been proposed to play a role in the limbic system, particularly in emotional regulation (Von Der Heide et al., 2013). This is of particular interest considering the involvement of limbic tracts that have been reported in tinnitus participants (Seydell-Greenwald et al., 2014). Indeed, in Seydell-Greenwald's study, a WM region in the inferior part of the isthmus, probably belonging to the UF, presented bilateral significant correlations between DTI metrics (FA and MD) and tinnitus loudness. In our study, alterations of AFD in the structural white matter tracts were also elicited in the UF, mainly in the right hemisphere but also in the left UF mirroring the location in the right hemisphere, when considering a smaller segment extent. Although the group characteristics, the data acquisitions and the analysis pipelines differed between both studies, these concordant findings in the same locations might reflect a general change in the WM in this particular region. Throughout the literature, the UF appears to be involved with a number of neuropsychiatric disorders, including PTSD following TBI (Williamson et al., 2013), depression (Bracht et al., 2015; Taylor et al., 2007), social anxiety disorder (Bas-Hoogendam et al., 2016) and Alzheimer's disease (Bozzali et al., 2016). Interesting here is the fact that the participants of the present study are free of neuropsychiatric disorders. We could thus hypothesize that the evolution of non-



Fig. 5. Significant correlation between AFD values and Hearing Loss.

bothersome tinnitus of acoustic trauma origin toward tinnitus with anxiety co-morbidities might be mediated by the alteration of the uncinate fasciculus. We might also relate our findings to the alteration of the UF in PTSD following TBI (Williamson et al., 2013), since the tinnitus participants of the present study experienced another type of trauma, of acoustic origin. There might be a common neurological pathway of tinnitus of acoustic trauma origin, TBI and PTSD as suggested in a study of military population sample (Moring et al., 2018). Our results support the idea that the right and possibly left UF may be one of the substrates of this common pathway. Furthermore, as part of the posterior termination of the UF is located in the superior temporal gyrus (Hau et al., 2017), the increased AFD found in the tinnitus subjects here may reflect an increased connectivity with auditory areas, playing a direct role in the tinnitus perception.



Fig. 6. Profiles of FA and significant correlation with hearing loss in two bundles.

The superior part of the isthmus between ventromedial prefrontal regions and temporal lobe, corresponding to the right IFO found in our study, could be related to a similar region from a DTI study in noise-induced tinnitus (Benson et al., 2014). Indeed, in this previous study, the authors found increased FA in the superior part of the isthmus, corresponding to right IFO. However, one must remain cautious when comparing with previous literature. Not only do the diffusion processing

methods differ with our study, but there also is a nomenclature issue since the naming of the tracts has evolved with time in the literature, leading to increased difficulty in the comparison. The IFO is an associative tract, composed of long fibers that connect the frontal, the temporal, and the occipital lobes (Catani and Thiebautdeschotten, 2008; Conner et al., 2018; De Benedictis et al., 2014; Hau et al., 2016). This tract is thought to be a major contributor for language, attention and

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Fig. 7. Profiles of the three metrics investigated in the study along the 27 tracts of interest.

affective behavior but also to visual recognition system. Finally, IFO could be directly related to tinnitus percept through its direct connectivity to Heschl's gyrus (Fernández et al., 2020).

Taken together, the implication of the isthmus of the UF and IFO in the right hemisphere supports the implication of the limbic system in chronic non-bothersome tinnitus subjects, confirming previous investigations.

4.3. Involvement of the superior parietal lobe

In our study the finding of increased AFD in the WM fanning underneath the superior parietal lobe is new in the tinnitus literature. The T-PAR is the parietal subdivision of the corona radiata that was found in the DTI study of noise-induced tinnitus (Benson et al., 2014) with an increased FA in tinnitus group in a location mentioned as left superior corona radiata, originating in Brodmann area 6 and terminating in the cortico-spinal tract (CST), thus potentially more anterior than what is found in our study. In the context of the tinnitus literature, other WM modifications in this region were not reported. The POPT is the tract connecting pontine nuclei with the parietal and occipital cortices, just posterior to the CST, which could also refer to Benson's findings. Together with T-PAR, we found increased AFD in the fanning portions of these tracts in the left hemisphere, suggesting a possible involvement of superior parietal regions in the tinnitus perception after acoustic trauma. This brain area is known to be an associative cortical region since it combines inputs from a number of brain areas including somatosensory, auditory, visual, motor, cingulate and prefrontal cortices, and it integrates proprioceptive and vestibular signals from subcortical areas (Whitlock, 2017). The implication of superior parietal cortex found here supports the view of an auditory-somatosensory plasticity taking place in tinnitus (Wu et al., 2016).

4.4. Involvement of the acoustic radiations

From a methodological point of view, the tracking of auditory radiations remains a challenge (Maffei et al., 2019). In this study, a specific pipeline (Xtract) enabled us to investigate the acoustic radiations between medial geniculate nuclei and the auditory cortices. The involvement of auditory cortices in the tinnitus percept remains debated. A review of previous literature using the tensor model showed that the auditory cortex and inferior colliculus of tinnitus patients were found to display changes in diffusion metrics, such as fractional anisotropy, compared to normal hearing controls (Tarabichi et al., 2018). Furthermore, a higher FA and lower MD in anatomically defined regions of interest in the white matter tracts underneath both auditory cortices in tinnitus patients compared with control subjects was observed (Seydell-Greenwald et al., 2014). However, when taking into account confounding factors it was shown that the general fractional anisotropy in the primary auditory cortex was rather related to age, duration of tinnitus and hearing loss (Yoo et al., 2016). In our study, in line with Yoo and also with Husain (Husain et al., 2011), after regression for hearing loss, THI, and tinnitus duration, we did not find changes underneath the auditory cortex. However, we found a remaining decreased FA in right AR in tinnitus group located above the posterior ventricle in the bending part of the radiation (Fig. 4, Supp. Mat. S2). With AFD, we only found a weak difference below statistical significance at this same location (Supp. Mat. S1), somehow in coherence with the FA result.

4.5. Impact of cofactors

The literature reports WM tracts modifications with hearing loss in tinnitus subjects (Husain et al., 2011; Yoo et al., 2016). Yoo and collaborators found effects of age and hearing loss in widespread nonspecific regions. In this study, where age was not different between the two groups, we found that AFD was negatively impacted and decreased with hearing loss in two fiber bundles, the left ILF and the left FPT (Fig. 5), a result also observed with FA (Fig. 6). These correlations were found in the inferior pole of the left temporal lobe, while Husain and collaborators found a correlation with FA in the ILF of the right hemisphere at a location further up in the brain close to the posterior thalamic radiation. We also found significant correlation with hearing loss in the fanning part of fronto-pontine tract underneath the left dorsal frontal lobe, a result that was not found up to now in the literature. We did not find any correlation with hearing loss in the acoustic radiations. Looking for other influences of THI or tinnitus duration on AFD, we found no further significant correlation, in line with other studies (Schmidt et al., 2018).

Laterality was evoked as a potential explanation for differences in results between studies using very similar voxel based morphometry methodologies (Landgrebe et al., 2009; Mühlau et al., 2006). But Landgrebe's study had unequal numbers of lateralized tinnitus, which would thus unlikely even out by averaging. In the present study with 13 bilateral tinnitus, 3 left sided tinnitus and 3 right sided tinnitus participants, we hypothesized that laterality would be compensated in the

averaging of the group statistical analysis. Furthermore, the subgroup analysis on bilateral tinnitus led to results that confirm those of the whole group study. The results of the main analysis are therefore likely not driven by tinnitus laterality.

4.6. Metric comparison derived from single- and multiple-fibers diffusion models

The main metric of interest in this study was the integral of the FOD lobes, also referred to as AFD. This measure relates in each voxel to the total fiber density of a given fiber bundle. The FOD peak amplitude metric relates to the fiber density per unit solid angle in the direction closest to that determined by the Track Orientation Maps. Both measures can be interpreted in relationship with the intra-axonal volume, and this interpretability is improved at high b-values (Raffelt et al., 2017). Although the b-value used in the present study is typical for clinical explorations (1000 m/s²), this should figure among the criteria to take into account for future study design. Furthermore, the differences observed between these two metrics likely relate to fiber orientation dispersion.

As the previous literature on tinnitus related to white matter modifications mainly reported tensor derived metrics (mostly FA but also mean, axial and radial diffusivities). The profiles of FA values were also derived in our study for comparison with AFD and FOD peak amplitude and displayed (Fig. 7) for the control group. These FA values were mapped on the bundle specific tractography that deals with the issue of crossing fibers. In general, anisotropy related metrics are biased by the degree of coherence of fiber tract directions (Basser and Pierpaoli, 1996). This means that even if the segmentation is performed successfully, one may not be able to disentangle between real biological changes and amounts of crossing fibers or partial volume effects (Dell'Acqua and Tournier, 2019). The interpretation of tensor derived metrics in voxels where fibers cross therefore remains subject to caution. Despite these limitations, the profiles of AFD and FA along the FOIs were very close in many bundles, in particular in the right UF and in the right IFO. In the isthmus of the right UF and the right IFO, one main anteroposterior fiber direction exists that may explain these similarities. This may also explain why the difference between tinnitus subjects and controls were congruent with findings of previous authors using FA (Seydell-Greenwald et al., 2014). In a few bundles (bilateral AF, bilateral CG, bilateral POPT), the differences are located close to the origin or termination of the bundle where not only large bundles, but also small U-fibers are present. In others (bilateral AR, bilateral FPT), they are located along the course of the bundle. This is particularly the case with acoustic radiations in the region where they present a large bending, possibly explaining the differences in results with the literature where angle thresholds could be used.

5. Methodological strengths and limitations

The two main strengths of this study are its analysis of tinnitus perception per se and its state-of-the-art methodology for white matter connectivity analysis. The population of the tinnitus group present the same etiology with trauma induced tinnitus, non-bothersome tinnitus characteristics reflected by small THI values and excluding comorbidities and known tinnitus duration providing a homogeneity in this group. The laterality of tinnitus doesn't impact the results of the present study. The control group was matched in age and gender. They differ in hearing loss, and this factor was taken into account in the analysis. They also differ in their socio-professional backgrounds, with nine professional military tinnitus participants and no military in the controls. However, the military included in the study did not present any mTBI or PTSD or other psychiatric disorders, since these were exclusion criteria. They are therefore not comparable with the participants found in the literature on blast exposure in the military. This is an attempt to answer the request in the field of tinnitus research for more

homogeneous groups of participants by design and confound mitigation (Bauer, 2018; Schmidt et al., 2018) and to further disentangle tinnitus perception from confounding factors that may explain the discrepancies in the results reported in the literature. The second strength relate to the methodology used here. Indeed, we acquired the diffusion data with high angular resolution (60 directions) in order to be able to better model the fiber orientation per voxel, this to better reflects the white matter organization and to be able to derive related metrics, that are AFD and FOD peak amplitudes. In addition, we used state of the art deep-learning approaches trained on high quality data from the HCP to segregate the different bundles of interest. On account of this approach, we think that the results of our study reflect tinnitus percept *per se* rather than its co-morbidities.

The comparison of our results with the literature remains a difficulty. Indeed, not only are the models in previous literature based on the hypothesis of a single bundle per voxel, but the statistical analysis often relies on the skeleton of white matter that may be merging different colinear bundles. The nomenclature of the bundles is an additional issue since it is not standardized yet and a single region in a given bundle may have received different names throughout the literature. In this study, we used the nomenclature from Wasserthal and collaborators that is the most accurate to our knowledge nowadays (Wasserthal et al., 2018). Furthermore, the statistical results reported in the literature mainly present p-values but not the effect size or the power, thus limiting the confidence one can have in those results. Statistical power analysis and effect sizes with both AFD and amplitude argues in favor of robustness of the results presented in this study. Furthermore, the fornix and anterior commissure are important fiber bundles of the limbic system and could not be analyzed here. This is another shortcoming of the present study which needs to be addressed in future work.

The reproducibility of TractSeg's deep learning based approach we used here for fiber tracking was tested along with other approaches during the TraCED challenge of the ISMRM diffusion study group (Nath et al., 2020). It performed outstandingly with respect to overlap measures (Dice scores > 0.8 for right UF and for right IFO) and reproducibility (ICC > 0.85 for right UF and > 0.8 for right IFO) which argues in favor of excellent robustness for this method and these bundles. The method was also shown to minimize angular error and maximize Dice scores for all 72 bundles when compared to other tract delineation and segmentation algorithms (Wasserthal et al., 2019). The fact that the anterior commissure and the fornix were not analyzed here constitutes a possible shortcoming of the present study. They are two bundles of importance in the limbic system which need to be addressed in the future. In addition, despite the state of the art methodology used, the AR reconstruction remains challenging and highly variable across subjects, even when taking a probabilistic tractography algorithm that can reconstruct the AR at b-values lower than 3000 s/mm² (Maffei et al., 2019). Although the results we obtained in the AR did not allow us to firmly conclude on their involvement in tinnitus perception (p-value slightly above the 0.05 probabilistic threshold after correction for multiple comparisons, with a power above 0.5), the segmentation and tracking were successful in all participants which is encouraging for future work with higher resolution acquisitions.

In conclusion, we provide evidence of white matter changes in the limbic system involving the orbitofrontal cortex but not between structures previously reported in tinnitus literature (hippocampus, parahippocampus, amygdala), since no changes were found in the cingulum or in the anterior thalamic radiations. The fornix and anterior commissure could not be investigated with the present acquisition conditions, but this could be solved with higher resolution acquisitions, multi-shell and higher b values combined with the advanced methods used here. Furthermore, the exact plasticity mechanisms cannot be settled using the present cross sectional study paradigm and remains an open question for future research. Causal relationships between acoustic trauma, tinnitus, and white matter plasticity could be addressed using a longitudinal analysis.

Author contributions

Experiment conception and design were carried out by A.J. and C.D.-M. Experiment execution was done by A.J. and C.D.-M. Data analysis was performed by C.J., A.A. and C.D.-M. Discussion of the study was carried out by A.A., A.J., C.J., and C.D.-M. Article writing was carried out by C.J., C.D.-M., and final version approved by all authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102696.

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4.3.2 TractLearn: Riemanian framework for anomaly detection

Building upon the previously obtained fibre bundle-specific tractography, we attempted to replicate our findings using an exploratory method of outlier detection, sensitive to relevant clinical variability while taking into account individual physiological variability, provided by TractLearn [261]. TractLearn, as presented in chapter 3, is a machine-learning algorithm which uses manifolds to approximate and project high-dimensional data into a subspace of reduced dimension. This subspace is leveraged to identify the location on the bundle of outlier diffusion metrics, as presented in figure 3.15. This work was presented as a poster at the OHBM congress in June 2021, and further developed into an oral presentation for the SFRMBM in Lyon, in September 2021.



Figure 4.1: Altered voxels were identified in a cluster of the parietal cortex.

Group differences (pFWE<0.05) were found in the thalamic radiations and in the corona radiata in the right hemisphere. The largest cluster was found in the thalamo-parietal tract, in the vicinity of the parietal operculum. These findings support the claim that the white matter fibres connecting the parietal operculum to the superior parietal cortex may be altered in noise-induced, non-bothersome tinnitus. However, further validation of this method is required.

4.4 Conclusion on the functional and structural connectivity studies targeting OP3 in tinnitus perception

In this chapter, the main objective was to investigate the role of the parietal operculum with respect to tinnitus-specific brain networks. We highlighted significant functional connectivity as well as structural connectivity differences between non-bothersome, noise-induced tinnitus participants and control participants.

The major finding of the functional connectivity study with respect to OP3 is a right lateralised, focal pattern of increased connectivity between OP3 and the ipsilateral dorsal prefrontal cortex, an analogous area of the premotor ear-eye field (PEEF) documented in primate literature. We discussed this finding with respect to the dorsal pathway of sound localisation in space and orientation, and auditory-visual integration. A connectivity pattern from the right posterior OP3 was found with the contralateral PEEF, suggesting a gradient of connectivity within OP3. A second pattern of right lateralised connectivity was found between OP3 and the inferior parietal lobule, known for its role in kinesthetic illusions. In the network analysis, the sensorimotor network presented tinnitus-related connectivity with the left inferior premotor area - also involved in sensorimotor illusions, the right associative auditory area - involved in higher order sound processing, and the paracingulate gyrus - involved in cognitive load management. Furthermore, the frontoparietal network presented an increased connectivity related to tinnitus with the right medial frontal gyrus, which is also involved in cognitive control. These results were proposed to reflect the increased functional load on cognitive resources of chronic, ongoing phantom sound perception. The phantom sound perception itself, may be rather reflected by an increased connectivity between regions of proprioceptive and sensorimotor integration, mainly located along the dorsal pathway of higher order auditory processing.

Is OP3 part of a functional network of tinnitus?

The results suggest a right-lateralised operculo-frontal connection specific

to tinnitus, with the involvement of several regions of the dorsal auditory pathway. Further research is required to determine the nature of these connections: their causal relationship, and dynamics.

The major findings of the structural connectivity study highlight a significant tinnitus-related increase in white matter density in temporo-frontal connections of the right hemisphere - in the uncinate fascicle and the inferior fronto-occipital fascicle in the isthmus between the temporal and orbitofrontal lobes, and in parietal radiations of two projection bundles of the left hemisphere. These bundles were not involved in hearing-loss. These increases of white matter density argue in favour of a reinforcement effect of tinnitus perception. The fronto-temporal connection was proposed to reflect the involvement of the limbic system, which is of interest with regards to a possible gating mechanism supported by the limbic system [92]. Interestingly, this increased density in the limbic tracts may reflect habituation, or adaptations attempting to decrease the subjective intensity of tinnitus perception. The right lateralisation of this significant difference is interesting with respect to the ventral auditory processing route, which is right lateralised in terms of frequency modulation processing and integration [79]. According to this study, tinnitus, which is a large-band frequency signal with frequency modulations prevailing over temporal modulations, should be processed in the right hemisphere. The parietal connections support the view that higher order integrative processes are reinforced, however these regions are highly un-specific.

Do the structural findings support the functional connectivity results?

The structural connectivity study provides results which are complementary to the functional study. The parietal increases in white matter density support the involvement of the left dorsal 'Where' route for integration processes involving the auditory, somatosensory, and possibly visual modalities. The right ventral 'What' route of auditory integration is found involved through increased white matter density in the connection between the temporal and frontal lobes, suggesting the involvement of the limbic system, possibly attempting to filter out the erroneous perception. These neuroimaging studies have provided complementary insight into functional and structural correlates for noise-induced, non-bothersome tinnitus. The functional results support the involvement of the parietal operculum, while the structural results are not as specific. The precise nature of the functional and structural modifications calls for further investigation, for example using a large-scale longitudinal study, to question whether habituation might preferentially drive limbic plasticity, and when exactly the operculo-frontal connection might be established. One step towards such further investigation is to look at the problem at hand from a different angle, for example using electrophysiology.

5 Intracortical exploration of the parietal operculum

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5.1 Introduction

Tinnitus perception, as previously mentioned, does not generally provide sufficient grounds for neuroimaging exploration. This is also true for intracortical electrophysiological exploration. The evidence in this field is thus scarce, and mainly provided by two study types. On one hand, by retrospective studies of participants undergoing invasive exploration for another condition, for example electrode implantation for deep brain stimulation (DBS) in Parkinson's disease, who also happened to have tinnitus [239]. On the other hand, by case studies of single or very small sample of subjects [240].

Intracortical exploration of tinnitus perception is thus essentially uncharted territory, with many open questions and potential for exploration of unique electrophysiological features at high spatial, temporal, and spectral resolutions. In this chapter, we present three studies examining brain function and tinnitus perception using intracortical recordings, relying on the clinical exploration of focal, drugresistant epilepsy. The first study makes use of high-frequency stimulation and auditory symptom generation, and compares auditory hallucinations, which tinnitus qualifies as, and auditory illusions. The second study builds upon low-frequency stimulation to evaluate functional connectivity patterns derived from cortico-cortical evoked potentials. Finally, the third study monitors local, intracortical activity during a listening task and its tinnitus-like perception after-effect.

5.2 Brain mapping of auditory hallucinations and illusions using direct electrical stimulation

Given that stimulation protocols at high frequencies can induce sensory perception symptoms, auditory symptoms can be investigated intracortically. In this framework, we specifically address the cortical regions involved in auditory hallucinations and illusions produced during direct electrical stimulation at 50 Hz, and we question the networks modulated during these perceptions. This study has been submitted as a publication in Neurology, entitled "Brain mapping of auditory hallucinations and illusions using 50 Hz Direct Electrical Stimulation", and is awaiting first round feedback. My contributions to the article included the participation in data curation and analysis, generating results and figures, and writing the manuscript, justifying my position as first author. Brain mapping of auditory hallucinations and illusions induced by Direct Intracortical Electrical stimulation

Running head: Brain mapping of DES-induced auditory responses

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Key words: Auditory hallucination and illusion, Stereo-electroencephalography, Direct electrical stimulation

Summary for Social Media If Published

- 1. @GINeuroGrenoble ; @nifm_gin
- 2. The auditory system is thought to be organized hierarchically from primary to higher order cortices with increasing complexity and decreasing specificity. Yet high resolution functional and microstructural studies of the temporal lobe show differing parcellations, implying that the precise architecture of the auditory cortex remains a subject of debate.
- 3. How are auditory perceptions presenting varying degrees of complexity processed in the brain? What implications does a precise localization of auditory perceptions have in clinical pathology?
- 4. The study provides evidence for a network-based organization of the human auditory cortex, with primary regions capable of higher order processing and secondary regions capable of low level processing. The dynamic interactions along the network reflect a specific role of the insula for integrating sensory information.
- 5. These results support the idea that auditory symptoms may involve regions outside the superior temporal lobe, with perspectives for neuromodulation targets for a range of pathological conditions with auditory manifestations such as epilepsy, schizophrenia, or tinnitus.

Abstract

Objectives:

The exact architecture of the human auditory cortex remains to date a subject of debate, with discrepancies between functional and microstructural studies. In a hierarchical framework for sensory perception, simple sound perception is expected to take place in the primary auditory cortex, while the processing and integration of complex perceptions is proposed to rely on associative and higher order cortex. We assumed that the auditory symptoms induced by direct electrical stimulation constitute a way to address the architecture and specificity of the brain networks involved during auditory hallucinations and illusions. The intracranial recordings underlying these perceptions of varying degrees of complexity provide the evidence to discuss the theoretical model.

Methods:

We analyzed SEEG recordings from 50 epileptic patients presenting auditory symptoms induced by DES. First, using the Juelich cytoarchitectonic parcellation, we quantified which regions induced auditory symptoms when stimulated (ROI approach). Then, for each major auditory symptom type (illusion or hallucination), we mapped the cortical networks showing concurrent high frequency activity modulation (HFA approach).

Results:

Although on average, illusions were found more laterally and hallucinations more posteromedially in the temporal lobe, both perceptions were elicited in all levels of the sensory hierarchy, with mixed responses found in the overlap. Spatial range was larger for illusions, both in the ROI and HFA approach. We noted that the limbic system was specific to the hallucinations network, and the inferior partietal lobule was specific to the illusions network.

Discussion:

Our results confirm a network-based organization underlying conscious sound perception, for both elementary and more complex components. While the localisation differences are interesting from an epilepsy semiology point of view, the hallucination specific modulation of the limbic system is particularly relevant to tinnitus and schizophrenia.

Body of the article: <4500 mots.

moins de 7 figures et tables, moins de 50 refs.
1 Introduction

Conscious experience, whether in health or disease, stems from the integration of cortical signals originating from a complex landscape of spatially distinct yet temporally synchronized brain regions¹. At the interface with the environment and the sensory organs, highly specific primary cortices have been proposed to occupy the ground level of a hierarchical perceptual architecture². In this framework, the incoming sensory signal is fed forward with growing levels of complexity but decreasing specificity to the higher order regions of this hierarchy, in order for perception and cognitive processes to take place³. In the auditory modality, one therefore expects simple sounds to be encoded in the posterior superior temporal gyrus, and modulations or emotional load to be added to the perception in secondary, associative, or integrative areas, such in the ventral and dorsal auditory streams and the insula⁴. symptoms⁵.

In epilepsy, conscious perceptions may originate not from peripheral sensory information but from neural discharges during seizure activity, directly in the brain regions usually responsible for these perceptions^{6,7}. Thus, the patient's experience of seizures, or semiology, which initially guides the evaluation and hypothesis on the possible location of the epileptogenic region⁸, also informs on the cortical localizations and interactions resulting in perception. In particular, auditory auras found in 1.3 to 2.4% of focal epileptic seizures^{9,10}, have mainly been attributed the ictal discharges involving the auditory cortex at the posterior portion of the superior temporal gyrus, including Heschl's gyrus and the auditory association cortex, as well as in cases of parietal or frontal seizure onset zones.

Furthermore, DES has proven a good proxy to study brain function and organisation outside of epileptic seizures, allowing to map functionally eloquent areas during the clinical work-up prior to surgery. Past studies using DES have shown that repeated stimulation of the same brain region did not consistently produce the same effect, and conversely, stimulation of widely distributed areas of the brain could yield similar symptoms⁵. These elements argue in favor of a distributed network of interconnected and synchronized neurons underlying perception and cognitive function, but the way this network is organized remains an open question.

With the present study, we thus aim at better characterizing the cortical networks underlying auditory hallucinations and illusions in a large cohort of 50 epileptic patients who underwent stereotactic intracerebral EEG (SEEG) recordings as part of their presurgical evaluation. We used DES to interrogate the influence of the type of perception on the cortical networks involved, with on one hand hallucinations occurring *sine materia*, and on the other hand illusions consisting in an abnormal modulation of an existing sensory input.

First, in a Region Of Interest – ROI – approach, we related the observed symptoms to the stimulation site. We hypothesized that both illusions and hallucinations would be evoked from auditory regions. However, owing to the hierarchical framework for sensory perception, we expected to find hallucinations mainly elicited in the primary auditory cortex (regions TE1.0, 1.1 and 1.2 in Jülich's atlas), while the modulatory component specific to illusions was expected to be triggered by stimulation to secondary associative or higher order auditory regions of the temporal

lobe, or even regions of the ventral and dorsal auditory streams. In addition, we expected to find no primary auditory sites to elicit illusions.

Then, we mapped high frequency activities (HFA, 70-150 Hz) elicited locally and at distant sites during stimulation, when auditory symptoms were produced, to establish the link between the observed symptoms and the cortical network disturbed by the stimulation procedure.

From a methodological standpoint we hypothesized that the cortical modulations observed during stimulation are representative of the subsequent behavioral consequence. By confining to the timewindow defined by the stimulation, and with appropriate management of the stimulation artefact, results will thus be free of post-discharge related biases.

From a symptom mapping point of view, we expect for both phenomena to be linked to networks of auditory processing, involving the superior temporal lobe from its posterior primary auditory cortex, to its anterior semantic processing related regions, as well as the fronto-parietal regions of the motor integration. We also expect the limbic system, with the insula, hippocampus, amygdala, and cingulate cortex¹¹, to play a significant role in the involved networks, particularly given that both illusions and hallucinations diverge from the normal sensory representations. There are two aspects of the limbic system that seem particularly relevant. First, the perception of abnormal sounds, identified as not originating from the normal environment, is likely to bear an abnormal emotional valence, which would be determined in particular in the anterior insula and amygdala. The second aspect relates to the gating mechanisms mediated by auditory limbic connections, which have been extensively studied in the context of tinnitus ¹²⁻¹⁵, a phantom sound perception which would belong to the hallucination category as defined in the present study.

1 Materials and methods

1.1 Participants

A total of 109 patients presenting focal drug resistant epilepsy found eligible for surgery underwent standard pre-surgical evaluations using intracerebral recordings at Grenoble-Alpes University Hospital. All patients gave written informed consent to carry out SEEG exploration as well as non-invasive examinations including high resolution magnetic resonance (MRI) imaging, video-EEG monitoring, neuropsychological assessment, and computed tomography (CT) scanning. For the purpose of this study, we reviewed the results of all DES procedures performed over the period of time, following standardized procedures used at the hospital ¹⁶. We identified 50 patients who experienced auditory symptoms during SEEG evaluation (patient characteristics are documented in supplementary material: Table 1).

1.2 Electrode implantation and localization

Cortical implantation selection was entirely based on clinical purposes, with no reference to the present experimental protocol. Eleven to fifteen semi-rigid, multi-lead electrodes were stereotactically implanted in each patient (stereotactic EEG –SEEG-)^{17,18} using a robot-assisted technique ¹⁹. The SEEG electrodes had a diameter of 0.8 mm and, depending on the target structure, consisted of 8 –15 contact leads 2 mm wide and 1.5 mm apart (i.e. 3.5 mm center-to-

center, DIXI Medical Instruments). Implantation was unilateral in 35 cases (11 right-sided, 24 leftsided) and bilateral in 16 cases. Patients underwent a preoperative MRI scan and a post-operative MRI or CT scan. Preoperative and postoperative scans were co-registered in order to obtain electrode position coordinates in subject space. Transform to standard space was computed using SPM12 (Statistical Parametric Mapping 12, Wellcome Department of Imaging Neuroscience, University College London, www.fil.ion.ucl.ac.uk/spm), and electrode positions were then expressed in MNI coordinates. Visual inspection for all electrode locations was performed, to check for correct co-registration and to detect whether contacts were in grey or white matter. Neuroanatomical labelling of MNI coordinates of electrode contacts was performed using an inhouse software, IntrAnat Electrodes²⁰. The Jülich Brain atlas parcellation scheme was chosen to define the regions of interest of the present study for its high precision, based on post-mortem cytoarchitectonic analysis, in the peri-auditory regions^{21,22}.

1.3 SEEG recordings and stimulations

SEEG recordings lasted from 1 to 3 weeks. A Micromed audio-video-EEG monitoring system was used to carry out experiments (Micromed, Treviso, Italy) offering up to 128 recording contacts, with a sampling frequency of 512 Hz, and acquisition bandpass filter between 0.1 and 200 Hz. Acquisition was performed using a referential montage with the reference electrode located in the white matter and all other recording sites in the grey matter. For signal analysis, a bipolar montage between adjacent contacts of the same electrode was used, to improve sensitivity to local current generators.

DES was typically performed in 1 to 3-hour sessions over multiple days under continuous video-EEG monitoring, to reproduce the patient's habitual clinical seizures and to map functionally relevant areas to be spared during surgery. DES was applied between two adjacent electrode contacts (bipolar stimulus) using a current generator delivering alternative square wave pulses (Micromed, Treviso, Italy), and according to parameters known to produce no structural damage²³. Following standard clinical procedure¹⁶, DES was performed at 1 Hz (pulse width: 1ms; DES duration: 40s) and at 50 Hz (pulse width: 0.5-1ms; DES duration: 5s), with stepwise increasing intensities (0.5 to a maximum of 5mA) until clinical responses were elicited (after-discharges or electro-clinical seizures).

The experimental setup allowed patients to be sitting upwards on the bed, facing the camera. Tasks typically included counting or listing series of words. Depending on the expected or observed clinical responses, other tasks could be undertaken (e.g., alternate forearm movements, finger tapping, listening to the observer's voice, picture naming, etc.). Patients were asked to report any symptom they experienced as soon as possible and were immediately examined and carefully questioned by the observer. Clinical and electrical findings were documented using a standardized form, and stored on hard drive.

1.4 Data analysis

1.4.1 Review of iEEG recordings and pre-processing

The raw data for each DES trial inducing an auditory symptom at 50Hz was reviewed and annotated. Because only three auditory symptoms were evoked using 1Hz stimulations, those were not further analyzed for the present study. Auditory experiences occurring in the absence of any corresponding sound input were characterized as *hallucinations*, and further divided into *simple* hallucinations (elementary sounds such as clicking, whistling, ringing, buzzing) or *complex* hallucinations (elaborate auditory phenomena such as music or voices). In contrast, altered perceptions of existing sensory input were categorized as auditory *illusions* (change in loudness, pitch, distortion, echo...). Perceptions bearing characteristics of both types were considered *mixed* responses (*i.e.*, echoing phenomenon accompanied by whistling sounds).

Each trial was annotated as follows: 1) stimulation start and end (visually identified based on the stimulation artefact), 2) auditory symptom onset (based on the video recordings), and 3) end of the post-discharge (fast oscillations occurring due to stimulation). The post-discharge activity was identified by visual examination of the recordings by an expert neurologist. The primary post-discharge management strategy was to implement ROI and HFA modulation analyses in a target time window excluding post-discharge activity, which was the case during stimulation. The risk of the results being biased by post-discharge activity was therefore mitigated. Furthermore, among all the stimulations performed, 30% of recordings were found to present a post-discharge. This thus provided insufficient data for robust HFA analysis in this selection of recordings to precisely map and compare whether results may have been influenced by subsequent post-discharges. In addition, the post-discharge activity in time-frequency domain is found to occupy the 3-45 frequency range, which was not the frequency range of interest in the present study. Finally, bad channels were automatically labeled and excluded from analysis²⁴.

1.4.2 ROI analysis

In this approach, the data was clustered by symptom type (i.e., illusion, hallucination, mixed). In case several auditory responses were obtained at different intensities for a given channel, only the response obtained at the lowest intensity was kept for analysis. To quantify the capacity of a given brain region to generate an auditory response upon stimulation, the responses from electrode contacts belonging to the same ROI were pooled together.

1.4.3 HFA analysis

To maximize the amount of data for robust network analysis, we kept all recordings during which a symptom was provoked using 50Hz DES, irrespective of whether a symptom had previously been evoked at a lower intensity.

Single trial processing

First, single trials were processed following the epileptogenicity mapping procedure developed in our team²⁵ and recently used for language mapping²⁶. Periods of interest of the SEEG recordings were taken during DES and baseline activity was chosen in the [30 5]s interval prior to stimulation onset (Figure 1.B). All timeseries were transformed into time-frequency maps for each channel (Figure 1.C). Spectral power was computed between [70 150] Hz with a 1Hz frequency resolution, using a Hanning-tapered decomposition with a fixed window length of 1s and a 100ms step size. A notch filter was applied to remove harmonics of line noise between [98 102] Hz and [148 152] Hz. Z-score normalization of DES time frequency maps was performed by dividing the DES signal to time frequency domain transform by the mean baseline estimate²⁷. Stimulation artefacts suppressed by ignoring values of z-scored SEEG power above 10, and outliers were ignored by averaging over the frequency dimension when computing SEEG power timeseries. For sake of caution, SEEG power matrix elements with a z-value above 10 in over 5% of channels were removed, including those for which the threshold was not reached. The time frequency maps in the selected time bins were log-transformed and spatially interpolated to produce images for statistical analysis. In standard space, the power values for each electrode contact were mapped to the corresponding electrode contact position. Spatial interpolation restricted voxels to the structures most often explored in presurgical protocols for temporal lobe epilepsy, namely the neocortex, the hippocampus, and the amygdala. The method used is described in depth in²⁸. Briefly, for each contact, mesh vertices within a 1cm radius are detected and each vertex detected for at least one electrode is assigned the weighted average of the SEEG power values of all nearby electrodes, with weights chosen as the inverse of the distance between the vertex and the electrodes, the closest electrode thus receiving the highest weight. Gaussian smoothing was performed using a 3 mm kernel width, in the same order of magnitude as the distance between contacts, for family-wise error rate control in the case of spatially correlated imaging data²⁹.

A two-sample t-test was used to compare symptom perception to baseline and statistical significance was determined by the FWE-corrected associated p-value using p<0.05 as a threshold. Thus, the regions displaying significant HFA modulations during DES induced auditory symptoms were obtained for each trial.

Group level analysis

To specify the group average spatial distribution of recorded responses for each auditory symptom type evoked during DES, analysis ran as follows: first, a binary mask was derived from the SEEG log power statistical maps previously obtained at a p=0.05 threshold (figure 1.D). Voxels displaying significant SEEG power values during an auditory response were kept for further analysis and assigned to their corresponding atlas ROI. Each ROI containing at least one significant voxel was therefore considered active during the evoked symptom, while regions having received no significant voxel attribution were considered inactive. For visualization purposes, the atlas resolution was set at 3mm isotropically and ROIs were dilated by one voxel to avoid gaps on surface-based representations.

ROI-level binary maps were averaged across trials to obtain group probability maps of symptom-

related SEEG power modulation. For each symptom type, an additional threshold of minimum 10 recordings per ROI was applied for sake of reproducibility. The group probability maps, further referred to as HFA maps, range from 0 (no significant HFA power increase in the ROI during any of the recordings) to 1 (systematic HFA increase during symptom perception).

2 Results

2.1 Initial assessment of recordings

A total number of 2610 cortical sites were recorded throughout the experiment, with 1578 sites in the right hemisphere and 1032 sites in the left hemisphere (Fig 2A). A total number of 141 stimulations were reported to have elicited an AR during DES at 50 Hz and at intensities between 1 - 3 mA (mean 1.6mA). Stimulations lasted between 0.5 seconds and 5 seconds (mean 4.1s). Among the 141 associated recordings, 4 had all channels labeled as 'bad' and were not subsequently analyzed.

For ROI-based analysis, recordings of symptom evocation at lowest intensity were kept, narrowing down the analysis to 127 recordings and a corresponding number of auditory responses. For network analysis of symptom-related high frequency oscillation modulation, we chose to keep all good quality recordings to maximize the amount of data for the group analysis, so a total number of 137 recordings. With the components of mixed responses considered independently, there was a total count of 144 auditory symptoms for HFA analysis.

2.2 Overview of Auditory Responses to DES

Auditory responses (AR) were in majority the only sign reported upon stimulation (80% of cases), with a leftward preference (58.7% of AR evoked from the left hemisphere). The occasional cooccurring symptoms included aphasia, visual illusion, tachycardia, thermic sensations, tactile sensation or loss of sensation, vertigo, and drowsiness (Table 1). AR were perceived as bilateral in 70 cases and unilateral in 61 cases (46.5%). Among the unilateral AR, the majority (93%) were perceived on the contralateral side to the stimulation site.

A total number of 57 hallucinations were reported (43.5% of all AR). They were mainly simple hallucinations (73.7% of all hallucinations) consisting of elementary sounds, either continuous (such as whistling, buzzing, ringing, resonating, non specific noise), or impulsive (drum, hammer, clapping, ticking). Complex hallucinations involved more elaborate perceptions such as sounds reminding a specific object (washing machine, train, doorbell) or animal (fly, cicada), voices, or music (Table 1). In one case, the hallucination was a combination of complex and simple perceptions.

Participants reported an illusion in 56.5% of cases (Table 1), mainly in the form of an echo (34%), a sensation of clogged ears (20%), variations in sound intensity, amplitude, pitch, or lag. Combinations of illusions were also observed (25%).

Mixed responses were reported for 10 stimulations, a majority of which (80%) consisted of an illusion and a simple hallucination. In 2 cases a complex hallucination was coupled with an illusion.

2.3 ROI analysis

The distribution of the total implanted electrodes and the electrodes having elicited a given symptom is illustrated in Figure 1. In the right hemisphere, we observed slightly more hallucinations (47%) than illusions (45%), and 6 mixed responses (7%). In the left hemisphere, illusions were predominant (60%) over hallucinations (32%) and mixed responses (7%). The covariance ellipses (Fig 1. C) indicate the centers of mass of illusion and hallucination distributions and quantifies their level of dispersion and overlap in the three directions. Illusions showed greater dispersion and an antero-lateral shift compared to hallucinations, in both hemispheres but predominantly in the right. Hallucinations were located on average more postero-medially, with an orientation of the ellipse towards the temporal pole in the right hemisphere.

Responses were evoked from 42 cortical Juelich ROIs in both hemispheres, out of 248 atlas ROIs (Fig. 2B). Hallucinations covered 27 regions (18 ROIs of the left hemisphere, 9 ROIs of the right hemisphere), while illusions extended over 36 regions (18 ROIs in each hemisphere). Mixed responses were found in 7 regions (3 in the right hemisphere, 4 in the left).

Among these 42 regions, 21 were common to both hallucinations and illusions (supplementary table 2). They included auditory regions of primary (in Heschl's gyri: bilateral TE1.1, left TE1.0), secondary (bilateral TE2.2 in the planum temporale, right TE 2.1, and left temporo-insular region Tel), associative (TI of the left planum polare), and higher order processing (bilateral STS1; right STS2). They also included integrative regions of the posterior insula (bilateral Ig1, right Ig2), mid insula (left Id1), and IPL (left area PFcm and right area PFop). The proportion of hallucinations versus illusions was greater in the primary areas in the right hemisphere, but not in the left. The proportion of hallucinations was also greater in the left posterior and mid insula, the left secondary areas Te1 and TE2.2. Conversely, illusions were predominant in the right secondary area TE2.2 and higher order area STS2. In the left hemisphere, illusions were predominant in higher order and secondary auditory areas as well as in primary auditory area TE1.1 of Heschl's gyrus.

Several ROIs were exclusively involved in only one symptom type. Indeed, 6 hallucination-specific regions were found in the left hemisphere, including areas of the posterior insula (Ig2), hippocampus, frontal cortex, superior temporal sulcus, frontal operculum (OP6) and parietal operculum (OP2) were specific to hallucinations, but no regions of early auditory processing.

Illusion-specific regions ranged over a wider spatial extent, and included auditory regions of the superior temporal lobe. Primary auditory area TE 1.0 and higher order area TE3 were found in the left hemisphere, as well as mid insular, inferior parietal sulcus, and inferior frontal gyrus areas. In the right hemisphere, secondary and higher order auditory areas TE 2.1 and TE 3 were found, alongside mid, posterior and anterior insular regions, inferior parietal, inferior frontal, and orbitofrontal regions (supplementary table 3).

2.4 HFA analysis

In this approach, the recordings performed across over 2000 cortical sites were pooled together to depict HFA modulations during AR. All regions represented in Figure 2 showed significant modulation compared to baseline, with a minimum threshold of 10 recordings per ROI, as required for reproducibility purposes. The level of probability provides an element of confidence: regions with high probability values were consistent in their HFA modulation with respect to symptom perception, while regions with low probability did not systematically show HFA modulation across trials during symptom perception.

The spatial coverage of HFA increase involved in hallucinations and illusions overlapped in 144 atlas regions bilaterally (out of N=248), with similar probabilities for both symptoms in regions including the primary, secondary, and associative auditory regions on the temporal lobe, as well as opercular, insular, parietal, and frontal regions. In addition, probability differences were found in this overlap.

Looking at 10% probability differences, hallucinations had a higher probability of HFA modulation than illusions in 13 regions of the right hemisphere and 23 regions of the left hemisphere (Table 2), including several non-primary auditory regions, several subdivisions of the parietal operculum, orbitofrontal regions, insular and limbic regions, where the difference was the strongest. We note that the left early auditory area TE 1.2 was found to modulate more strongly in hallucinations.

HFA modulations due to illusions were more likely than due to hallucinations in 4 regions of the right hemisphere and 7 regions of the left hemisphere, all located outside the auditory cortex. Several bilateral inferior parietal lobule regions, frontal and parieral opercular regions, modulated more strongly in response to illusions. Right early auditory area TE 1.2, insular regions and one limbic region were additionally more influenced by illusion perception.

Outside this intersection, we found patterns of HFA modulations specific to each symptom type.

For illusions, with a lower threshold set at p=0.6, 12 regions presented specific modulation. In the left hemisphere, two regions were found: in the orbitofrontal cortex and in the anterior cingulate cortex. In the right hemisphere, specific modulations were found in regions of the sensorimotor cortex (areas 4a and 4p of the precentral gyrus, supplementary motor area 6mp), the somatosensory cortex (area 1 of the postcentral gyrus, area 2 in the postcentral sulcus), the anterior (rostral) inferior parietal lobule (area PFt), the inferior frontal cortex (BA 45), and of the orbito-frontal cortex (Fo3, Fo6, Fo7).

For hallucinations, three regions presented HFA modulation probabilities above 0.6, in the sensorimotor cortex (areas 4p and 4a) and in the posterior anterior cingulate cortex.

3 Discussion

The main findings of the present study were 1) illusions and hallucinations distribute differently in the brain but these distributions overlap to a large extent, with illusions more dispersed than hallucinations and more in the right hemisphere than in the left, 2) contrarily to what was expected, certain primary regions were found to evoke only illusions and certain higher order regions were found to evoke only illusions and certain higher order regions were found to evoke only hallucinations, 3) the probability maps of HFA power modulations span similarly far for each perception, however hallucinations modulated the limbic regions more strongly than illusions and conversily, illusions modulated inferior parietal lobule regions more strongly than hallucinations.

Do our findings support a hierarchical organisation of the auditory cortex?

Our results shed a nuanced light on the hierarchical model proposed for sensory cortices, owing to the mix of perceptions induced at all levels of the proposed auditory architecture. Within this framework, DES of primary sensory areas is proposed to act as input at the initial perception level, and be fed forward as such to the next processing level in the hierarchy. In downstream processes, this signal is considered as an original perception, in other terms: a hallucination³⁰. In the case of auditory perceptions, the characteristics of the hallucinations provoked by DES of the primary auditory cortex are defined depending on the precise location of the electrode contact, owing to the fine tonotopy and periodotopy of the primary auditory cortex³¹⁻³³. On the other hand, stimulation of secondary sensory regions is expected to yield a different component of perception, with the stimulation not being recognized as initial input but as a piece of integrative information, thus an element of modulation of primary perception – an illusion³⁰. In line with this model, illusions induced in our study were indeed found, in our ROI-analysis, specifically in regions of higher auditory, in multiple insular sites, in inferior parietal regions, and in the inferior frontal gyrus. In contrast however, no regions of the primary cortex were found exclusively evocative of hallucinations. Instead, the second part of the left posterior insula was specific to hallucinations, as well as the secondary auditory area STS2. Furthermore, the left primary area TE 1.0, supposedly core auditory, related to illusions, not hallucinations. These results indicate that the primary auditory cortex is capable of higher order processing and that conversely, higher auditory areas such as the left STS2 of the ventral auditory processing stream and IPL of the dorsal processing stream, as well as posterior insular regions can be involved in early auditory processing, in line with previous suggestions of non-core auditory areas presenting sensitivity to acoustic features of sound³³⁻³⁵. This fuels the debate on the precise organization of auditory processing in humans: the parallel with the core-belt-parabelt model described in non-human primates remains to be fully established³⁵. High-resolution multimodal brain atlases do not fully align with the precise subdivisions obtained using cytoarchitectonic mapping techniques: Glasser's atlas³⁶ depicts a medial belt region overlapping over primary regions Te1.0 and 1.2 in Juelich's atlas²². The existence of mixed responses, as well as previous evidence of different symptom types being evoked at the same electrode contact, may reflect how certain cortical assemblies act as gateways between the components of the sensory structure.

With the HFA analysis, the aim was to further contrast the network of regions involved in each perception, with modulations mirroring the emergence of conscious perception³⁷. The common,

consistent involvement during illusions and hallucinations of opercular, insular, and inferior parietal lobule regions in addition to periauditory cortices argues in favor of a widespread functional network underlying both perceptions. This is in line with previous findings on dorsal and ventral streams of auditory processing ^{38,39}.

The main differences were found in the distribution of probabilities in the HFA-modulated network overlap. Strikingly, hallucinations modulated the limbic system to a much greater extent than illusions, which is in line with the two aspects of limbic involvement in auditory processing. Firstly, it may be that hallucinations, as the perception of a non existing sound, may bear a more salient emotionnal content than illusions, and this emotional content would be mediated by the amygdala and hippocampus. Secondly, this finding is relevant with respect to the role of the limbic system in gating phantom perceptions, identified as deviating from the normal sensory environment. Interestingly, illusions were found to modulate the inferior parietal cortex more strongly than hallucinations. This region belongs to the dorsal auditory stream and is involved in localisation of moving sound sources, which is coherent with the majority of illusions in the present study involving spatio-temporal features such as echoes and sound lag.

Interestingly, the insula was involved at the ROI level as well as in the HFA analysis. The left posterior insula was a key region of auditory hallucinations, while illusions were evoked bilaterally towards more anterior sections of the insula. The posterior insula is directly adjacent to the somatosensory and the auditory cortices, and has been described as the primary region of interoception, involved in a wide range of sensory perceptions, as well as in contemplative activities and fine motor behavior. The mid insula integrates the posterior multisensory components with vegetative cues and emotional load, and connects to the anterior insula. The anterior insula together with the anterior cingulate cortex, constitutes the main nodes of the saliency network, responsible for tuning in attention to relevant stimuli among the wealth of incoming sensations. Our results thus agree with a differentiated role played by the insula depending on the level of complexity – or the degree of integration – of the perception.

Relevance for pathological conditions

Intracortical exploration for severe epilepsy has a history of auditory signs mostly being elicited by stimulating the superior temporal gyrus (STG) or the middle temporal gyrus (MTG)^{40,41}, as well as the temporal pole^{41,42}, the mesio-temporal lobe⁴³⁻⁴⁵, the temporo-occipital junction⁴¹, the parietal lobe⁴⁰, and the insular cortex⁴⁶⁻⁴⁸. These elements, however, result from different stimulation approaches (intra-operative electrocorticography, extra-operative subdural or depth electrodes) with stimulation paradigms varying across series, and the exact locations of the stimulated contacts were often not provided. Furthermore, auditory symptoms have mainly been reported as a side-effect of studies targeting other brain processes⁴⁰⁻⁴⁹. The present study proposes a unified approach in a large cohort of participants to establish the value of auditory symptoms in semiology to guide the location of the epileptic zone.

The large amount of spatial overlap between the regions inducing each symptom type, the presence of illusions in primary regions and primary auditory perceptions in secondary or higher

order areas, and finally, the presence of mixed responses, do not argue in favor of a strong localizing value of specific auditory signs based on their level of complexity in epileptic semiology. The lack of univoqual anatomical specificity of auditory symptoms rather illustrates how the emergence of ictal signs and symptoms depends not only on the initial location of the epileptic discharge but also on its spread, type, and the complex spatial-temporal interactions that it produces within a multiconnected brain network⁶.

This study also presents a particular interest for auditory related pathologies. The auditory-limbic emotional processing and gating mechanisms are in line with previous findings regarding tinnitus, which qualifies as an auditory hallucination. In tinnitus, the perception itself and the associated distress and annoyance may be respectively facilitated by both auditory-limbic mechanisms ^{12,14}. Another result which is relevant specifically to tinnitus perception, and not its distress component, is the involvment of the parietal operculum and in particular OP2 in the ROI analysis and OP3 in the HFA analysis. These regions have been shown to participate in auditory-somatosensory integration, and have been proposed to mediate erroneous phantom sound perception following acoustic trauma^{50,51}.

In schizophrenia, hallucinations are a salient symptom, often loaded with negative emotion, however whereby tinnitus has been used as a basis of understanding⁵². Similarly, a lack of top-down auditory-limbic regulation to block out irrelevant or erroneous incoming sensory information has been suggested as facilitating the emergence of hallucinations⁵³. However, the perceptions differ by far with respect to the psychiatric components specific to schizophrenia. Interestingly, it has recently been demonstrated that impaired ability to recognised emotions conveyed in auditory stimuli was related to poor disease outcome in schizophrenic patients, and related to impairments in a wide range of auditory functions ⁵⁴.

Strengths and Limitations

The superior temporal plane shows considerable individual variability. We cannot fully neglect a possible influence of interindividual variability on our results, despite spatial realignment. This may account for a certain amount of dispersion in spatial mapping, but we do not think that this would lead to primary regions merging with spatially remote secondary regions such as the STS, therefore our major observations hold.

To the best of our knowledge, the present dataset is the largest existing report of DES-induced auditory symptoms, providing a large spatial coverage of brain regions. Yet we cannot deny that this coverage remains sparse and is subject to a sampling bias. The ROI approach and the thresholding used – a minimum of 10 recordings per ROI, acknowledges and deals with this issue, at the cost of dimishing the very high spatial resolution of the raw SEEG data.

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6. Author contributions

PK, OD contributed to the conception and design of the study. CJ, RAL, PD, MPB, FC, ASJC, LM, DH, OD, PK contributed to data acquisition and analysis. CJ, MPB, OD, PK contributed to drafting the manuscript and figures.

Potential conflicts of interest

No competing interests to declare.

Data availability statement

The data can be made available upon request to the corresponding authors.

TABLES

Table 1. Synthesis and classification of DES-evoked symptoms examined in the present study.

| | All AS | Ha | allucinatio | ns | | Illusions | | Mixed | |
|--|---------|-------|-------------|---------|---------|-----------|-------|--------|--------|
| | | all | simple | complex | HS + HC | | all | HS + I | HC + I |
| | n=131 | n=57 | n=42 | n=12 | n=1 | n=64 | n=10 | 8 | 2 |
| DCS side : Right / Left Hemisphere | 53 / 77 | 19/36 | 12/31 | 5/6 | 0/0 | 28 / 35 | 5/5 | 3/5 | 1/0 |
| Mean DES intensity (1-3 mA) | 1,49 | 1,44 | 1,60 | 1,52 | 3 | 1,54 | 1,40 | 1,50 | 1,00 |
| Mean DES duration (1-6 sec) | 4,04 | 3,88 | 3,88 | 4,58 | 3 | 4,19 | 5,00 | 4,63 | 6,50 |
| AS lateralization | | | | | | | | | |
| Contralateral to the DES site | 57 | 30 | 24 | 5 | 1 | 25 | 2 | 1 | 1 |
| Ipsilateral to the DES site | 4 | 3 | 3 | 7 | | 1 | | 7 | 4 |
| | 70 | 24 | 17 | / | | 30 | 0 | / | I |
| none | 105 | 47 | 37 | 10 | | 49 | 9 | 8 | 1 |
| somato-sensory / visual | 7/2 | 4/0 | 3/0 | 10 | 1/0 | 3/2 | Ű | Ũ | |
| vestibular / vegetative | 4/1 | 1/1 | 1/0 | 0/1 | - | 3/0 | | | |
| facial flushing / feeling of warmth | 1/2 | 0/2 | 0/2 | | | 1/0 | | | |
| strangeness (environment) / feeling lost | 1/1 | | | | | 1/1 | | | |
| cephalic sensation / auditory déjà-vu | 1/1 | 0/1 | | 0/1 | | 1/0 | | | |
| akinesia / tonic motor / aphasia | 1/1/5 | 0/1/2 | 0/1/2 | | | 1/0/3 | | | |
| DCS sites | 2 | 1 | | 1 | | 1 | | | |
| Temporal pole - BA38 | 2 | 1 | | I | | 1 | | | |
| STG - BA22 (anterior part) | 6 | 3 | 2 | | 1 | 2 | 1 | 1 | |
| STG - BA22 (posterior part) | 7 | 3 | 2 | 1 | | 3 | 1 | 1 | |
| STG - BA22/42 | 12 | 3 | 3 | | | 7 | 2 | 1 | 1 |
| STG - BA52 STG - BA52/41 | 3 | 1 | 1 | | | 2 | | | |
| TTG - BA41 | 27 | 13 | 13 | 1 | | 12 | 2 | 1 | 1 |
| TTG (BA41/42) | 1 | 1 | 1 | • | | | _ | | |
| TTG - BA42 | 15 | 7 | 7 | | | 7 | 1 | 1 | |
| TTG - WM | 2 | 2 | 2 | 0 | | | | | |
| STS - BA22 (anterior part) | 4 | 2 | | 2 | | 2 | | | |
| STS - BA22/21 (anterior part) | 2 | 1 | | 1 | | 1 | | | |
| STS - BA22/21 (posterior part) | 2 | 1 | | 1 | | 1 | | | |
| STS - posterior part (BA21) | 1 | 1 | 1 | | | | | | |
| STS - BA22/21 (posterior part) | 3 | 1 | | 1 | | 2 | | | |
| MTG - anterior part (BA21) | 2 | | | | | 2 | | | |
| MTG - posterior part (BA37) | 1 | | | | | 1 | | | |
| Insula - anterior part | 2 | 2 | 2 | | | | | | |
| Insula - posterior part | 14 | 9 | 6 | 3 | | 4 | 1 | 1 | |
| IPL (BA39/40) | 5 | 2 | 2 | | | 3 | | | |
| IPL (WM) | 1 | | | | | 1 | | | |
| posterior cingulate gyrus (BA23) | 1 | | | | | | 1 | 1 | |
| posterior cingulate gyrus (BA31) | 1 | | | | | 1 | | | |
| OFC (BA11/12) | 2 | 1 | 1 | | | 2 | | | |
| IFG (WM) | 1 | 1 | I | | | 1 | | | |
| Mean latency (0-16 sec) | 2,86 | 2,61 | 2,48 | 3,25 | 6 | 3,19 | 2,20 | 2,00 | 3,00 |
| Bilateral AS ipsiL>contraL | 1 | | | | | 1 | | | |
| Bilateral AS contraL>IpsiL | 6 | | | | | 4 | 2 | 1 | 1 |
| Bilateral AS non predominance | 57 | 14 | 7 | 7 | | 37 | 6 | 6 | |
| nign pitched noise / low pitched noise | 9/5 | 7/9/2 | (/4 | | 1/0/0 | | 2/1 | 2/1 | |
| whooshing / whirring sound | 9/10/4 | 1/0/3 | 3/3 | | 1/0/0 | | 2/2/1 | 2/2/1 | |
| other sound | 9 | 9 | 9 | | | | | | |
| song, music / speaking voices | 3/4 | 3/4 | 1/0 | 2/3 | 0/1 | | | | |
| noise evoking a specific animal / object | 1/5 | 1/4 | | 1/4 | | | 1/1 | | 1/1 |
| other HC | 1 | 1 | | 1 | | | | | |
| clogged ear | 15 | | | | | 13 | 2 | 2 | |
| clogged ear + resonance | 4 | | | | | 4 | | | |
| clogged ear + echo | 1 | | | | | 1 | | | |
| intensity | 6/6 | | | | | 6/5 | 0/1 | 0/1 | |
| decreased tonality / increased tonality | 5/2 | | | | | 4/0 | 1/2 | 1/1 | 0/1 |
| decreased intensity + tonality | 1 | | | | | 1 | 172 | 17.1 | 071 |
| echo | 25 | | | | | 22 | 3 | 2 | 1 |
| echo + decreased intensity | 2 | | | | | 2 | | | |
| echo + decreased tonality | 1 | | | | | 1 | | | |
| echo + increased tonality | 5 | | | | | 4 | 1 | 1 | |
| ecno + delayed perception | 1 | | | | | 1 | | | |
| delayed perception + resonance | 4/2/2 | | | | | 4/2/2 | | | |
| aciayed perception - resoliance | | | | | | | | | |

Table 2

Regions of HFA network overlap where hallucinations have a greater than 10 % higher probability than illusions, with a minimum threshold for hallucinations at p=0.6.

| Hemisphere | Brain region | Jülich parcel | Probability (hal) | Probability (ill) | Difference (hal - ill) |
|----------------------|-------------------------|-------------------|----------------------|----------------------|---------------------------|
| | Early auditory | TE 1.2 | 0,87 | 0,75 | 0,12 |
| | Superior temporal gyrus | TE 2.1 | 0,95 | 0,82 | 0,13 |
| | | ТІ | 0,87 | 0,71 | 0,16 |
| | Parietal operculum | OP3 | 0,97 | 0,85 | 0,12 |
| | Fuendal en anadema | OP6 | 0,92 | 0,77 | 0,15 |
| Frontal operculum | | OP5 | 0,88 | 0,75 | 0,13 |
| | Orbito-frontal cortex | Fo7 | 0,92 | 0,74 | 0,18 |
| | Post-central gyrus | 3b | 0,81 | 0,69 | 0,12 |
| | | IF | 0,85 | 0,48 | 0,37 |
| | | LB | 0,76 | 0,53 | 0,23 |
| | Limbic Amuadala | СМ | 0,73 | 0,24 | 0,49 |
| | LIIIDIC - AITIYguala | VTM | 0,63 | 0,41 | 0,23 |
| Left | | SF | 0,63 | 0,32 | 0,31 |
| Limbic - Hippocampus | | MF | 0,57 | 0,26 | 0,31 |
| | CA1 | 0,87 | 0,67 | 0,2 | |
| | CA2 | 0,75 | 0,46 | 0,29 | |
| | | HC-prosubiculum | 0,73 | 0,57 | 0,16 |
| | Limbic - Hippocampus | HC-subiculum | 0,73 | 0,55 | 0,18 |
| | | DG | 0,73 | 0,58 | 0,15 |
| | | HC-presubiculum | 0,71 | 0,46 | 0,25 |
| | | CA3 | 0,67 | 0,55 | 0,12 |
| | | HC-parasubiculum | 0,65 | 0,44 | 0,21 |
| | | HC-transsubiculum | 0,63 | 0,25 | 0,38 |
| | | ΗΑΤΑ | 0,56 | 0,33 | 0,22 |
| | Entorhinal cortex | Entorhinal cortex | 0,71 | 0,57 | 0,15 |
| | | TE 2.1 | 1 | 0,86 | 0,14 |
| Right | STG | TE 3 | 1 | 0,87 | 0,13 |
| | | Tel | 0,95 | 0,81 | 0,14 |
| | Frontal Operculum | OP6 | 1 | 0,83 | 0,17 |
| | | OP9 | 1 | 0,88 | 0,12 |
| | IFG | 44 | 1 | 0,89 | 0,11 |
| | Post-central gyrus | 3a | 0,94 | 0,71 | 0,23 |
| | Fusiform gyrus | FG3 | 0,63 | 0,45 | 0,17 |
| | Entorhinal cortex | Entorhinal cortex | 0,62 | 0,44 | 0,18 |

Table 3

Regions of the network overlap where illusions have a greater than 10 % higher probability than hallucinations, with a minimum threshold for illusions at p=0.6.

| Hemisphere | Brain region | Jülich parcel | Probability (hal) | Probability (ill) | Difference (ill - hal) |
|------------|------------------------|---------------|----------------------|----------------------|---------------------------|
| | Frontal operculum | OP9 | 0,77 | 0,88 | 0,11 |
| | Parietal operculum | OP4 | 0,97 | 0,85 | 0,12 |
| | IPL | PFm | 0,68 | 0,79 | 0,11 |
| Left | | PGp | 0,64 | 0,86 | 0,21 |
| | Fusiform gyrus | FusG | 0,64 | 0,87 | 0,23 |
| | Inferior frontal gyrus | 45 | 0,59 | 0,88 | 0,28 |
| | Orbitofrontal cortex | Fo4 | 0,6 | 0,88 | 0,27 |
| | Early auditory | TE 1.2 | 0,77 | 0,88 | 0,11 |
| Right | IPL | PFcm | 0,88 | 1 | 0,13 |
| | | PF | 0,81 | 0,92 | 0,11 |
| | | PFm | 0,81 | 0,96 | 0,15 |
| | Insula | ld3 | 0,77 | 0,91 | 0,14 |
| | | la | 0,72 | 0,88 | 0,16 |
| | | lg3 | 0,67 | 0,8 | 0,13 |
| | Parietal operculum | OP3 | 0,64 | 0,78 | 0,14 |
| | | OP2 | 0,63 | 0,75 | 0,13 |
| | Amygdala | IF | 0,62 | 0,72 | 0,11 |



Figure 1. Graphical representation of the processing pipeline.

A. Electrode localization, after intra-subject coregistration and transformation to MNI space. According to their MNI coordinates, each contact is then paired with its correspond ROI from the Juelich parcellation scheme for ROI analysis.

B. SEEG timeseries from 2 contacts, in the case of a 50Hz stimulation. The symptom produced during this trial was a simple hallucination (buzzing sound). Stimulation lasted 5 seconds (between t=0 : DES ON and t=5s : DES OFF). The auditory symptom started immediately after stimulation onset. The after-discharge ended at the PD mark, 8 seconds after stimulation cessation, as visible in the r9r8 channel, and not in the t5t4 channel.

C. Time-frequency decomposition for the 2 channels after notch filtering and baseline normalization. The 50 Hz stimulation (bright horizontal lines) and its harmonics are visible, and the stimulation artifact is seen at the beginning and end of the stimulation (vertical lines). In channel t5-t4, no effect is observed during and after the end of the stimulation at any of the analyzed frequencies. Channel r9-r8 displays activity in the 80-140 Hz frequency band during the stimulation, and a low frequency activation corresponding to the post-discharge starting at the end of the stimulation.

D. For HFA analysis, the SEEG power values are averaged for each channel and located at the corresponding MNI coordinates. A cortical map is produced for each participant and each trial using spatial interpolation of the sparse contact locations. The number of trials ranges from 1 to 8 per subject. The cortical maps are binarized, pooled together and clustered according to symptom type (hallucinations in green, illusions in red). The superposition of the binary maps yields the probability map, represented in example here, reflecting for all regions the likelyhood of having SEEG power modulation due to a given induced symptom. In the ROI analysis, the process is simpler : the binary maps are directly taken as the ROIs that elicited a symptom for each trial. The probabilistic maps represent the likelyhood that a given region may elicit a symptom if stimulated.



Figure 2. Distribution of electrode contacts invovled in the present study.

A. Electrode contact location in MNI space for all recorded contacts during the span of the experiment.

B. Distribution of the contacts having generated an auditory perception, per symptom type.

C. 3D ellipsoid representation using mean and covariance of the contact distributions for hallucinations and illusions.



Figure 3. Results of ROI and HFA analyses

Top: results of the ROI analysis. Bottom: results of the HFA analysis, with a full (first line) and a thresholded (second line) colormap, to enhance differences between hallucinations and illusions.

Supplementary Materials

Table S1.

| Pat. ID | Age | Sex | Disease Onset (y.) | Nb of elect. | MRI lesion | Epileptogenic zone | Surgery | histopathology |
|---------------------|-----|-----|-----------------------|--------------|-------------------------------------|-----------------------------|-----------|------------------------|
| PAT_51 | 24 | m | 19 | 13 R / 2 L | R STG hypersignal | R STG | resection | ANET |
| PAT_52 | 17 | f | 13 | 13 R | R T-P-O PMG + NH | R T-P-O | resection | PMG + NH |
| PAT_53 | 31 | m | 25 | 13 R / 2 L | R HS | R T ant-mesial & ant Ins | resection | HS |
| PAT_55 | 49 | m | 20 | 14 L | L T post-surgical scar | L T-P | resection | scar |
| PAT_56 | 27 | f | 23 | 4 R / 10 L | no | bi-T | no | na |
| PAT_57 | 13 | m | 6 | 14 L | L Ins infarct | L perisylvian | resection | non specific |
| PAT_58 | 32 | m | 15 | 11 R / 4 L | R T post-surgical scar | R T-Ins | resection | non specific |
| PAT_59 | 23 | f | 13 | 15 L | no | L multifocal | no | na |
| PAT_60 | 18 | m | 11 | 15 R | no | R F-basal & ant Ins | resection | mMCD |
| PAT_61 | 39 | f | 12 | 14 R | R HS | R T ant-mesial & ant Ins | resection | HS |
| PAT_63 | 37 | m | 14 | 14 L | no | L mes-T | resection | non specific |
| PAT_64 | 47 | m | 29 | 13 L | L F basal cavernoma | L F-basal & ant Ins | resection | cavernoma |
| PAT_65 | 58 | f | 56 | 16 L | no | L T ant-mesial | no | na |
| PAT_66 | 16 | f | 1.5 | 9 R / 6 L | no | R T antero-mesial | resection | HS |
| PAT_67 | 18 | m | 10 | 13 L | L post PVNH | L T-O | resection | FCD la + NH |
| PAT_68 | 34 | m | 18 | 10 | no | L T ant-mesial | resection | non specific |
| PAT_69 | 31 | f | 0.5 | 3 R / 13 L | L O post-surgical scar | L O-T | resection | FCD la |
| PAT_70 | 37 | m | 17 | 13 L | no | LT | resection | non specific |
| PAT_71 | 29 | m | 15 | 16 L | no | R F basal & T lateral | resection | FCD lia |
| PAT_72 | 26 | f | 22 | 12 R | no | R T ant-mes | resection | non specific |
| PAT_73 | 32 | f | 2.5 | 15 R | no | R T ant-mes | resection | HS |
| _PAT_74 | 22 | f | 2 | 13 R / 3 L | Bilateral PVNH | R > L T-O | no | na |
| PAT_75 | 24 | m | 17 | 14 R | no | R FG | resection | FCD la |
| PAT_76 | 23 | m | 17 | 14 L | no | L mes-T | resection | scar |
| PAT_77 | 52 | m | 22 | 13 R | R post T-Ins post- surgical scar | R post STG | RFTC | na |
| PAT_78 | 27 | f | 20 | 14 L | no | L mes-T | resection | non specific |
| PAT_79 | 30 | m | 16 | 15 R / 3 L | bi-F post-traumatic scar | R F premotor | resection | scar |
| PAT_80 | 22 | m | 18 | 14 R / 3 L | no | R post Ins | resection | FCD lb |
| PAT_81 | 22 | f | 14 | 16 L | no | L SMA | resection | FCD lia |
| PAT_82 | 23 | f | 13 | 4 R / 14 L | no | R ant Ins | resection | FCD la |
| PAT_83 | 31 | f | 18 | 2 R / 16 L | no | L mes-T | resection | non available |
| PAT_84 | 39 | f | 30 | 12 L | no | L T ant-mesial | resection | FCD la |
| PAT_85 | 24 | f | 14 | 15 L | L thalamic infarct | L post CG | resection | non specific |
| PAT_86 _1 | 15 | m | 6 | 15 L | no | L post Ins | RFTC | na |
| PAT_87 | 52 | m | 27 | 15 L | L T-O tumor | L T-O | resection | FCD IIIb |
| PAT_88 | 51 | f | 46 | 11 R / 2 L | R T-polar abnormal sulcus | R T ant-mes | resection | FCD IA |
| PAT_89 | 23 | f | 7 | 16 L | no | L mes-F | resection | FCD la |
| PAT_90 | 24 | f | 10 | 14 R | R perisylvian PMG | R T-Ins-Operc | resection | FCD la |
| PAT_91 | 39 | f | 28 | 17 L | no | L T ant-mesial | resection | FCD IIIa |
| PAT_92 | 42 | f | 13 | 3 R / 10 L | no | L T ant-mesial | HS | FCD 3a |
| PAT_93 | 20 | f | 12 | 5 R / 10 L | L HS | L T ant-mesial | FCD IIIa | FCD 3a |
| PAT_94 | 48 | m | 12 | 15 R | no | R T ant-mesial | FCD la | FCD 1a |
| PAT_95 | 34 | f | 15 | 17 L | L perisylvian infarct | L post Ins | RFTC | na |
| PAT_96 | 16 | f | 7 | 16 R | R T-polar blurring | R T-Ins-Operc | resection | FCD IIIa |
| PAT_97 | 31 | f | 24 | 11 L | no | L T ant-mesial | resection | heterotopic neurons |
| PAT_86 _1 | 16 | m | 6 | 6 L | no | L post Ins | RFTC | na |
| PAT_2 | 48 | m | 38 | 9 R / 7 L | R HS | bi-T | VNS | na |
| PAT_3 | 29 | m | 25 | 15 R | R F tumor residue | R F basal | resection | DNET |
| PAT 4 | 34 | f | 28 | 12 R / 4 L | no | R F basal | resection | FCD IIb |
| PAT 5 | 29 | m | 12 | 13 L | L post PVNH | L T-P | RFTC | na |
| PAT 6 | 15 | f | 12 | 15 | | L post T basal | resection | non specific |
| | . • | | | | | | | |

FG: fusiform gyrus; Ins: insula; SMA: supplementary motor area; STG: superior temporal gyrus; T: temporal; O: occipital; Operc: opercular; ANET: angio-neuroepithelial tumor; DNET: dysembryoplasique neuro-epithelial tumor; FCD: focal cortical dysplasia; HS: hippocampal sclerosis; mMCD: mild malformation of the cortical development; PMG: polymicrogyria; (PV)NH: (periventricula nodular) heterotopia; RFTC: radio-frequency thermocoagulation; VNS: vagus nerve stimulation;

Table S2. Roi analysis, regions eliciting both illusions and hallucinations, organized by major regions, from early auditory to higher order cortices. STG: superior temporal gyrus; STS: superior temporal sulcus; IPL: inferior parietal lobule;

| Hemiphere | Brain area | Jülich brain parcel | Numbre of evoked illusions | Numbre of evoked hallucinations |
|-----------|----------------|---------------------|----------------------------|------------------------------------|
| Left | Early auditory | TE 1.1 | 4 | 3 |
| | STG | TE 2.2 | 6 | 8 |
| | | TE 2.1 | 7 | 4 |
| | | Tel | 3 | 3 |
| | | TI | 3 | 2 |
| | STS | STS 1 | 2 | 1 |
| | Insula | lg1 | 1 | 5 |
| | | ld1 | 1 | 2 |
| | IPL | Area PFcm | 4 | 3 |
| | GapMap | Temporo-parietal | 2 | 2 |
| | | Fronto-occipital | 1 | 1 |
| | | Fronto-temporal | 3 | 1 |
| Right | Early auditory | TE 1.0 | 1 | 2 |
| | | TE 1.1 | 2 | 5 |
| | STG | TE 2.2 | 8 | 4 |
| | STS | STS 1 | 4 | 5 |
| | | STS 2 | 2 | 1 |
| | Insula | lg2 | 2 | 2 |
| | IPL | Area PFop | 1 | 1 |
| | БарМар | Temporo-parietal | 4 | 3 |

Table S3. Roi analysis : description of regions identified as specific to each symptom type, organized by decreasing frequency of responses.

| Symptom Type | Hemisphere | Jülich brain parcel | Number of auditory responses |
|----------------|------------|----------------------------|---------------------------------|
| | | STG – TE 3 | 2 |
| | | Heschl's gyrus – TE 1.0 | 1 |
| | L | Insula mid - Id 6 | 1 |
| | | Insula mid - Id3 | 1 |
| | | IPS - hlP1 | 1 |
| | | IFG – area 44 | 1 |
| Illusion | | IFG – area 44 | 3 |
| | | STG – TE 3 | 2 |
| | | IPL – Pfcm | 2 |
| | | Fronto-occipital GapMap | 2 |
| | R | STG – TE 2.1 | 1 |
| | | Insula post – Ig1 | 1 |
| | | Insula mid – Id6 | 1 |
| | | Insula ant – Ia | 1 |
| | | OFC - Fo6 | 1 |
| | | Fronto-temporal GapMap | 1 |
| | | Insula post – Ig2 | 5 |
| | | Frontal operculum – OP6 | 2 |
| Hallucinations | L | Parietal operculum – OP2 | 1 |
| | | STS 2 | 1 |
| | | Hippocampus – HC-subiculum | 1 |
| | | Frontal – II GapMap | 1 |

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5.3 Intracortical connectivity derived from CCEP

Stimulation at low frequencies is a means of mapping the connectivity of the brain at rest. This approach is complementary to the functional connectivity using fMRI, since the temporal resolution is sufficient to provide the directionality of the connections, in terms of afferences and efferences, and their direct or indirect nature based on temporal thresholding. We thus interrogate in the second part of this chapter the intracortical functional connections of the parietal operculum and its neighbouring regions. This work was included as part of a review on the parietal operculum submitted to Brain Sciences, and currently under minor revision.

My contribution to the article included literature review, data analysis, figure generation, discussion, and manuscript writing, justifying my position as first author.



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Review Tinnitus perception in light of a parietal operculo-insular involvement: A review

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| Jedynak,M;David O.; Delon-Martin | Keywords: tinnitus: parietal operculum: OP3: insula: integration area: neuroimaging: F-Tract: |
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| | involvement. |
| | therapeutic interventions for tinnitus provide additional evidence of the right parietal operculum |
| | involvement in tinnitus perception. Finally, a small number of neuroimaging studies of |
| | of direct electrical stimulation of this area eliciting auditory hallucinations further suggests its |
| | discuss how a dysfunction of these muscles could induce hyperactivity in the OP3. The evidence |
| | and somatosensory representation of the orofacial muscles in the healthy population. We further |
| | right parietal operculum, known as OP3 according to the Jülich atlas, in the integration of auditory |
| | erroneous perceptions, such as tinnitus. More precisely, we highlight the role of a subregion of the |
| | healthy brain. Disrupted integration processes between these modalities may thus result in |
| | of inter-connections and a strong connectivity with auditory and somatosensory areas in the |
| | derived from cortico-cortical evoked potentials show that these subregions present a dense tissue |
| | somatosensory cross-talk. Both previous literature and new results on functional connectivity |
| | the microscopic, mesoscopic, and macroscopic scales arguing in favor of an auditory- |
| | review of available investigations of the human parietal operculo-insular subregions conducted at |
| | conventional auditory areas, such as the right parietal operculum. Here, we aim to conduct a |
| | on resting-state and activation fMRI protocols, highlighting the involvement of regions outside the |
| | perception itself can be more specifically investigated: this has provided a body of evidence, based |
| | between tinnitus perception and tinnitus-related distress. In non-bothersome tinnitus, the |
| | Abstract: In tinnitus literature, researchers are increasingly advocating for a clearer distinction |
| | Citation: Jaroszynski, C.; Job, A.; Jedynak,M;David O.; Delon-Martin |

1. Introduction

Tinnitus, the chronic perception of a phantom sound, is a public health issue estimated to have about 15% of prevalence in the adult population [1, 2] with about 1% to 2% of the population suffering from unremitting tinnitus [3].

A recent international multidisciplinary group proposes to distinguish between *tinnitus* and *tinnitus disorders* where *tinnitus* describes "the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source", corresponding to the percept *per se*, leading to *tinnitus disorders* "when associated with emotional distress, cognitive dysfunction, and/or autonomic arousal, leading to behavioral changes and functional disability"[4]. Indeed, most tinnitus studies are prone to confounding biases related to the difficulty in disambiguating effects attributable to the presence of tinnitus perception per se from those related to comorbidities such as hearing loss, reduced sound tolerance threshold, anxiety disorders, or impaired quality of life often experienced by tinnitus sufferers. Facing heterogeneity of tinnitus, authors now recommend focusing studies on tinnitus sub-types, in terms of etiology (for instance resulting from noise exposure or from head or neck injuries), in terms of chronicity (lower than 3 months duration for acute tinnitus or lower for chronic tinnitus) [5, 6], or in its mildest forms (bothersome or non-bothersome) whereby comorbidities may be strongly limited. In this review, we attempted to focus

C. Tinnitus perception in light of a 30 parietal operculo-insular involvement: A review. Brain Sci. 2022, 12, x. 31 https://doi.org/10.3390/xxxxx 32 33 Academic Editor: First Lastname 34 35 Received: date 36 Accepted: date 37 Published: date 38 39 Publisher's Note: MDPI stays 40 neutral with regard to jurisdictional 41 claims in published maps and 42 institutional affiliations 43 44 (\mathbf{i}) (cc 45 46 Copyright: © 2022 by the authors. 47 Submitted for possible open access 48 publication under the terms and 49 conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/lion tinnitus without associated disorders despite the heterogeneity of the recruitment reported in the literature.

Since tinnitus is perceived as an auditory phenomenon, the auditory pathway was historically the main focus of tinnitus research. The mechanism prevailing as responsible for triggering tinnitus, occurring for example after an acoustic shock, was based on a cascade of events following peripheral damage. In this view, cochlear hair cell impairment leads to deafferentation of acoustic nerve fibers, which in turn drives plastic changes within auditory circuits and cortical structures. Similar changes have been described in other sensory modalities, such as in the somatosensory cortex after amputation [7, 8] or in the visual cortex following visual field loss [9, 10]. In line with these findings, tinnitus perception was therefore suggested to result from maladaptive plasticity similar to the maladaptive plasticity observed in amputees with phantom limb pain [11]. However, functional MRI studies in tinnitus participants with hearing loss revealed that hearing loss rather than tinnitus was responsible for the plasticity in the auditory cortex [12], and that tonotopic map reorganization in the auditory cortex is not a causal factor of tinnitus [13, 14]. These findings, alongside evidence of tinnitus existing without hearing loss altogether or existing despite cochlear nerve ablation, reignited the debate on the cortical representation of tinnitus. Nowadays, the idea that changes in brain regions outside the auditory pathway, in particular the somatosensory pathway, the emotional and the attentional systems, could trigger the development and maintenance of tinnitus is more widely accepted in the community [15]. Additional noninvasive human studies support the involvement of somatosensory pathways in tinnitus [16] and of attentional and limbic networks with possible interactions with the auditory network [17].

In a particular population of subjects professionally exposed to impulse noise, Job and colleagues have shown that impulse noises affects middle-ear function and may play a role in the early stage of auditory fatigue encompassing tinnitus [18]. Investigating further the potential role of the middle ear in noise-induced tinnitus, this author sought for its cortical representation and found it in the parietal operculum (OpP) [19]. Furthermore as tinnitus may have a masking effect on sounds, Job and colleagues investigated the capacity of detecting a target sound among regular sounds using an oddball paradigm in functional MRI. In a group of participants with tinnitus compared to controls, they found a differential activation in the parietal operculum which was correlated with the chronicity and intensity scores of tinnitus perception [20]. No differential activity was found in auditory regions. This led this group to suspect the parietal operculum to be a core region of a tinnitus network. Further connectivity studies between non-bothersome tinnitus participants and controls evidenced the presence of a differential connectivity from the OpP and a frontal region posterior to the frontal eye field [21]. These authors also used a strategy that by passed the question of comorbidities completely, by studying healthy subjects perceiving transitory phantom sounds resembling tinnitus. By using click trains at specific frequencies it was proven possible to reliably induce auditory after-effects mimicking the tinnitus perception (when using a 30 per second stimulation). This perception of sound in the absence of a corresponding external source thus makes for a proxy of tinnitus. The central representation of this latter stimulus has been explored with a high resolution fMRI method and compared with a stimulus inducing no after-effect, revealing an increased activity in the somatosensory cortex in the face area and in the right OpP [22]. The induced phantom perception did not reveal any activation in the auditory cortex.

The near-complete absence of literature on OpP with regards to tinnitus raises the question of the lack of this region in the literature. One explanation relates to its vicinity with the primary auditory cortex (A1) (Figure 1). Due to the spatial smoothing and the spatial normalization of MR images, the fMRI activations in OpP could be mistakenly reported as activations of the primary auditory cortex or of the posterior insular cortex (post-Ins). Indeed, located on the opposite banks of the lateral sulcus, OpP, post-Ins and A1 are in close neighborhood, OpP being more anterior and superior and post-Ins more medial and anterior than A1 respectively. In the human cortex, regions that lie on opposite banks of a main sulcus generally present mirror organization, with mirror somatotopy around the central sulcus for primary motor on the anterior side and primary sensory on the posterior side, with mirror retinotopy around the calcarine sulcus with inferior part of an hemifield above the sulcus and the superior part below the sulcus. Up to now, no such mirror tonotopy has been observed in human areas opposite to A1. To our knowledge, a single study reported a tonotopic organization in the insula, but in a rodent model [23].

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Figure 1: Auditory area (A1), parietal operculum (OP) and posterior Insula (Ins) are lying on opposite banks of the lateral sulcus (underlined in black). Image derived from neurosynth.org

Considering these elements, we propose a review of the current knowledge about the parietal operculo-insular region to interrogate its involvement in tinnitus perception. We review findings at different scales: first, the microscopic level from multi-unit neuronal recordings in awake as well as retrograde tracing in monkeys up to postmortem invasive explorations in humans; second, the mesoscopic level using intracerebral explorations in humans and third, at a macroscopic level as described in the MRI literature. The reviewed elements suggest the existence of a multimodal integration behavior in the target regions, namely somatosensory, auditory, more precisely in the antero-medial part of the OpP, coherent with the subregion of the Jülich atlas named OP3. Finally, we hypothesize that a dysfunction of this opercular region could be related to tinnitus perception as was observed in previous studies which provide novel avenue for future treatments.

2. Microscopic scale

Regions around the lateral sulcus were studied in non-human primates using single and multi-unit recordings. They include auditory cortex and its subdivisions [24], the somatosensory cortex [25], the insula [26], the gustatory cortex [27]. More recently, authors demonstrated the presence of multisensory integration area, just caudomedial to primary auditory cortex having robust somatosensory and auditory COrepresentation [28] and in the most medial regions of SII of awake macaque monkeys, sensory and auditory and visual inputs [29] supporting the presence of multisensory integration area, in the vicinity of primary auditory and primary sensory areas. Additional support for this view comes from injection of retrograde tracers to directly explore potential links between unimodal areas. A study on marmosets provided evidence of specific projections linking areas of different modalities [30]. A multisensory cortical region adjacent to the posterior tip of the lateral sulcus projecting to auditory, somatosensory and visual motion areas was found. Other studies in macaque monkeys found auditory-somatosensory integration areas in the caudal belt of the auditory cortex [31]. Along the evolution, the amount of cortex in the lateral sulcus varies greatly across primates, from a rather shallow fissure in some prosimians to a deep fissure with a large fundus, the insula. The upper bank of the lateral sulcus includes the operculum and is largely devoted to somatosensory areas, while the lower or temporal bank is associated with auditory areas. In the greatly enlarged human operculum and insula as compared to those in apes and other primates, new regions have emerged, outgrowing the areas described in non-human primate literature as involved in processing taste, pain, temperature, touch and internal states [32].

In humans, investigations of the opercular and insular regions began with the pioneering brain mapping performed by Brodmann at the beginning of the XXth century. Based on cytoarchitectony in the cortical layer and on homologies with other mammalian species, he was able to describe up to 52 different cortical areas. In the opercular part of the human cortex, he defined a single region, the area 43, located on the lateral side of the cortex. However, the masked part of the operculum remained undescribed. In the insula, he did not find the three respective homologue areas of the insular cortex of old world monkeys. Instead, he described the anterior and the posterior

 parts of the insula, without providing any corresponding nomenclature, and the parainsular area 52 located between the posterior insula and the temporal area 41. In recent years, a remapping of the whole human brain was undertaken by the group led by K. Zilles in Jülich, providing a 3D probabilistic atlas of the human brain based on cytoarchitectony and receptor mappings [33]. This atlas contains the probabilistic maps derived from cytoarchitectonic studies of over 200 areas of the human brain including cortical areas and subcortical nuclei. The operculum presents nine subdivisions, five in the frontal operculum and four in the parietal operculum [34, 35]. Lateral parts of the OpP contains OP1 posteriorly and OP4 anteriorly while medial parts contains OP2 posteriorly and OP3 anteriorly. The insula is subdivided in 16 regions, 3 in the agranular part, 3 in the granular part and 10 in the dysgranular part. Their respective probabilistic locations are displayed in Figure 2 derived from the online interactive viewer of the Human Brain Project (https://interactive-viewer.apps.hbp.eu/). Additionally, two periauditory regions at the interface between insula and Heschl's gyrus, have been recently documented [36]. The functional evidence provided seems to advocate for the existence of junction regions presenting characteristics of both adjoining cortices, and allowing a transition from early processes in the core auditory, towards insular integration.



Figure 2: Posterior operculum of the right hemisphere show four cytoarchitectonic subregions as defined by the Jülich group: the OP1 (camel color) lateral posterior, the OP4 (grey) lateral anterior, the OP2 (blue) medial posterior and OP3 (dark green) medial anterior. Different views: (A) 3D, (B) axial view, (C) sagital view and (D) coronal view. Image derived from (<u>https://interactive-viewer.apps.hbp.eu/</u>)

These post-mortem studies provide very direct insight into brain structure at multiple scales. However, they build upon small datasets of ten post-mortem brains, which may be problematic in regions, such as Heschl's gyrus, where individual variability is high.

3. Mesoscopic scale

Invasive electrophysiological measurements provide a complementary brain investigation approach, with increased scalability potential. It provides the closest insight into *in vivo* human brain function combining high temporal and spatial resolution. The trade-off resides in the discrete spatial sampling dictated by the location of implantation chosen, based on clinical requirements: for obvious ethical considerations, no healthy subjects are included in invasive studies, therefore functional brain mapping derived from intracerebral recordings is a fringe benefit from pathological brain exploration [37]. These issues are compensated by the large number of intracranial recordings, owing to their integration in the clinical investigation of prevalent conditions such as epilepsy. For example, the F-TRACT database has been recently constituted to centralize the direct electrical stimulations (DES) and stereoelectroencephalographic recordings of multiple areas of the human cortex, hippocampus and amygdala of several hundreds of subjects. The associated F-TRACT atlas provides functional connectivity information, which is oriented and direct according to the dynamical properties of the stimulation and recording data [38, 39].

In this section, we first review the data from intracerebral electrical recordings of the insulo-opercular regions. Then, we consider the behavioral impacts of direct electrical stimulation paradigms and finally we review the state of the art provided by intra cortical connectivity of these regions.

3.1 Intracerebral recordings of the operculo-insular cortex

The involvement of the posterior insula in response to auditory stimuli has been addressed using intracerebral EEG. Zhang and colleagues [40] collected iEEG data from epileptic patients, as well as fMRI and DTI in both epileptic and control subjects, listening to emotional and non-emotional stimuli, in order to determine the roles of the different subdivisions of the insula. Recording sites within the posterior insula responded to a wide range of acoustic stimuli, irrespective of emotional content, in line with previous findings [41-45]. The study also highlighted strong connections between the posterior insula and the auditory cortex with a stronger connectivity in the right as compared to the left hemisphere, and suggested a shared role of sound feature extractions, namely the central frequency and amplitude envelope of acoustic stimuli.

Yet, with the iEEG technique, it is not possible to know whether the parietal operculum responds also to acoustic stimuli since, to our best knowledge, the literature does not report iEEG data in this region during auditory stimulation.

3.2 Perceptions mapping in the operculo-insular cortex induced by DES

DES provides direct insight into the behavioral response reported by the patients, induced by electrical impulses. This technique provides a direct link between perception and anatomical location, as long as the emergence of perceptions occurs. It has been used in vivo to help delineate the precise boundaries of the human primary auditory cortex on Heschl's Gyrus [46].

Fewer studies have addressed the perceptions induced by DES in the operculoinsular cortex. To our knowledge, only one study specifically targeted the operculum [47], two others focused on the insula [45, 48] and a third one targeted both regions [49]. An additional study explored the auditory responses to DES with contacts in forty-two different regions including these two regions [50]. In Maliia's publication [47] reporting DES explorations of the operculum, the authors report the existence in the OpP, not only of somatosensory responses, including pain, but also of diverse effects with an asymmetry between sides. In the left OpP, there were mainly motor, visceral, language and vegetative effects, while the right OpP elicited mainly pain and auditory responses. In Mazzola's publication [48] reporting DES explorations of the insula, the authors showed that the predominant modality was somatosensory (including pain) but auditory responses were also evoked mainly located in the posterior long gyrus of the insula. Descriptions of the evoked sounds were 'sizzling', 'buzzing' or 'drumming', a vocabulary currently used by tinnitus sufferers. As other modalities were also reported such as vestibular, cardiovascular or gustatory, there is converging evidence for multimodal representations with clear spatial overlap of the modalities. However, no auditory responses were found following OpP stimulation in Yu's publication [49]. One reason might be that the location of the electrodes were limited to its inferior part, with a risk of a sampling bias as is likely in DES studies, and by missing some effects. The recent exploration with DES of regions producing auditory hallucinations and illusions within the brain brings new evidence for a large territory eliciting auditory responses [21](Jaroszynski et al., in press 2022). Indeed, DES in up to 42 cortical regions,

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described as simple hallucinations (elementary sounds such as clicking, whistling, ringing, buzzing) or complex hallucinations (elaborate auditory phenomena such as music or voices), where most descriptions of simple hallucinations were in line with tinnitus experience. Taken together, these studies support the view that auditory and somatosensory modalities are not integrated in a single area, as could be suggested by animal studies, but are rather somehow overlapping in the posterior insula and the parietal operculum with some percepts similar to tinnitus.

3.3 Operculo-insular connectivity

The term 'cortico-cortico evoked potential' (CCEP) describes the pattern of responses to stimulation applied on a cortical target measured from all the other electrode contacts placed stereotactically inside the brain. The aim of the approach is to enable simultaneous mapping of functionally synchronized regions and their anatomical connections [51].

These responses to brief electrical pulses mimic the physiological propagation of signals along axonal populations and manifest as modulations of cortical activity in the connected regions. After stimulation artifact correction [52], the first CCEP component is considered to reflect direct connectivity with the stimulated region. Using such methodology, these investigations are able to demonstrate causal interactions between brain areas in vivo, known as effective connectivity [53]. To infer reliable connectivity information, large amounts of data are required, which is what the multicenter F-TRACT initiative strives to do. Ultimately, the goal of the F-TRACT project is to provide a large-scale functional atlas for each region of the main brain parcellations, at different resolution scales (https://f-tract.eu). Using our latest internal version of the F-TRACT atlas including a total of 942 implantations, we examined connectivity patterns from the posterior operculum (OP1, OP2, OP3 and OP4) and two insular regions (Ig1 and Ig2) presenting borders with OpP and auditory areas, as defined in the Jülich atlas of brain parcellations. Stimulation contacts belonging to the same parcellation region were pooled together and their responses, binarized by statistical thresholding with z-score threshold = 5, were averaged to yield connectivity probability (for details see [38]). Thresholding was performed by excluding regions where less than 5 stimulations were performed, or where recordings originated from fewer than 5 different subjects. Thus, a square matrix of connectivity was generated, representing the probability that a response be detected in one region, when stimulating from another.

In Figure 3, all connections of the parietal operculum subregions are displayed as red dots, with the radius varying with connectivity strength. The lines represent the connections that survive the thresholding, and the colormap is set to represent connectivity values. The probability matrices are not symmetrical due to afferent and efferent connections: this is considered by modulating the coloring of the connection if the nodes at the extremities of an edge have different values in the connectivity matrix. This represents causal relationships between regions. It appears that parietal opercular subregions (OP1-OP4) are strongly inter-connected. They are also connected by efferences with frontal opercular subregions and with granular and dysgranular subcomponents of the insula within the same hemisphere. In addition, left and right OP1, OP2 and OP3, but not OP4, present efferent connectivity with somatosensory cortex ipsilaterally. Interestingly, connections from the OP1, OP2 and OP3 subregions to the temporal auditory regions of the superior temporal gyrus (TE1, TE2.1, TE2.2) were only found in the right hemisphere and only OP2 in the left one. Connections to subregions of the Heschl gyrus were found from OP1, OP2 and OP4 in the right hemisphere and from OP2 in the left hemisphere. This asymmetry between right and left hemisphere could be related to the asymmetry of the auditory cortex with left hemisphere more sensitive to speech and right hemisphere to melodic contents [55]. Other efferences from all OpP subregions were found to inferior parietal lobule and from bilateral OP1 and OP3 to frontal area 44. No interhemispheric connectivity was reported here probably because the CCEP amplitude decays with distance and thus the chance of observing an existing connection decreases with the distance between regions. However, lowering the probability threshold permitted to find connectivity with homotopic regions of the opposite hemisphere. Notably no connections with the limbic system could be observed. To summarize the connections from OpP to both auditory and somatosensory cortices, only right OP1, bilateral OP2 and right OP3 were

CCEP in the human operculum has been published based on the data acquired in 31 patients' brain [47]. The data of this group and others' are collected in the database of the F-TRACT project. Since, only the connectivity from a given region that present strict threshold (at least 10 stimulations from at least 5 patients) are further considered, this may explain why some results described by these authors were not reproduced here. The fact that all red dots, including some with probability close to 1, are not connected also reflects the strict thresholding applied in the process.



Figure 3: Intracortical connectivity of the four subregions of the parietal operculum from Jülich ('JB connectivity' stands for Jülich Brain connectivity'). From top to bottom: area OP1, area OP2, area OP3 and area OP4. Left column for the subregions of the left hemisphere and right column for the subregions of the right hemisphere. Image derived from the data of the F-TRACT project (https://f-tract.eu)

In Figure 4, all connections from the granular subregions Ig1 and Ig2 of the insula, which present borders with both the parietal operculum and the temporal cortex, are displayed with the same methodology and threshold as for the Fig. 3. These regions show strong connections with one another and with Ig3, as well as with dysgranular parts of the insula. They also present connections with the subregions of the OpP and with the subregions of the Heschl gyrus and the superior temporal gyrus. Additional connection was found with the motor area 4p and frontal area 44 from right Ig1. All but left Ig2 were connecting to the inferior parietal lobule.

The richness of the connections between OpP and the insula, the auditory and the somatosensory areas confirms that OpP can be considered as a multimodal region, potentially involved in sensory and auditory integration. However, since electrodes



Figure 4: Intracortical connectivity of the two granular subregions of the insula. From top to bottom: area Ig1 and area Ig2. Left column for the subregions of the left hemisphere and right column for the subregions of the right hemisphere. Image derived from the data of the F-TRACT project (https://f-tract.eu)

4. Macroscopic scale

If the intracerebral recordings provides a ground truth for neural brain activity, their main drawback relates to the sparsity of the electrodes implantations. The non invasive findings, mainly related to functional MRI provides an entire brain exploration that complements the invasive findings. In addition, if operculo-insular connectivity is provided thanks to the F-TRACT database, their functions are not solved, an issue that neuroimaging can contribute to alleviate. In this section, we review the current knowledge on the functions and connectivity of the opercular and insular cortices, then we review its involvement in the tinnitus literature.

4.1 Integration of auditory and somatosensory stimuli in the operculo-insular cortex

If parietal operculum integrates auditory and somatosensory modalities, then this region should be involved in studies related to bimodality integration. Several human activities require such integration such as speech production or music playing, for instance. Indeed, the left parietal operculum was found to be involved together with the auditory and somatosensory areas when looking to the language network [56], with a location in OP4 also covering OP3 and extending to the insula. In music playing, concomitant activation of sensorimotor and auditory systems are required. In fMRI studies related to music, functional connectivity analysis suggested the parietal operculum to be a connector hub linking auditory, somatosensory and motor areas [57]. This region was further found to be more connected to other cortices in musicians than in non-musicians [58] with an asymmetry between both hemispheres. Interestingly, feelings evoked with music activated the parietal operculum bilaterally extending on the posterior insula and was found to be of particular importance for the encoding of emotion percepts [59]. An auditory frequency discrimination task was also found to involve the parietal operculum bilaterally [60]. A recent study manipulating sung speech stimuli by filtering them either temporally or spectrally permitted to solve the asymmetry in auditory cortex between left and right hemispheres. Using fMRI, the authors showed that the neural decoding of speech and melodies depends on activity patterns in left and right auditory regions, respectively [55]. These fMRI studies support the view for an integrative function of the OpP with an asymmetry related to the spectral content of auditory stimuli. However, only few of these studies attempted to further identify which of the subregions of the OpP were activated.

One issue with the functional study of the opercular cortex comes from its vicinity with the insula. For instance, the meta-analysis provided for the insula in the neurosynth database (<u>https://www.neurosynth.org/analyses/terms/insula/</u>) shows that this region encompasses not only the insula but also the medial part of the operculum, thus potentially medial opercular subregions. This is mainly a side effect of the preprocessing of the fMRI data that usually includes a spatial smoothing of up to 8-mm. Another issue

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comes from the popular inflated representation of activation on the brain. In such figures, the limit between adjacent operculum and insular cortex is unclear. It is thus difficult to disentangle between activities related to each of these regions. However, despite these methodological limitations, several functions are known to be encoded in the insula. As expected from DES experiments, the presence of a specific network corresponding to pain, known as 'pain matrix', with a core posterior insular region has been described by Wager and co-authors [61]. It is noteworthy to notice that not only the posterior insula but also the parietal operculum are both involved in this network, among other areas. The insula subserve a variety of functions in humans ranging from somatosensory, affective processing to high-level cognition [62]. A meta-analysis of nearly 1,800 functional neuroimaging experiments by Kurth and colleagues suggested the existence of four functionally distinct regions in the human insula: first a sensorimotor region located in the mid-posterior insula; second, a central-olfactogustatory region; third, a socio-emotional region in the anterior-ventral insula; and fourth, a cognitive anterior-dorsal region [63]. Coherent with the findings from DES, the insula is also involved in auditory processing such as sound detection. Finally the insula seems to be involved in speech production, probably through higher-order articulatory processes. Other functions reported in the literature include olfactory, gustatory, visceroautonomic, and limbic function for the anterior insula, and auditory-somestheticskeletomotor function for the posterior insula, but these studies bear the aforementioned uncertainty on their location.

4.2 Functional and structural connectivity of the parietal operculum and insular cortex

Connectivity analysis using seed-based methods can further precise the functional networks each of these subregions are pertaining. Such study based on resting-state fMRI have shown that OP4 is more closely connected to areas responsible for basic sensorimotor processing and action control, while OP1 is more closely connected to the parietal networks for higher order somatosensory processing [64]. Meta-analysis have shown that the cytoarchitectonic area OP2 is a core region for a human vestibular network with a predominance in the right hemisphere [65, 66]. The involvement of the OP2 is further confirmed by patients with chronic bilateral vestibular failure [67]. Finally OP3 seems to be involved in oral somatosensory stimulation, comprising the gustatory network [68], the swallowing network [69] and laryngeal cortical network involved in deglutition [70]. Its involvement was also described in laughing and tickling [71], in the central representation of the tympanic membrane and middle-ear muscles in response to 1Hz mechanical pressure variation [19] and in relation to temporomandibular joint disorder [72]. Taken together, the stimuli involving orofacial muscles seem thus to be represented in cortical OP3 region. In the insula, the functional connectivity presents different patterns for anterior and posterior parts, the former connecting with frontal and limbic regions, while the latter connecting to the sensorimotor, the auditory and the visual cortices [40].

Data from the Human Connectome Project provide additional information about the functional and structural connectivity of parietal operculum and posterior insula. Based on the parcellation described by Glasser and numerous colleagues [73], Baker and colleagues described high mutual interconnectedness within the parietal opercular regions and granular part of the insula [74]. In short, functional connections were found with sensory motor network, auditory network, components of the visual network, cingulate areas, parietal opercula subregions, superior posterior insula. Most structural connections were local connecting parietal opercular subdivisions, granular and anterior parts of the insula, and the auditory area, while some presented long-distance connections with sensorimotor cortex [74]. While the HCP describes the cortico-cortical connections, other authors described the connectivity with the basal ganglia, the amygdala and the hippocampus showing a rich insular connectivity pattern with subcortical structures [75].

4.3 Encoding of tinnitus in the parietal operculo-insular cortex

Tinnitus is a percept whose temporal fluctuations are almost absent while the frequency component is broadband, thus closer to melody than to speech. This is why tinnitus can be expected to be represented more predominantly in the right hemisphere than in the left.

If tinnitus frequency band is partially masking other sound frequencies then the discrimination of sound might be modified. Based on this hypothesis, a fMRI study was designed to explore the differential capability of tinnitus subjects without comorbidities to discriminate auditory target stimuli as compared to standard stimuli, as is done in an

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oddball paradigm [20]. These authors found a set of regions differentially involved between the two groups, in particular in the parietal operculum of the right hemisphere. According to Jülich atlas, its location is at the border between OP1, OP2 and OP3 subregions. Moreover, in this region they showed that the differential activity in tinnitus subjects was increased with increasing tinnitus periodicity and handicap. As presented above in this review, this region is activated by movements of the orofacial muscles, and in particular the middle ear muscles [19]; [76]. One of the interests in this particular study comes from the inclusion criteria for the tinnitus group of subjects. They all present a same etiology that is a chronic tinnitus following acoustic trauma and none of them have bothersome comorbidities. In this case, the overactivity reported is probably related to tinnitus percept. How to explain the involvement of this opercular region? The acoustic trauma likely generates a mechanical trauma of the middle-ear muscles, leading to abnormal excitability of middle-ear muscle spindles. Given that muscle spindles are related to proprioception, which presents a central representation in the parietal operculum [77], the hypothesis is that a hyperactivity is produced in the corresponding operculum subregion corresponding to the middle-ear and interpreted by the cortex as an auditory percept. The fMRI study about temporomandibular joint disorder and its occlusion therapy evidenced an overactivity in the very same location as in Job's 2012 study. As tinnitus is known to be a comorbidity for temporomandibular joint disorders [78], the mediating role of the OP3 subregion of the parietal operculum might be considered. Since, as above-mentioned, the OP3 seems to be an integration area for auditory and somatosensory representation of the orofacial muscles, and given that stimulation in this area, as observed by direct electrical stimulation, can elicit auditory hallucination, we could hypothesize that a dysfunction of these muscles could lead to tinnitus perception. This hypothesis may further explain why a majority of tinnitus sufferers could manipulate their tinnitus perception by moving their face and neck [79, 80].

Another original method is of interest to study tinnitus perception *per se*. It consists in inducing a transitory tinnitus sound in control subjects without tinnitus. This strategy allows the intrasubject comparison of conditions with tinnitus percept vs. no tinnitus percept, which presents the advantage of using a paired t-test at group level analysis, which is more sensitive to small differences than the two-sample t-test used in group comparisons. This has been performed with a train of click sounds at 30 Hz, which generates a tinnitus like after-effect, vs. a train of click sounds at 8 Hz which does not generate such after-effect. This fMRI study has been performed with high spatial accuracy and low scanner noise in the fMRI acquisition sequence to allow the perception of the auditory after-effect. It provided two small cortical foci of activation, one in the somatosensory cortex and the other one in the parietal operculum OP3 of the right hemisphere [22].

In tinnitus literature, only few studies reported the parietal operculum involvement. The large heterogeneity in the recruited participants for non-invasive studies with different comorbidities, different etiologies and auditory characteristics is likely responsible for under the radar findings. Another issue relates to the noisy environment of the MR scanner during fMRI acquisitions that limit the auditory studies. Another reason relates to the gross spatial resolution that would gain from improving accuracy and from including the recent atlases based on post-mortem cytoarchitectony Jülich or based on the in vivo data of the HCP. We here advocate for a gain in the methodology to better address the central representation of tinnitus and to better evaluate the therapeutic interventions that are currently under development.

4.4 Functional and structural connectivity with the parietal operculum in tinnitus

To study the specific connectivity related to tinnitus perception while excluding confounding factors, two functional connectivity studies using resting-state fMRI, including only tinnitus subjects not impacted by comorbidities, were reported in the literature. The first one performed between non-bothersome tinnitus participants and control group, sought to the between-group differential connectivity between 58 seed regions and the whole brain, the seeds being chosen in the main functional networks in the default mode, attention, auditory, visual, somatosensory, and cognitive networks [5]. As the study could not elicit any significant differences between both groups, the authors suggested the non (or only poor) involvement of this pathways in the tinnitus perception. The second functional connectivity study with resting state fMRI explored more specifically the connectivity with the parietal operculum OP3 [21]. The authors found an increased connectivity between the right OP3 and two mirror regions of the dorsal prefrontal cortex, thought to correspond to the human homologue of the
premotor ear-eye field bilaterally, and the inferior parietal lobule involved in proprioception.

The study of structural connectivity associated with tinnitus present large discrepancies depending on the authors [81]. We found only one study with nonbothersome participants and controls, using diffusion MRI and a crossing-fibers model that resolve more accurately the main 27 white matter tracts [82]. In this study, the authors have revealed white matter changes underneath the superior parietal cortex in tinnitus participants in a location supporting the implication of an auditory-somatosensory pathway in tinnitus perception. They also specifically investigated the acoustic radiations, that are challenging to model, but could not found any significant differences between groups.

5. Perspectives for treatment of tinnitus

The reviewed studies at different scales show the parietal opercular region, and more precisely OP3, as an integrative area for auditory and somatosensory information from the orofacial muscles. Highly connected to the different subregions of the parietal operculum and of the posterior insula, it seems to be involved in the tinnitus perception *per se*, in particular in the right hemisphere. It may thus be a good candidate for therapeutic interventions.

Yet, many therapeutic treatments have been proposed to attempt to alleviate tinnitus where neuroimaging is a tool of choice to evaluate them. They can be classified in four main methods. A first group involves some specific acoustic stimulations. This is the case of dedicated hearing aid, sound therapy or music therapy. A second group relates to brain stimulation, either non-invasive such as repetitive Transcranial Magnetic Stimulation (rTMS) or transcranial Direct Current Stimulation (tDCS), or invasive such as deep brain stimulation (DBS). A third group relates to peripheral bimodal stimulation such as bimodal somatosensory and auditory stimulation or such as autonomic and auditory stimulation. The fourth group pertains to the cognitive controls of tinnitus such as mindfullness or in tinnitus retraining therapy [83] or neurofeedback. A few but growing number of studies present longitudinal neuroimaging investigations to objectify the changes induced by the therapeutic intervention while correlating with tinnitus perception scores.

In the therapies based on the auditory stimulations strategies, the impact of a 6 months-hearing aids in tinnitus subjects was evaluated by imaging metabolic glucose consumption with PET [84]. The authors found a pattern of increased and reduced glycolitic metabolism in many regions throughout the cortex. The neural correlates of sound therapy were evaluated by a single group by measuring variation of grey matter thickness [85], of white matter volume [86] and amplitude of the low frequency fluctuations [87]. These studies found different modifications without showing a clear pattern of coherent results. Finally, the effects of Heidelberg neuro-music therapy were investigated through measures of the grey matter volume in acute tinnitus subjects [88]. These authors found significant modifications in different brain areas including the right parietal operculum following the music therapy.

In the therapies based on brain stimulation, rTMS with a target above the left temporal lobe or above the left dorsolateral prefrontal cortex was proposed with only moderate efficacy with high interindividual variability in treatment response [89]. The present review indicates that the right parietal operculum could be considered as a new target for stimulation, but given its depth below the cortical surface, dedicated coils should be introduced in this case, providing it is not too painful. The non-invasive tDCS has also been proposed as a therapeutic tool over the right dorsolateral prefrontal cortex, in particular in its high-density version that allows a finer accuracy of the target [90] with a significant improvement. Further investigations with neuroimaging tools are expected to better understand the neural correlates of this therapy. Invasive deep brain stimulation has recently been proposed with a target within the caudate nucleus which showed moderated efficacy, but other targets along the auditory pathways such as medial geniculate body or in the limbic networks are also proposed [91]. To date invasive or non-invasive stimulations in the right operculum OP3 might be considered as new avenue for tinnitus perception release.

Therapies based on bimodal stimulations seems promising. The central effects of transcutaneous vagus nerve stimulation (tVNS) at different sites of the outer ear were explored by functional magnetic resonance imaging (fMRI) in patients with tinnitus. At tragus site, deactivation of a large bilateral region encompassing both auditory areas and also parietal operculum could be observed [92]. Combined with auditory stimulation, the tinnitus was alleviated in tinnitus subjects. It is postulated that the auditory-somatosensory integration process is disrupted during tVNS resulting in a suppression

of tinnitus [93]. Recently Conlon and co-authors proposed a joint stimulation of tongue somatosensory and sound stimulations to modify the central integration of these modalities [94]. If encouraging clinical results are found, with strong interindividual variability, the central mechanisms induced by this therapy would benefit from some neuroimaging explorations studies to objectify these results.

Finally cognitive methods have been proposed. Habituation is a core mechanism in the tinnitus retraining therapy and has been recently investigated using quantitative EEG [95]. The authors found an increased EEG power in the alpha 1 band in the right insula. Given the uncertainties provided by the source reconstruction methods used in this EEG study, the region encompasses also the right operculum and the right temporal pole. Mindfullness based cognitive therapy has been proposed to reduce tinnitus severity. Zimmerman and colleagues could find functional connectivity modifications in different networks of the brain [96] but disentangling between those related to psychological modifications and those related to tinnitus perception remains an issue. Neurofeedback methods based on fMRI have recently been proposed to alleviate tinnitus by decreasing the neural activity in the auditory cortex [97]. The effect of neurofeedback of the auditory cortex revealed a pattern of regions where the activity is decreased, in particular in the right operculum [98].

6. Conclusions

In this review, we examined the evidence pertaining to an operculo-insular crosstalk hypothesis explaining tinnitus perception as an erroneous integrative process between multiple sensory inputs, mainly somatosensory and auditory. First and foremost, we review the current knowledge about subregions in the parietal operculum / posterior insula that present a dense tissue of connections and strong connectivity with auditory and somatosensory areas in normal brain function. These results give ground to the idea of a multiple sensory integration in this region. In tinnitus percept literature, hyperactivity was observed in the parietal operculum, suggesting dysfunctional integration properties. In the specific case of acoustic trauma tinnitus, the pathway leading to dysfunctional integration is proposed to be mediated by the middle ear as somatosensory input and inner ear as auditory input. Finally, the most encouraging therapeutical avenues today combine auditory and somatosensory stimulation, that may restore functional multisensory integration leading to alleviate tinnitus.

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Data Availability Statement: Data used for CCEP analysis can be found on the F-TRACT website (https://f-tract.eu/atlas/).

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5.4 Intracortical exploration of an induced transitory tinnitus-like perception

Task-based protocols can be conducted for monitoring local brain activity. In this section, we provide the first exploration study using intracortical recordings of a tinnitus-like perception robustly induced in a group of tinnitus-free participants. This study is ongoing, and was awarded a grant from the Fondation pour l'Audition to be continued and completed over a six months period after the end of this PhD. The following is a draft of the article in preparation with respect to this study.

5.4.1 Aim of the project and Rationale

The present project aims to validate OP3 as a candidate region for therapeutic intervention, using a unique approach combining invasive intracortical recordings (iEEG) with a transitory tinnitus-induction protocol, in a group of participants undergoing exploration for focal drug resistant epilepsy. It constitutes a valuable opportunity to gain direct insight into the location and frequency band characteristics of tinnitus, which we believe will help guide emerging therapeutic interventions.

The proposed experiment falls within the scope of an active research project using intracortical recordings (MAP-COG). It builds upon the model, developed in our team, of tinnitus as a middle ear proprioceptive dysfunction. The middle ear contains two small antagonist muscles whose function is the maintenance of the ossicular chain for optimal transmission of sound to the inner ear. The intrafusal fibers contained in these muscles convey proprioceptive information to the brain. In other muscles of the body, it has been shown that an illusion of movement can be induced when a mechanical vibration is applied at a specific frequency (about 60 Hz) to the muscle, short-circuiting the input from intrafusal fibers. In the same way, we found that a specific mechanical frequency of 30Hz generates an illusion of sound that mimics tinnitus. The paradigm for transitory tinnitus induction was validated in an fMRI study [21].

5. Intracortical exploration of the parietal operculum

| Subject N° | Sex | Age (y.) | Handed- ness | Age of epilepsy onset (y.) | Clinical observations | After-effect perception |
|---------------|-----|-------------|-----------------|----------------------------------|---|---|
| 1 | М | 31 | R | 21 | Auditory symptoms as part of epileptic aura. Left insulo-opercular hypometabolism. IHz stimulation to the left A1: echo (illusion), 50 Hz stimulation to OP3: sensation of electricity | Yes |
| 2 | М | 39 | R | 19 | Visual symptoms in epileptic aura. Right ganglioglioma, surgically removed in 2016. Auditory hallucination upon stimulation to A1 | Yes |
| 3 | М | 32 | R | 19 | Visual aura, left lateralised. Right fronto-orbital metabolism. Right temporal and suprasylvian abnormal EEG activity. Auditory illusion upon 50 Hz stimulation to A1. | Yes, a deep sound |
| 5 | М | 25 | R | 15 | Polymicrogyri | Yes, a deep sound |
| 7 | F | 25 | L | 13 | RAS, auditory hallucination (whistling) and illusion (mouthed ears) upon 50 Hz stimulation to A1 | Does not recall an after-effect |
| 8 | М | 21 | L | 10 | Right cavernoma, surgically removed. Auditory hallucination upon 50 Hz stimulation to A1 | Yes, with additional rumbling feeling |
| 9 | F | 25 | L | 13 | RAS, somatosensory symptoms upon functional exploration mainly. | Yes, ressembles the sound of crickets, or waves on the seaside |
| 10 | М | 38 | R | - | Auditory hallucination upon stimulation to U'4, rumbling | Yes |

Table 5.1

5.4.2 Materials and methods

5.4.2.1 Participants

The participants of the present study were recruited amongst focal drug resistant epileptic patients of the Grenoble Alpes University Hospital according to the following inclusion criteria: a minimum age of 18 years, and at least one electrode contact in OP3 or in the periauditory regions (including Heschl's gyrus, right or left hemisphere). Participant specific demographic data were systematically collected (table 5.1) including age, gender, handedness and existence of prior, present, or no experience of tinnitus or hearing related disorders. Except for subject n°1 who experienced tinnitus perception as part of their epileptic aura, the participants reported no auditory related disorders. According to the implantation scheme, two groups of patients were defined. On one hand, the participants with a contact in the target region OP3. On the other hand, the participants with contacts in the periauditory regions.

5.4.2.2 Data Acquisitions

Participants underwent presurgical SEEG exploration, as well as MRI and CT scanning for anatomical localisation purposes. The anatomical images included a pre-implantation T1-weighted image, and a post-implantation CT scan. SEEG implantation schemes were defined exclusively with respect to the patient's clinical

needs, and typically included over 100 contacts, half of which are likely located in the grey matter. On average, 11 to 15 multilead electrodes are implanted stereotactically in each participant. Electrodes had a diameter of 0.8 mm and, depending on the target structure, contained 6 to 18 2 mm wide contact leads every 1.5 mm (Dixi Medical, Besançon, France). Acquisitions were performed with a Micromed (Treviso, Italy) system with a sampling rate of 512 Hz and an online band-pass filtering from 0.1 to 200 Hz. A referential montage with a reference electrode chosen in the white matter is used. For data analysis, a bipolar montage between adjacent contacts of the same electrode was used to improve sensitivity to local current generators. For clinical purposes, functional mapping was performed using low frequency and high frequency direct electrical stimulations. This exploration phase lasted several days and aimed to quantify and precisely locate the epileptogenic zone, prior to surgical removal. During this phase, the patients were given the opportunity to participate in various tasks, for complementary functional mapping.

5.4.2.3 Experiment description



Figure 5.1: Illustration of the experimental setup for the listening task in the 30 Hz and 8 Hz conditions, the data monitoring and recording.

The protocol was composed of a passive listening task, with six repetitions, of two sound stimuli (fig 2). The stimuli can be found in the supplementary materials of [21]. Each listening task lasted three minutes and was followed by a 30 seconds interval of silence. Participants were asked to focus on any auditory or other sensory perceptions during the silence intervals. Both stimuli were repetitive click trains, one at a frequency of 30 clicks per second and the other at a lower frequency of 8 clicks per second. After listening to the 30Hz stimulus, participants were expected to experience a tinnitus like auditory perception, lasting under 30 seconds. The two stimuli were presented in random order. The experiment was configured using E-PRIME2, with triggers determined for each condition, to appear in the SEEG recordings. Prior to the start of the experiment, a comfortable sound volume was defined by the participant, who listened to excerpts of each stimulus with the experiment headphones. Participants were informed on the context of the experiment, and on the possibility that they might perceive a persistent tinnitus-like sound, as part of a normal after-effect experience, which healthy volunteers had previously also perceived under similar experimental conditions. At the end the full protocol, an interview was performed with the participants to check for systematic perception of an after effect in the 30Hz condition, and to discuss any other effects. The entire experiment lasted 47 minutes.



Figure 5.2: Examples of three configurations with the regions of interest highlighted. Subject 1 had electrodes in the target region OP3, while Subjects 2 and 3 had electrodes in the primary auditory cortex only.

5.4.2.4 Preprocessing of anatomical images

For each patient, the preimplantation T1-weighted MRI and the postimplantation CT scan were anonymised using a defacing algorithm, and spatially co-registered. The electrodes were localised in the Montreal Neurological Institute coordinate system using Statistical Parametric Mapping 12 (SPM12, Wellcome Department of Imaging Neuroscience, University College London, www.fil.ion.ucl.ac.uk/spm). Automatic labelling was performed to identify cortical regions of interest using IntranatElectrodes software [263] and Freesurfer [271].

5.4.2.5 SEEG preprocessing

The preprocessing of the raw data was performed using ImaGIN and SPM scripts. Recordings were first converted to SPM .mat format for processing in MATLAB (The Math Works, Inc., version 2018a) using functions based on the SPM toolbox. Event occurrences were checked and saved, channel quality was assessed and bad channels were automatically removed from analysis [264]. The data were then divided into epochs based on the desired duration: in our case, the time window of interest spanned the 10 seconds prior to the listening task, the 3 minutes of the audio recording, and the 30 seconds of silence after each listening task. We then processed the 12 epochs, divided into phantom perception condition and control condition, using time frequency decomposition based on Morlet wavelets. A wavelet factor for time-frequency tradeoff was set to 7 (MFact = 7 in ImaGIN_computeTF), and a band-pass filetering parameter was set to 15 (FactMod = 15). Time-frequency maps were normalised in the time-frequency domain using a baseline chosen at the end of the silence period. The normalised maps were saved to nifti format for further statistical analysis, yielding one image per contact and per subject. Spatial smoothing was performed prior to statistical analysis, using a [5 Hz, 100 ms] kernel.

5.4.2.6 Preliminary statistical analysis

In order to propose some preliminary results in this thesis, regarding the acquisitions obtained until January 2022, the 30 Hz condition was compared to the 8 Hz condition

in all participants, for each contact, using a two sample Student's t-test.

5.4.3 Results

5.4.3.1 Behavioural results

All participants, except one who fell deeply asleep, perceived a persisting sound after-effect. However, this perception did not appear to be perceived consistently across participants. Three participants perceived a pure tone high pitched sound, two participants perceived a low pitched sound, and one participant perceived a sound resembling crickets or waves. Subjects 5 and 7 fell asleep intermittently during the experiment.

5.4.3.2 Preliminary time-frequency results

Among the participants recruited before January 2022, 6 out of 8 had an electrode placed in OP3, and all participants had an electrode placed in the auditory cortex. Subjects 2, 3, 8, and 9 were implanted in the right hemisphere, while the remaining participants were implanted in the left hemisphere. In figure 5.3, the statistical maps (spm T) in the 30 Hz compared to 8 Hz condition are shown at a p < 0.001 threshold, except for patient 7 who had a statistical threshold at p < 0.05 for sake of exploration. The 30 Hz activation was visible in all participants, timelocked to the stimulus between -180 seconds and 0, and its 60 Hz harmonic was visible in a subset of patients. The 8 Hz condition did not appear as saliently as the 30 Hz oscillation in the statistical maps, although it was visible in a subset of patients.



Figure 5.3: Time-frequency statistical maps in OP3, p < 0.001 uncorrected except for patient 7 (p < 0.05, unc.), comparing 30 Hz auditory stimulation to 8 Hz stimulation. The 30 Hz activation is visible in all participants. However, a reproducible pattern corresponding to the tinnitus-like after-effect cannot be established yet. For subjects 1, 8, 9, the 60Hz harmonic is clearly visible. For subject 1 the 8 Hz and its harmonics emerge, and the 16 Hz harmonic of the 8 Hz stimulation is also visible in subject 9. Subject 7 did not perceive an after-effect and fell asleep during the acquisition an presents a weaker activation map compared to the other subjects, hence the lower statistical threshold for sake of exploration.



Figure 5.4: Time-frequency statistical maps in A1, p < 0.001., in the 8 subjects included so far in the experiment. Here, all subjects present an activation of the 30Hz frequency. Harmonics are visible in most subjects, and the 8 Hz condition is particularly visible in subjects 3, 5, and 10. No after-effect pattern can be determined yet in this anatomical location.

5.4.3.3 Discussion

The main goal of this study was to identify the neural response of OP3 during auditory stimulation using click trains, and to elicit the neural signature of a tinnitus like after effect expected to be perceived by participants in the 30 Hz condition. To achieve this, we used a time frequency analysis of the electrophysiological signal and compared the two conditions in the time period spanning the entire listening task and the silence interval.

We were able to generate a tinnitus-like after-effect perception in all participants except one, who fell asleep. The behavioural results argue in favour of a highly reproducible paradigm. In all participants with an electrode in OP3, the auditory stimulation manifested clearly as a continuous and focal oscillation at 30 Hz. A similar pattern was elicited in the primary auditory cortex. However, a specific time-frequency pattern reflecting a tinnitus-like after-effect was not clearly and reproducibly visible in the presented preliminary results.

These findings highlight the involvement of OP3 in the processing of a percussive, beat-like sound, which has not been typically documented in the literature on the functional mapping of OP3, known rather for its somatosensory involvement [273]. We propose two explanations for this observation. First, it is possible that the parietal operculum may be involved in auditory processing, either directly, or indirectly as the recipient of efferent messages from the primary auditory cortex, through a pattern of dense operculo-temporal connections [274]. In this case, the timing of the steady-state like response observed in the primary auditory cortex would likely be preserved in the next hierarchical level of integration. The second possible interpretation to explain these findings relates to the projection of middle ear muscle movement information to the parietal operculum, and to OP3 in particular. In this framework, OP3 would reflect not the sound processing of the incoming signal, but the repetitive activation of the middle ear structures. The stimulation imposed by the click trains translates into a frequency-tagged proprioceptive stimulation, which is reflected in OP3, as demonstrated in our results.

Relevance for hearing health and tinnitus research:

This study is based on a robust protocol that has proven successful in previous work, and a strong hypothesis on the anatomical target: OP3. The preliminary findings provide evidence to support the role of OP3 in the processing of sound, either its acoustic component through primary auditory pathway connections to OP3, or its proprioceptive component through the projections of middle ear movements to OP3.

Further work is required to elicit the neural signature of the tinnitus-like after effect, once inclusions will have been completed. This work outlines the perspective for the tinnitus community, that OP3 may be a relevant target for neuromodulation and thus for new treatment options. The spectral evidence could provide a neural signature to guide neurofeedback protocols, while deep brain stimulation to OP3 may provide relief to chronic tinnitus patients. Furthermore, this work shows the tinnitus community that research in the field remains active and makes progress, with new hopes as the mechanisms of tinnitus are unraveled. We hope that an increased interest in this type of tinnitus induction protocol may help to validate it as a relevant proxy to study tinnitus perception, free of comorbidities.

5.5 Interim conclusion on electrophysiological exploration and implications for tinnitus research

The main electrophysiological findings regarding the parietal operculum highlight its involvement in a network of auditory processing. In particular, OP3 was found to be involved in a network of regions presenting high-frequency modulations to erroneous auditory perceptions, mainly in the left hemisphere for hallucinations, and mainly in the right hemisphere for illusions. In line with this observation, we found intracortical connectivity evidence of a dense network of connections between the opercular and temporal regions. This finding was strongly corroborated by evidence of OP3 activation during a percussive sound listening task, with no lateralisation preference according to the preliminary results. In this last result, there is a possible ambiguity between the auditory processing relating to the actual sound, which would typically appear in the steady-state response - as documented in the auditory cortex, and the processing corresponding to the stimulation through the vibration component, which is somatosensory. Further research is required to establish this distinction precisely, and to confirm whether OP3 is involved in the sound processing, the somatosensory processing, or both.

Furthermore, there was a striking difference between auditory hallucinations and illusions in the limbic system, known for its involvement in both auditory emotion processing and sensory gating mechanisms. Hallucinations act as a proxy for tinnitus in the high-frequency direct electrical stimulation protocol, and this involvement of the limbic system relates to our structural connectivity findings [272], as well as to previous models of limbic involvement in the literature [92]. Among the symptoms documented during the stimulations, participants did not report any form of anxiety, or sudden emotional surges - which have been documented on occasion in this type of experimental setting. It is thus unlikely that the limbic system involvement in hallucinations should reflect an emotional component resembling tinnitus distress. This particular activation may rather reflect the inhibitory mechanisms that are called upon during phantom perception to evacuate this perception. Interestingly, an operculo-parietal connection was found in the CCEP analysis, namely between OP3 and the inferior parietal lobule. This connection was replicated in the HFA modulations mainly of auditory illusions. While illusions, in this framework, are not the direct reflection of tinnitus, they likely share some common mechanisms. In particular, in the model proposed by Job and colleagues [21], tinnitus is portrayed as a proprioceptive illusion. The inferior parietal lobule is a known integrative region, with major contributions in movement and somatosensory processes, crucial for proprioception. This finding confirms the need for further investigation of this region, in the framework of auditory somatosensory integration underlying tinnitus.

6 General discussion and Perspectives

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The involvement of the parietal operculum in tinnitus perception was brought into the spotlight in this thesis. The major aim of the research presented was to examine the role of the parietal operculum within a brain network specific to tinnitus perception. Our reflection builds upon the investigation of previous findings presented in the literature, as well as on a multimodal body of work conducted during this thesis. By adopting complementary methodological standpoints, we strove to piece together the missing connections left in the blind-spot of each method taken independently. We dedicated the first part of this thesis to the question of the involvement of OP3 in a functional network of tinnitus, and in the underlying structural network. In the second part of this thesis, we focused on the electrophysiological correlates of tinnitus perception, with respect to the responses of the parietal operculum to direct electrical stimulation and to sound stimuli. Three studies constituted this second axis, based on high-frequency symptom evocation, low frequency cortico-cortical evoked potentials, and unprecedented tinnitus-like perception induction through acoustic stimulation during passive SEEG recordings.

6.1 Summing up and interpreting the findings of the thesis

The findings presented in this thesis provide compelling evidence for the involvement of OP3 in tinnitus perception. The functional connectivity study using fMRI highlighted a tinnitus-specific, right-dominant connection between the parietal operculum and the dorsal prefrontal cortex, and between the parietal operculum and the inferior parietal lobule. Using a different functional connectivity approach, reflected by cortico-cortical evoked potentials, the temporal, parieto-opercular, and insular regions were highlighted as densely connected, suggesting mutual influence between auditory-specific areas in the superior temporal lobe, and non-specific regions rather known for their integrative properties, OP3 and posterior insular cortex. Furthermore, in DES-induced auditory perceptions, the parietal operculum was found to be involved with a left dominance in the case of hallucinations, and a right dominance in the case of illusions. This suggests the involvement of OP3 in a common integrative process underlying these two types of perceptions, which may both share common ground with tinnitus perception. Finally, the parietal operculum presented a significant and stereotyped response to auditory stimulation using trains of clicks at 30 Hz. This has been proposed to reflect the somatosensory processing of the repetitive stimulus, possibly underlying the emergence of a tinnitus-like after-effect.

To sum up the results obtained during our research, we propose the following graphical representation (figure 6.1) for tinnitus perception of acoustic trauma origin, based on these findings, and on the surface representation of Jülich parcellations. In normal brain function, OP3 receives input from the middle ear, through a pathway likely involving the non-lemniscal nuclei in the brainstem [16]. OP3 also receives information from and delivers commands through trigeminal connections involved in orofacial movement, such as swallowing or chewing, amongst other functions [275]. The primary auditory cortex receives input from the cochlea, through the primary, lemniscal pathway, and presents connections with neighbouring parietal opercular and insular regions (chapter 5, section 5.2). OP3 in the right hemisphere additionally presents connections with the inferior parietal lobule (chapter 4, section 4.2). Auditory emotions are mediated by the limbic system, and in particular the amygdala [87–89]. Sound attention shifting has been suggested to result from topdown regulation from the frontal cortex [88, 89], while filtering out of irrelevant sensory input has been suggested to stem from cortico-striatal connections involving the limbic structures [91, 141, 240].

After an acoustic trauma, the damage causes cochlear cell death and deafferentation, resulting in hyperactivity and hypersynchrony in the primary auditory pathway, and ultimately causing hearing-loss with a possibly decreased activity in the primary auditory cortex, and decreased input from the periphery. The acoustic trauma, or other forms of exposure to long lasting noisy environments, also causes fatigue or disruption in the middle ear structures, leading to patterns of hyperactivity in the somatosensory pathway [127], and in particular an increased activity in OP3, the region of proprioceptive integration of the middle ear [21]. In the non-lemniscal nuclei of the auditory brainstem, it has been suggested that the somatosensory hyperactivity might cause an upregulation and hyperactivity in the primary auditory route [46]. A specific connectivity pattern between OP3 and the dorsal prefrontal cortex possibly becomes established in the case of tinnitus perception, as evidenced in our findings (chapter 4, section 4.2), suggesting the existence of coping mechanisms and habituation, as well as an increased connectivity between OP3 and the IPL, involved in proprioceptive kinesthetic illusions [276]. In addition, plasticity to the white matter takes place in the fronto-temporal junction, possibly relating to the limbic structures involved in the coping mechanisms and the attempts to filter out the persistent sound perception [92].

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Figure 6.1: Connectivity patterns involved in healthy and tinnitus brain networks. Top: White arrows represent normal input from the periphery and documented connections with the limbic system recruited in auditory emotion processing [90]. Black arrows indicate bidirectional findings from the cortico-cortical evoked potentials. Bottom: in acoustic trauma tinnitus, input from the cochlea is reduced, while increased input from the middle ear is reflected by hyperactivity in OP3 as evidenced during a tinnitus-like perception [21]. Functional connectivity between OP3 and the H-PEEF is established in tinnitus [242], and the connectivity with the IPL is increased. White matter density in the tract between the temporal lobe and orbitofrontal cortex, possibly between amygdala and anterior insula, is increased. The limbic system is additionally found specifically modulated in auditory hallucinations, analogous to tinnitus. LB: laterobasal amygdala. SF: superficial amygdala. Hippocampus

6.2 Does a tinnitus network clearly emerge from this research work?

Building upon the findings obtained from different perspectives, the present work emphasises the possibility of an operculo-fronto-parietal network of tinnitus with limbic contributions, in a combined engagement of the ventral and dorsal auditory processing routes. The dorsal processing stream is suggested to play a significant role in tinnitus perception, with a possible differentiated contribution in the right and left hemispheres. In particular, a parietal-opercular frontal interplay was reflected in a connectivity gradient in the posterior-anterior direction involving the ipsilateral and contralateral hemispheres, while additional evidence connected OP3 to the inferior parietal cortex. Furthermore, with the evidence of i) operculo-insular connections in cortico-cortical evoked potentials, ii) temporo-orbitofrontal increased white matter density in non-bothersome noise-induced tinnitus, and iii) the specific involvement of multiple limbic structures in induced auditory hallucinations, this thesis supports the involvement of the limbic system in tinnitus perception. This result is in line with previous findings in the literature, proposing a limbic-based filtering mechanism, which may be impaired following acoustic trauma, with tinnitus emerging as a result of a dysfunctioning noise cancelling loop in the brain [91, 92].

Our results further suggest that the dorsal and ventral streams of sensory integration may play a differentiated role in the right and left hemispheres in tinnitus perception. This observation mirrors the laterality preferences found in the processing of different sound features [79]. Sounds with predominant temporal modulations, such as rhythmic patterns typically found in speech, or percussion music, present a notable leftward cortical activation. This underlines the leftward preference found in speech processing. Conversely, musical sounds with typically reduced temporal modulation but increased spectral modulation patterns are preferentially processed in the right hemisphere. This distinction can relate to the nature of the tinnitus perception, which is typically a continuous sound of varying spectral content, with evidence of pure-tone tinnitus, or wide-band, white-noise type tinnitus. The temporal modulations of this perception are negligible, and should thus be preferentially processed in the right hemisphere. However, tinnitus typically impairs speech comprehension, which could be interpreted as an increased requirement imposed on the left hemisphere processing stream.

6.3 How does this thesis contribute to therapeutic perspectives?

This thesis portrays the parietal operculum as an essential component of tinnitus perception in the perspective of a balanced multisensory integration process. By acting upon the parietal operculum, it is possible to act upon its connections. By decreasing the observed increased functional connectivity patterns evidenced between OP3 and the dorsal prefrontal cortex and IPL, it may be possible to achieve tinnitus modulation or alleviation. We suggest that the parietal operculum may act as a gateway into tinnitus network modification. In parallel, an enhancement of the limbic gating network performances may contribute to improving the coping mechanisms and thus provide additional relief. To this end, several modulation paradigms are possible. From the periphery, it may be possible to consider rehabilitating the middle ear structures, through small implants or through delicate mechanical stimulation such as performed to induced movements in the ossicular chain [16]. In a different approach, osteopathic management and mobilisation of the orofacial articulations may need to be further investigated for their ability to go beyond modulating tinnitus perception, and provide long-lasting relief. At the central level, we further review several options which may prove relevant, with an action on the somatosensory-auditory connection, the auditory-limbic connection, or the autonomous pathway connection.

6.3.1 Neurofeedback protocols

In neurofeedback, brain activity modulation is achieved through visual cues informing the participant on the level of activity in their target brain region. The participant is instructed to modulate, through self-determined strategies, the level of activity in this target area. For tinnitus, the target chosen in the experiments described in the literature is typically the primary auditory cortical activity. Due to the proximity between OP3 and the auditory cortex through their mutual connections, it may be that targeting the auditory cortex should induce a modulation of the parietal opercular activity. Evidence from simultaneous neurofeedback and neuroimaging seems to support this idea, as reviewed in the following paragraphs.

6.3.1.1 EEG neurofeedback

Currently, as of February 2022, 5 clinical trials for tinnitus treatment are registered on clinicaltrials.gov based on neurofeedback using electrophysiological measurements of cortical activity. Electrophysiology-based protocols build upon the evidence in tinnitus participants of reduced alpha (8.5-12 Hz) power, associated with a loss of inhibitory function of this frequency band [102], sometimes combined with increased delta (3-4 Hz) power, associated with an increase in neuronal synchronisation [215].

The first registered trial (NCT00748475), conducted between 2008 and 2013, targeted alpha desynchronisation, in a non-randomised, single-group assignment, open-label study. The aim of the protocol was to assess the effect on tinnitus perception of alpha-neurofeedback, whereby training used acoustic stimulation with a sound matching the tinnitus perception, and the participants practised deflecting their attention from the sound. In total, 12 patients were included and the data from 8 subjects were fully analysed [277]. A significant decrease in tinnitus distress scores was obtained with the neurofeedback treatment, while a control treatment using rTMS showed no such improvement. Interestingly, an increase in alpha power was found in the parietal cortex (presented as BA41) following treatment targeting the right auditory cortex [277]. The decrease in tinnitus distress scores found in this study provided the justification for further development of this technique for tinnitus alleviation.



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Figure 6.2: Illustration adapted from Hartmann et al. [277], highlighting alpha power increase in the vicinity of the parietal operculum area OP1, rather than the primary auditory cortex (a). Effect was higher for neurofeedback treatment than for sham and rTMS (b).

In trial by Güntersperger and colleagues (clinical trial number NCT02383147), patient inclusions were performed between 2015 and 2018 to conduct an individualised EEG-based neurofeedback protocol, targeting the alpha and delta frequency bands within tinnitus subgroups [183]. In this study, patients observed a space ship automatically navigating through a narrow tunnel: increased power in the alpha band led the ship to accelerate, while delta as the defined inhibited band related to autopilot accuracy. Tinnitus distress was durably reduced following this protocol, and tinnitus loudness was reduced but this effect subsided after the end of the protocol. This protocol did not include a control group, therefore the promising results require replication in future work with an evaluation of the placebo effect. Currently, the University of Zurich where this trial was performed is hosting a second neurofeedback protocol, for which inclusions are ongoing, targeting older adults and using tomographical neurofeedback protocol (NCT03895047).

Aiming to enable participants to increase their exposure time to the treatment paradigm, Guillard and colleagues (trial number NCT03773926) developped a portable device to allow participants to conduct the neurofeedback treatment paradigm from home [278]. In a non-controlled, single arm design, several strategies for modulating brain activity were suggested by a user interface to help patients adhere to the protocol and complete the treatment. A decrease in THI scores was observed, although qualified as moderate by the authors. However, here, too, promising results require further validation using a placebo controlled design.

Finally, Jensen and colleagues proposed a three-armed randomised controlled neurofeedback study design, to assess the specificity of alpha-delta modulation to alleviate tinnitus perception and distress [279]. The first arm consisted in the target treatment, whereby participants modulated their alpha and delta oscillations, similarly to the previously mentioned studies. In the second arm, an active control group, participants modulate the beta/theta activity. The third arm consisted of a passive control group, whereby participants simply log their evaluation of tinnitus perception in a diary twice a week. To date, no results have been made available. With inclusion completion estimated to have been achieved in March 2021, it is likely that some results should become available in future months.

6.3.1.2 fMRI Neurofeedback

In a different approach, some studies have used functional MRI to assess local cortical activity and provide feedback to participants [280]. In tinnitus research, to our knowledge, this has been implemented in one research group by Haller and colleagues, using real-time fMRI with feedback provided by a sliding bar to indicate the level of auditory cortex activity [231]. A comparison was conducted to determine the best study parameters, between continuous feedback, and intermittent feedback. While better task achievement was achieved over several runs using continuous feedback, the results do not show, in a small group of 14 tinnitus participants, any effect of the protocol on tinnitus perception. The authors discuss the fact that the neurofeedback protocol is a challenging task, involving a wide cortical network. Among the regions involved in this task, the parietal regions are clearly involved in the activity reduction pattern (figure 6.3).



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Figure 6.3: Illustration, adapted from Emmert et al. [231], highlighting activity increase and decrease in the vicinity of the target region (green). The inferior parietal cortex seems to activate as the participants try to decrease auditory-related activity, which also inhibits the activity in the parietal operculum.

6.3.1.3 Conclusion on neurofeedback

Both in fMRI and in EEG, the main target of all existing protocols is the primary auditory cortex, with the combined objective to achieve tinnitus loudness reduction and tinnitus distress reduction. To measure the impact of neurofeedback on tinnitus distress, a randomised, placebo controlled study design is required. However, this is rarely the case, due to a number of constraints. Regarding tinnitus perception modulation, we suggest that the modulations achieved in the vicinity of the parietal operculum, in both EEG and fMRI neurofeedback, could play a particular role. It may be that through the connections found between OP3 and the temporal lobe, targeted A1 modulations may achieve OP3 modulations, and vice-versa. Therefore, an investigation and reanalysis targeting the modulations of OP3 in the data produced during these protocols, if made publicly available, should provide some insight into further understanding of the role of OP3 in reducing tinnitus perception.

6.3.2 Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) combined with sound stimulation has provided promising results in tinnitus management [235]. Vagus nerve stimulation has been proposed to drive general purpose neural plasticity, while the auditory stimulation is expected to help target the region of interest, where the plasticity is intended to happen. Its mechanisms involve the autonomous nervous system, which via the anterior insula, may indirectly act on the parietal opercular connections. Currently, four protocols are registered in clinicaltrials.gov, one having been withdrawn and the other three having been completed. One study used only VNS, which did not prove successful in improving tinnitus perception or distress [281].

In a proof of concept study, authors proposed a case study to prove safety and efficacy of VNS paired with tones, targeting sound frequencies in the vicinity of the tinnitus frequency [237]. This study was thus based on a tonotopic model of tinnitus, whereby stimulation around the tinnitus frequency may drive cortical reorganisation. In a case study report, authors highlight a significant THI score decrease, by up to 48%. In addition, EEG reduction of beta band activity in the dorsal anterior cingulate cortex was observed, and was proposed to be associated with reduced tinnitus distress.

A randomised controlled trial was subsequently proposed [232], including 30 patients with chronic tinnitus recruited between 2014 and 2015 (NCT01962558), with stimulation devices implanted to target the cervical vagus nerve. In the treatment arm, VNS was performed combined with tones 2.5 hours a day, for 6 weeks, whereby the tones were activated asynchronously in the frequency range surrounding the tinnitus frequency. In the active control arm, VNS remains paired with tones, such that the blinding may be maintained. However, the tones were not implemented in the same way as in the treatment arm, and were expected to be ineffective. Outcomes varied widely across participants. In the treatment arm, it was proposed that the best responders were participants with specifically acoustic trauma tinnitus. Among control participants, several successfull THI reductions were achieved, highlighting a possible placebo effect, or a success from the non-paired stimulation protocol. In this study, no imaging was conducted, therefore it is not possible to assess any potential modulations in the parietal operculum.

In an attempt to establish optimal stimulation parameters for transcutaneous VNS to treat tinnitus, Yakunina and colleagues conducted a review pertaining to electrode placement strategies, stimulation parameters, relevant sensory pairing, as well as imaging evidence for the mechanisms of tVNS [235]. Transcutaneous VNS applied to the outer ear structures, as opposed to VNS of the cervical nerve in the neck, involves a deactivation of the auditory cortices. This has been linked to the different routes involved, and to multisensory integration of the somatosensory and auditory systems [235]. Interestingly, this review reports the authors' previous efforts to optimise stimulation configurations, and highlights different activation patterns found in fMRI during tVNS: the parietal opercular cortex, possibly OP4, was found activated in tVNS to the tragus and to the earlobe. Our proposed tinnitus-induction protocol may be of interest to define a relevant tone pairing paradigm in tVNS. Considering its ability to activate OP3 as well as the auditory cortex, tVNS during 30 Hz click train auditory stimulation may achieve a modification of the somatosensory-auditory integration processes that have been suggested to be altered in noise-induced tinnitus.

6.3.3 Bimodal stimulation: a tongue - ear connection

We have proposed that OP3 could be involved in somatosensory-auditory integration contributing to tinnitus perception. This cross-modal influence has been specifically targeted in a body of animal studies by Shore and colleagues, and more recently in humans by Conlon and colleagues, who proposed a dual stimulation paradigm, aiming to reverse possible erroneous integrative processes. Here, the somatosensory modality was used as a complement to the auditory modality, with an electrode array delivering impulse stimulations to the tongue, while sounds were delivered to the ears. Again, a specific pairing of auditory-somatosensory stimulation parameters was proposed [110, 282]. The study was a multicentric, double-blind, randomised, placebo controlled (however with the placebo being the third arm) trial, and recruited a total of 326 out of 698 screened patients. Treatment was self-administered by participants at home, for at least an hour a day during a 12 week period. The first arm used a wide range of pure tones and broadband noises, synchronised with the burst of the electric impulses delivered to the tongue and with a specific tone to tongue location mapping. This design builds upon the concept of paired plasticity driven by cross modal stimulation [110]. In the second arm, the timing of the impulses was slightly desynchronised compared to the sound, and with no specific tone to tongue mapping. A larger desynchronisation was proposed in the third arm. The outcome measures reported by the authors were encouraging and abundantly relayed in the press, since THI reductions were observed within each arm, and up to twelve months after the protocol. However, no between-arms differences were found, which may argue rather in favour of a beneficial effect of the tinnitus management and counselling performed during this protocol. This also underlines the difficulty in the choice of

the placebo control design. In a short article for France Acouphènes, we reviewed the methodology and promising results, in order to make these findings available to the French tinnitus community, and to point out possible interpretation risks.

6.3.4 Deep Brain Stimulation

Several attempts have been made to alleviate tinnitus using DBS, mainly targeting the primary auditory cortex and the caudate nucleus, building upon the hypothesis of dysfunctional corticostriatal networks in tinnitus. While DBS to A1 has provided interesting results in a few cases, these observations have yet to be reproduced in group studies, as highlighted in chapter 2. Following up on a retrospective analysis of the effect of DBS on co-occurring tinnitus as well as on animal models of tinnitus conducted at Maastricht University [239], a new double-blind randomised DBS protocol with cross-over has been registered in clinicaltrials.gov, targeting the primary auditory pathway at the level of the medial geniculate body of the thalamus (NCT03976908). Depending on where exactly in the MGB the stimulation is performed, due to the presence of tonotopic and non-tonotopic areas as described in chapter 2, this protocol may modulate different subcortical functions, specific to lemniscal or non-lemniscal processing. Patient inclusions are documented as having not yet begun. It is possible that this protocol may achieve modulation of both the direct auditory pathway, and the non-primary pathway, receiving multisensory input and thus likely involving parietal opercular regions.

In a different approach, targeting the gating mechanisms proposed to be mediated by corticostriatal connections, the area LC of the caudate nucleus, a striatal structure, Cheung and Larson and colleagues have proposed several case studies as well as a pilot clinical trial (NCT01988688). First, the authors provided evidence of incidental tinnitus modulations upon DBS to the caudate nucleus in patients with Parkinson's disease [283] and specified that this modulation occurred particularly in area LC, in the body of the caudate nucleus [240]. Then, the authors highlighted the capacity of DBS in area LC to generate phantom sounds, interpreting these findings as evidence for a gating function of this area [284]. Building upon this evidence, a pilot study was proposed, specifically targeting area LC in tinnitus participants (NCT01988688), and highlighting differences in effectiveness between regions of the body of the caudate nucleus [285]. A combined analysis of the 6 patients included in the clinical trial and 14 subjects included as part of a functional connectivity study, connectivity patterns of the different areas of the caudate nucleus were established and related to whether or not stimulation to these areas achieved tinnitus alleviation. The stimulation was successful in 4 areas of the body and one area of the head of the caudate nucleus. However, 15 locations of the head of the caudate nucleus were unsuccessful in reducing tinnitus perception.



Figure 6.4: Image taken from [285], highlighting an increased connectivity between the left caudate body, successful in alleviating tinnitus, compared to the caudate head. The increase is found with the left superior temporal lobe, likely corresponding to the primary auditory cortex. However, an increased connectivity is also found in the vicinity of OP3, as well as with the right anterior insula, and right inferior parietal lobule.

Interestingly, the connectivity pattern from the responsive areas of the left caudate body, compared to that of the left caudate head, was found to have increased with the bilateral superior temporal areas, according to the authors. However, it seems that in the figure, increases in the connectivity patterns from the successful areas compared to the unsuccessful areas were found in the right parietal opercular cortex, right inferior parietal lobule, and right anterior insula. This pattern is in correspondance with the major findings presented in this thesis. While the mechanistic explanations differ, between our proposed model of a modified auditory-somatosensory integration process in noise induced tinnitus, and the gating role of the striatal network proposed by the authors of this study, some common ground seems to exist. According to these new findings by Perez and colleagues, OP3 is part of a corticostriatal network involved in tinnitus. Thus, this supports from a different perspective the idea that stimulation to OP3 might be expected to also achieve modulation of tinnitus.

This is precisely the objective of the last DBS clinical trial registered in clinicaltrials.gov: to achieve tinnitus perception decrease by stimulating the right OP3. The trial is taking place in Grenoble with collaborations from our team. Initially, the project had been designed to start in 2018, and was to provide the data and empirical grounds for the present thesis. However, due to unforeseen circumstances, this was not possible. The first participant was successfully included and implanted in January 2022. The stimulation parameters are currently under optimisation, with behavioural results expected to take place over an extended period of time for brain plasticity to occur. Therefore, the results presented in this thesis will be confronted with ground truth in the coming months, providing a final answer to the question: can stimulation to OP3 successfully reduce tinnitus perception?

Appendices

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A.1 Publications

Brain mapping of auditory hallucinations and illusions induced by Direct Intracortical Electrical stimulation, Chloé Jaroszynski, Ricardo Amorim-Leite, Pierre Deman, Marcela Perrone-Bertolotti, Florian Chabert, Anne-Sophie Job-Chapron, Lorella Minotti, Dominique Hoffmann, Olivier David, Philippe Kahane, Neurology, 2022 Submitted.

Tinnitus perception in light of a parietal operculo-insular involvement: A review, Chloé Jaroszynski, Agnès Job, Maciej Jedynak, Olivier David, Chantal Delon-Martin, Brain Sciences, 2022, Accepted - minor revisions.

Tracking white-matter brain modifications in chronic non-bothersome acoustic trauma tinnitus, Chloé Jaroszynski, Arnaud Attyé, Agnès Job, Chantal Delon-Martin, NeuroImage: Clinical, 2021.

Stimulation bimodale : une nouvelle piste thérapeutique pour diminuer les acouphènes ? Une relecture de la publication de Conlon et coauteurs dans Science Translational Medicine, octobre 2020, Chloé Jaroszynski, Agnès Job, Chantal Delon-Martin, France Acouphènes, 2021

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A.2 Article in France Acouphènes

Recherche: La stimulation bimodale

Chère lectrice, cher lecteur,

Concernant les annonces sur Internet ou dans les médias, les pistes thérapeutiques pour les acouphènes se succèdent apportant des informations de tous les cotés souvent sensationnelles, quelques fois décevantes ou donnant une lueur d'espoir sur une possibilité de traitement. L'article que nous vous proposons dans ce numéro est une relecture d'un article de la revue « Science Translational Medicine ». Le procédé décrit dans cet article a été annoncé depuis plusieurs années déjà et a été diffusé dans plusieurs médias connus. Les autrices travaillant à l'Inserm nous ont proposé d'en faire une relecture en évaluant le dispositif et en pensant que vous seriez intéressé par cette relecture. Nous les remercions pour cette proposition.ndlr

Stimulation bimodale : une nouvelle piste thérapeutique pour diminuer les acouphènes ? (Une relecture de la publication de Conlon et coauteurs dans Science TranslationalMedicine, octobre 2020)

Les autrices



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Ces 3 chercheuses n'ont aucun lien ni scientifique ni financier avec les auteurs de l'étude décrite.

Introduction

Conlon et co-auteurs ont publié en octobre 2020 un article dans « Science TranslationalMedicine » sur un nouveau traitement par stimulation de la langue et de l'oreille pour réduire les effets des acouphènes. Cet article a ensuite été relayé dans la revue « Scientific American »(https://www.scientificamerican.com/article/new-tinnitus-treatment-alleviates-annoying-ringing-in-the-ears1/) puis en France entre autres dans la revue « Sciences et Avenir » (https://www.sciencesetavenir.fr/sante/orl/un-traitement-prometteur-contreles-acouphenes_149422).

Que dit cet article et quel espoir peut il apporter aux patients ?

Les résultats sont-ils probants ? Le but est ici de décrire le contenu de ce travail et de montrer les limites actuelles. Il y a fort à parier que cette nouvelle méthode, par sa simplicité de mise en oeuvre, va conduire à de nouvelles études cliniques dans les années à venir.

Les objectifs :

L'étude décrite a pour but d'évaluer un nouveau dispositif non invasif visant à soulager les acouphènes par une stimulation simultanée de la voie auditive et somato-sensorielle. Faisant suite à plusieurs études de moins grande ampleur du même groupe de chercheurs, les objectifs principaux ici sont d'abord de confirmer l'efficacité et la tolérance du traitement sur un groupe de patients correctement choisis, puis d'évaluer les effets liés à l'application de différents paramètres de stimulation dans le temps.

Le système :

Ce dispositif a fait l'objet d'une première évaluation

de tolérance et est d'ores et déjà fabriqué par une start-up 'NeuroModDevices' (https://www.neuromoddevices.com/) située en Irlande. Commercialisé sous le nom de Lenire (R), il a déjà été utilisé par près de 600 personnes souffrant d'acouphènes et a obtenu la certification CE, qui est une garantie de respect de normes de sécurité, mais pas une garantie de résultats.

Pour être validé scientifiquement, il est donc nécessaire de conduire des études sur un groupe de participants. En groupant les forces de plusieurs laboratoires, il est possible d'inclure un grand nombre de participants en un temps contraint.

Le principe de fonctionnement (hypothèses de travail)

Ce système permet la stimulation simultanée de la langue et de l'audition. Pour la stimulation de la langue, le système comporte 32 plots situés sur un support en forme de sucette qu'on met sur la langue. Des impulsions électriques sont envoyées sur les 32 plots dans une séquence prédéfinie et adaptée à chaque participant.

Ces impulsions stimulent la branche mandibulaire du nerf trijumeau qui se projette dans le cerveau dans le cortex sensoriel primaire et l'operculumparietal. La stimulation sonore, un son émis dans le casque fourni qui alterne entre un bruit blanc et des séquences de sons purs, stimule quant à elle le nerf auditif qui se projette dans l'aire auditive primaire (gyrus de Heschl). Or on sait que ces régions sont fortement interconnectées (Skipper et al., 2017).). Les paramètres de synchronisation, de fréquence et d'intensité des signaux sonores et électriques sont gérés par un
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contrôleur dans un boîtier externe. L'idée derrière ce système est la suivante. Lorsque ces 2 stimulations sont synchronisées, les régions interconnectées ont un effet de synergie et peuvent induire une modulation de l'activité dans la région de convergence des 2 stimulations, conduisant à une potentielle plasticité cérébrale, donc une réorganisation locale susceptible d'apporter une amélioration. C'est l'hypothèse de travail sur laquelle s'appuie ce système. lci les stimulations auditives ciblées visent les fréquences entre 500 Hz et 7 kHz, soit des fréquences de la parole et des sons correspondant plutôt aux acouphènes qui seraient ainsi perçus moins fortement. Les participants inclus dans le premier groupe du protocole ont été stimulés de cette manière.

La sélection des participants :

Un total de 326 participants ont été sélectionnés parmi 698 candidats et inclus dans 2 centres en Irlande et en Allemagne. Les caractéristiques de la cohorte sont les suivantes :

avoir entre 18 et 70 ans (moyenne de 48 ans +/-11 ans);

 avoir des acouphènes chroniques depuis au moins 3 mois et au plus 5 ans (moyenne 2 ans et demie +/- 1 an et demie);

 avoir un score de THI (handicap lié aux acouphènes) compris entre 28 et 76 sur 100, ce qui correspond à un handicap modéré, moyen ou lourd (score moyen de 44 +/- 13). De fait, la plupart présentaient un handicap moyen. Les acouphènes sévères n'ont pas été inclus car ils sont souvent associés à des troubles anxieux ou dépressifs.

• Le score de TFI, qui traduit l'impact sur les activités quotidiennes de la semaine précédente, était de 48 +/- 15 sur 100, reflétant un impact moyen.

• La perte auditive devait rester inférieure à 40 dB dans les basses fréquences et inférieure à 80 dB dans les hautes fréquences. En moyenne, ils présentaient une perte auditive sur l'ensemble de la gamme de fréquences de 18 dB +/- 10 dB, valeur qui correspond à une perte auditive modérée.

• Enfin les participants ne devaient pas avoir de traumatisme de la tête ou du cou, de troubles anxieux, ni de désordres de la jonction temporomandibulaire.





Légende : "Evolution du THI enregistré au cours du traitement chez les personnes ayant réalisé l'ensemble du protocole (d'après Conlon et coauteurs, 2020). Les résultats moyens par groupe ainsi que les incertitudes sont reportées. Les chevauchements entre les barres d'incertitudes pour ces 3 groupes reflètent l'absence de différence avérée entre eux."



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Le protocole randomisé en double aveugle :

Les participants ont été séparés en 3 groupes d'une centaine de personnes chacun, et ce de manière aléatoire sans savoir à quel groupe ils appartenaient. Il y a ainsi à peu près le même nombre de participants dans chacun des groupes pour chaque type d'acouphènes (acouphène atonal; acouphènes avec hyperacousie; acouphènes sans perte auditive; acouphènes liés au bruit). Les soignants en charge du suivi des participants n'ont pas eu connaissance de l'attribution des groupes pendant toute la durée du traitement.

- Dans le 1er groupe, le traitement était celui dont on pense qu'il est efficace, avec une stimulation auditive et de la langue synchronisée, et une correspondance unique entre la fréquence de la stimulation auditive et la position sur la langue.

- Dans le 2è groupe, le traitement était sensiblement le même mais avec un léger décalage dans le temps entre les 2 stimulations et une absence de correspondance entre le son et la position sur la langue.

- Enfin dans le 3è groupe, les stimulations sont désynchronisées et il n'y a pas de correspondance entre le son et la position sur la langue. On pense donc qu'il ne devrait pas y avoir de plasticité induite dans cette condition, par rapport au 1er groupe.

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Les participants devaient effectuer les stimulations chez eux, pendant 1 heure par jour et pendant 12 semaines. Au bout de 6 semaines, ils revenaient pour une première évaluation, puis une seconde à la fin du traitement au bout des 12 semaines. Un suivi sur 1 an était enfin effectué avec des jalons à 6 semaines, 6 mois et un an après la fin du traitement.

Les résultats portent sur les scores de THI et de TFI tout au long du traitement chez les 80 % de personnes qui ont suivi le traitement jusqu'au bout.

Les résultats actuels :

A court terme, au bout de 6 semaines, les scores de THI et de TFI (voir figures) étaient significativement diminués dans les 3 groupes, respectivement de 12 points et de 10 points. Ces valeurs ne sont que peu changées en fin de traitement au bout des 12 semaines, ce qui peut traduire un phénomène d'habituation au traitement. Ces résultats correspondent à des moyennes. Il faut ici noter qu'environ 80% des participants répondent au traitement et 20% soit ne présentent pas de bénéfice, soit présentent une dégradation de leurs acouphènes. Ce qui nous semble intrigant, est de noter la similitude des réponses au traitement dans les 3 groupes. Cela tend à montrer que les conditions liées aux stimulations, qu'elles induisent ou non une plasticité, n'ont pas d'importance sur les résultats.

A long terme, **l'effet est maintenu pendant 1 an**, avec toutefois un bénéfice un peu moindre pour le 3è groupe, mais sans que cela ne soit significatif.

Les analyses n'ont pas été réalisées selon le type d'acouphènes dans cet article. Les auteurs indiquent que celles-ci feront l'objet d'une future publication.

Quelles limites ?

Les limites, abordées à la fin de la discussion dans l'article, viennent de ce que la double stimulation soit réalisée dans les trois groupes de l'étude, autrement dit **il n'y a pas de contrôle effectif de l'effet placebo**.

Il est également fait mention du problème d'interprétation des résultats qui ne sont pas significativement différents entre les groupes de l'étude à la fin du traitement, ce qui aurait dû être observé pour valider l'hypothèse.

Un certain nombre d'autres d'éléments restent inconnus. On aurait aimé savoir si le volume sonore des acouphènes avait évolué et si oui dans quel sens. On aurait aimé avoir une analyse plus fine chez les participants les plus impactés par leurs acouphènes : ce traitement est-il aussi efficace chez ces participants là ?

La durée des acouphènes des personnes sélectionnées pour cette étude n'est pas très longue. Qu'en estil chez ceux qui subissent depuis plus de 5 ans ces acouphènes chroniques ? ... Il reste de nombreuses questions en suspens et il est clair que de futures études pourront et devront apporter des réponses à ces questions légitimes. En plus de ces questions, tout un chapitre de cette étude porte sur les effets indésirables, dont le taux est de 18 %. Ceux ci sont catalogués selon qu'ils sont faibles ou modérés, liés au traitement ou indépendant de celui-ci. Parmi les 59 effets indésirables modérés, 16 sont attribuables au système utilisé (augmentation des acouphènes, ulcères de la bouche ou de la langue, par exemple), 39 sont possiblement liés au système (augmentation des symptômes liés aux acouphènes, maux de tête, douleurs de la bouche ou de la langue...). Aucun effet indésirable grave n'a été observé. Comme pour tout système médical, on évalue le bénéfice par rapport au risque. Ces effets montrent qu'il existe des risques concernant l'utilisation de ce système.



Notre interprétation :

Pour l'heure, il n'a pas été démontré qu'il existe une correspondance entre une fréquence auditive et une position sur la langue. La sensibilité de la langue est spécifique aux tonalités de goût, pas de son. Néanmoins, la stimulation bimodale présentée est soutenue par les études précédentes de ce groupe de chercheurs chez l'animal pour déterminer la zone de stimulation adéquate.

1/Effet de la stimulation ou effet placebo?

Si l'utilisation de ce protocole montre une amélioration de l'impact des acouphènes sur la vie de tous les jours (scores de THI et TFI diminués de 14 points en moyenne après 12 semaines) chez 80 % des patients qui sont allés au bout du protocole, cette étude ne montre pas si cet effet est dû au traitement luimême ou au fait que les patients, très en demande de traitement, soient soulagés par la prise en charge exigeante de leurs acouphènes (1h par jour consacrée au 'traitement' pendant 12 semaines, beaucoup de rendez-vous de suivi) via un protocole clinique, autrement dit un effet placebo. Il faudrait pour cela un vrai groupe contrôle, par exemple avec une stimulation du front ou d'une région qui n'est pas connectée au nerf trijumeau. Dans cette étude, le groupe 3 semble être considéré comme contrôle. Or, la provenance supposée de la plasticité cérébrale est la stimulation bimodale acoustique et somatosensorielle, qui est présente dans les trois groupes. Pour caractériser la part réelle du traitement dans les effets observés,

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il manque un groupe pour lequel aucun traitement n'est prodigué, mais pour lequel la prise en charge reste la même avec des rendez-vous médicaux, des entretiens, et un suivi identique, tout en maintenant l'aveugle dans l'étude. Cette demande ne semble pour l'heure pas sur les rails (rien n'est mentionné sur le site clinicaltrials.com, site qui répertorie les essais cliniques).

Un élément est intrigant : si le troisième groupe est considéré comme un réel groupe témoin (pas de synchronisation temporelle ni de concordance spatiale), l'absence de différence avec les autres groupes devrait amener à la conclusion d'une absence d'effet du traitement.

2/Beaucoup d'inconnues.

Si un bénéfice a été obtenu chez des participants présentant des acouphènes chroniques de moins de 5 ans avec un impact moyen sur la vie quotidienne, on ignore encore ce qu'il en est avec des acouphènes plus invalidants.

3/Conflits d'intérêt ?

Si l'étude est bien conduite sur le plan clinique, il n'en demeure pas moins que 8 des auteurs sont les responsables et personnels de la Start-up, inventeurs des brevets associés, et que 3 sont membres du conseil scientifique de l'entreprise, tous rémunérés par l'entreprise. Cette remarque ne signifie pas que les résultats sont erronés, mais plutôt que **des biais pourrait être présents dans cette étude**.

4/Les effets indésirables ?

Les participants pour cette étude ont été sélectionnés pour répondre à un certain nombre de critères, liés à leur audition, leur état neurologique et psychologique. Notamment, la majorité des participants présente un niveau de handicap lié aux acouphènes (mesuré par le THI) entre 20 et 60 donc un handicap modéré à moyen et peu de participants avec des handicaps lourds ou invalidants, une durée des acouphènes moyenne de 2 ans et demie, et une perte auditive inférieure à 20 dB. Concernant l'observance du traitement, elle a été obtenue chez 80 % des participants. Finalement, **un ensemble d'effets indésirables** a été répertorié dont 18 % sont évalués comme 'modérés'. Ceux ci correspondent typiquement à une augmentation de leurs acouphènes ou à des douleurs buccales, tandis que des effets plus bénins comme un goût métallique dans la bouche sont rapportés.

Conclusions :

Cette étude suggère bien une amélioration de leur qualité de vie après utilisation de ce système. Tant mieux pour les personnes qui obtiennent un bénéfice de ce traitement (80 % de ceux qui sont allés au bout). Mais est-ce que tout traitement qui proposerait un accompagnement long ne permettrait-il pas le même type de bénéfice ? En l'état, **il faut rester prudent sur l'interprétation des résultats qui ne permettent pas de trancher sur une efficacité avérée du traitement**.

En tout état de cause, pour le moment, il reste de nombreuses questions en suspens. Ces questions n'obtiendront des réponses que grâce à de nouvelles évaluations cliniques : d'abord contre placebo, ensuite selon le type d'acouphènes, puis avec des personnes plus fortement impactées, avec des modes de stimulation évaluées plus finement, avec d'autres modes de traitement comme les thérapies comportementales ou l'hypnose par exemple.

Tant que ces données ne sont pas réunies, que des protocoles ne sont pas établis, que les limites ne sont pas précisées et que les résultats ne sont pas publiés, le résultat pour les personnes souffrant d'acouphènes semble à ce stade encore bien fragile.



White Matter Alterations in Noise Induced Tinnitus: A Deep and Manifold Learning based Study, Chloé Jaroszynski, Agnès Job, Chantal Delon-Martin, Arnaud Attyé, OHBM - Rome 2021, conference poster.

Phantom sound perception or tinnitus is a highly prevalent condition, affecting between 10 and 15% of the population. Although much research has gone into finding out the localisation and nature of brain changes that could explain initial generation, chronification, habituation, or long term maintenance of tinnitus, no consensus has been reached. In the present study, we explored the effects of non-bothersome tinnitus perception on white matter plasticity, using advanced Diffusion Weighted Imaging (DWI) methods and specifically targeting chronic tinnitus induced by acoustic trauma.

White matter alterations in noise-induced tinnitus: A deep and manifold learning based study

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Context & Study goals



Phantom sound perception, aka tinnitus, is a highly prevalent yet poorly understood condition affecting up to 15% of the population. To date, no consensus has been reached on the location of brain changes responsible for initial generation, chronification, habituation, or long term maintenance of tinnitus. The **aim** of the present study was **twofold**:

explore the correlates of non-bothersome tinnitus on white matter plasticity, specifically targeting acoustic trauma etiology.

preserve sensitivity to potentially subtle tinnitus related group level differences whilst taking into account individual **variability**, using advanced Diffusion Weighted Imaging (DWI) methods.

Materials & Methods Participants

N=19 Chronic tinnitus Age: 42 +/- 12 y.o. Hearing Loss: 20.2 +/- 10.3 dB Duration: 11.6 +/- 7.6 y. Tinnitus score (THI): 16.2 +/- 10.5 --- Slight to mild tinnitus ---

N=19 Controls Age: matched Hearing Loss: 13.2 +/- 3.8 dB

3T Philips MRI | 32 chan. head coil | IRMaGe | Acquisitions

3D T1 MPRAGE 150 ax. sl., .9x.9x1.2 mm³ TI: 800ms - flip angle: 15° TR/TE: 25/3.9ms

DWI - SENSE factor: 2 70 ax. sl., 1.6x1.6x2 mm³ TR/TE: 5500/72ms 60 dir. b=1000s/mm | 1 b=0s/mm

Preprocessing <



+ rigid body registration to standard MNI space

SS3T-CSD [3]:

Signal deconvolution by group average tissue-specific response function



Deep learning | bundle specific tractography: **TractSeg** [1]



Riemanian framework for group statistics: TractLearn [2]



> Learn reduced space from healthy subjects **Project** tinnitus patients and compute geodesic distance to determine voxel alterations

> Project back into image space to visualize location of altered voxels







Conclusion

By combining deep learning for bundle segmentation and manifold learning for quantitative analysis, DWI gives us some insight into the way tinnitus impacts the brain. With alterations found in the **parietal opercular** region, the present findings are in line with a model of tinnitus based on middle ear proprioception. The Riemanian framework, as opposed to the general linear model, takes into account the way voxels interact in pathophysiological alterations, rather than analyzing each voxel independently and risking lacking in sensitivity.

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Results -

Significant group

differences (pFWE<0.05) were found in the thalamic radiations and in the **corona radiata** in the right hemisphere. The largest cluster was found in the right thalamoparietal tract, near a cortical region responsible for **somatosensory** integration : OP3. This supports previous findings involving OP3 in tinnitus

perception in fMRI [6].

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A.5 Diffusion metrics comparison

FA and AFD were found highly correlated in commissural bundles, with large fanning geometries and low reproducibility in the statistical analysis. In the association bundles, connecting remote ipsilateral grey matter regions, and likely to cross other bundles, the correlations ranged from 0.26 to 0.81 for the cingulum (which also presents large faming geometries) or from 0.21 to 0.77 in the superior longitudinal fasciculus. These bundles also presented a higher level of variance. In the projection bundles, connecting deep grey nuclei with cortical grey matter, two main geometries were observed. On one hand, some bundles presented a compact geometry where similar profiles of FA and AFD were observed, such as in the thalamo-parietal bundle (T-PAR, with correlation of 0.96 and 0.98). On the other hand, certain projection bundles displayed a high likelihood of having many voxels with multiple crossing fibres, and also presented weaker correlations between FA and AFD as in the case of more compact geometries (0.79 and 0.83 in the left and right Fronto-Pontine tracts). When comparing the group statistics between these two metrics, we found increased Cohen's d for AFD compared to FA, which argues in favor of using AFD rather than FA, when applicable, in the case where a bundle specific approach has been conducted.



Figure A.1: FA (blue line) and AFD (red line) compared along 50 bundles included in the main diffusion weighted analysis.

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A.6 Acoustic radiations tractography additional results



Figure A.2: Example of the tractography obtained in one subject for the right acoustic radiation, and profiles of AFD metric variations along left and right acoustic radiations, between controls and tinnitus participants. A significant difference was found in the right hemisphere (see chapter 4 for interpretations)

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