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Mismatch Negativity a Neural Marker of Auditory Spatial Adaptational Plasticity in Unilateral Hearing Loss patients

Mariam Alzaher

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THÈSE

**En vue de l'obtention du
DOCTORAT DE L'UNIVERSITÉ DE TOULOUSE
Délivré par l'Université Toulouse 3 - Paul Sabatier**

**Présentée et soutenue par
Mariam ALZAHER**

Le 17 septembre 2020

**Mismatch Negativity, un Marqueur Neuronal de la Plasticité
Spatiale Auditive chez les Sujets Sourds Unilatéraux**

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Mismatch Negativity a Neural Marker of Auditory
Spatial Adaptational Plasticity in Unilateral Hearing
Loss patients.

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Mariam ALZAHER

Abstract

Objectives: This thesis investigates different spatial hearing functions in 3 types of populations: Normal Hearing Subjects (NHS), Unilateral Hearing Loss patients (UHL) and Bilateral Hearing Loss patients (BHL). To discover the mechanisms underlying the adaptive strategies that are observed in UHL with acquired deafness. The main aim of the thesis is to verify whether spatial Mismatch Negativity (MMN) could be a neuronal marker of spatial auditory plasticity observed in UHL patients, and to verify whether these neural correlates are consistent with the spatial auditory performance.

Materials and Methods: Two types of investigations were applied to 20 NHS, 21 UHL and 14 BHL. The first investigation is a sound source identification task measured by the root mean square error (RMS). The second assessment is an electroencephalography (EEG) study where we analyzed the amplitude and latency of the MMN. MMN is defined as an auditory evoked potential that reflects the brain's ability to detect a change in one physical property of a sound. We used a standard sound in a reference position (50°) with three deviations from the standard (10° , 20° , and 100°), in binaural and monaural conditions.

Results: UHL patients were divided into 3 groups according to their spatial performances. The group of good performers (UHL *low rms*) showed better RMS scores in comparison with NHS with earplugs (NHS-mon), with performances similar to those of NHS subjects in binaural condition. A progressive increase of the MMN with the angle of deviation from the standard was noted in all groups. With a significant reduction of MMN amplitude in monaural NHS when the ear plug was applied on the ipsilateral side of the standard. MMN showed consistent variation with the behavioral observations, where UHL *low rms* patients had larger MMN amplitudes than those of monaural NHS and similar to those of binaural NHS.

Conclusion: UHL patients have adaptive spatial auditory strategies. Our study was able to demonstrate that spatial auditory plasticity that occurs after deafness can be reflected by the MMN. Neural observations (i.e. the MMN) are correlated with behavioral observations

of spatial source identification. This means that the spatial cortical plasticity, that took place in these subjects, is not limited to the functions of identification of the sound source, but exceeds these capacities towards more complex mechanisms such as deviance detection and short-term memory, that are involved in the spatial discrimination function.

Keywords: Mismatch Negativity, spatial localization, spatial discrimination, monaural condition, unilateral deafness, reorganization, plasticity.

Résumé

Objectifs: Cette thèse évalue les différentes fonctions d'audition spatiale chez 3 types de populations : Normaux entendants (NE), sourds unilatéraux (SU) et sourds bilatéraux (SB). Afin de découvrir les mécanismes qui soulignent les stratégies spatio-auditives adaptative qui sont observés chez les SU avec surdité acquise. Le but principal de la thèse est de vérifier si la MMN pourrait être un marqueur neuronal de la plasticité spatiale auditive observée chez les patients SU, et de vérifier se les corrélats neuronaux sont cohérentes avec les performances spatiales auditives.

Matériels et Méthodes: Deux types d'investigations ont été appliqués sur 20 sujets NE, 21 SU et 14 SB. La première investigation s'agit d'un test d'identification de source sonore mesuré par l'erreur quadratique moyenne (RMS). La deuxième évaluation est une étude électroencéphalographie qui sert à analyser la MMN. La MMN étant défini comme un potentiel évoqué qui reflète la capacité du cerveau à détecter un changement dans les propriétés physiques d'un son. Nous avons utilisé un son standard dans une position de référence (50°) avec 3 déviation par rapport au standard (10° 20° et 100°). Dans des conditions binaurales et monaurales.

Résultats: Les sujets sourds unilatéraux ont été divisé en 3 groups selon leur performance spatiale. Le groupe des bons performeurs (SU low rms) a montré des meilleurs scores RMS en comparaison avec les NE munie d'un bouchon d'oreille (NE-mon), avec des performances similaires à ceux des sujets NE en binaurale. Une augmentation progressive de la MMN avec l'angle de la déviation par rapport au standard a été noté chez tous les groups. Avec une réduction importante de la MMN chez les NH en monaurale quand le bouchon a été appliqué du côté du standard. La MMN a montré des résultats cohérents avec nos observations comportementales, ou les sujets SU avec un bon score RMS avait également des amplitudes de la MMN plus importantes que celles des sujets NE en condition monaurale et similaires à celles des NE en condition binaurale.

Conclusion: Les sujets SU possèdent des stratégies adaptatives spatio-auditives. Notre

étude a pu démontré que la plasticité corticale spatio-auditive qui a lieu suite à la surdit  est refl t  par la MMN. Les observations neuronales (MMN) sont corr l es avec les observations comportementaux de localisation spatiale. Ce qui signifie que la plasticit  corticale qui a lieu chez ces sujets, n'est pas limit es aux fonctions d'identification de la source sonores, mais d passe ces capacit es vers des m canismes plus complexes tel que la detection de deviation et la m moire   court terme, qui interviennent dans la fonction de discrimination spatiale des sons.

Mots Cl s: Mismatch Negativity, localisation spatial, discrimination spatiale, condition monaurale, surdit  unilat rale, r organisation, plasticit .

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List of Terms and Abbreviations

MMN	Mismatch Negativity
ILD	Interaural Level Difference
ITD	Interaural Time Difference
HRTF	Head Related Transfer Function
ICC	Inferior Colliculus
MGB	Medial Geniculate Body
AI	Primary Auditory Cortex
PAF	Posterior Auditory Field
AN	Auditory Nerve
CNS	Central Nervous System
CN	Cochlear Nucleus
DCN	Dorsal Cochlear Nucleus
PVCN	Posterior Ventral Cochlear Nucleus
AVCN	Anterior Ventral Cochlear Nucleus
SH	Stria of Held
TB	Trapezoid Body
DNLL	Dorsal Nucleus of Lateral Lemniscus
VNLL	Ventral Nucleus of Lateral Lemniscus
SOC	Superior Olivary Complex

MSO Medial Superior Olivary Complex

LSO Lateral Superior Olivary Complex

ICX External Nucleus

AAF Anterior Auditory Field

SNR Signal to Noise Ratio

MAA Minimal Audible Angle

SAM Sinusoidal Amplitude Modulation

RMSE Root Mean Square Error

EEG Electro Encephalo Graphy

MEG Magneto Encephalo Graphy

fMRI functional Magnetic Resonance Imagery

PET Positron Emission Topography

BOLD Blood Oxygen Level Dependent

SRT Speech Reception Threshold

NHS Normal Hearing Subjects

UHL Unilateral Hearing Loss

BHL Bilateral Hearing Loss

PTA Pure Tone Audiometry

SPIN Speech in Noise

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Chapter 1

Introduction.

Since the early embryonic life, the auditory system of human starts to develop following a process of multi stages that allows the human infant to make sense of his auditory world [1]. Our auditory system provides us with an incredibly rich and nuanced source of information about the world around us. Listening is not just a very useful function, but also often a very enjoyable activity. If your ears and your auditory brain, works as they should, you will be able to distinguish thousands of sounds due to binaural integration [2].

Binaural integration is characterised by a flow of information from two functioning ears through the cochlea to the cortex. This information, extracted from the external environment is distributed over divergent and convergent pathways allowing a serial and parallel transfer of information to higher auditory stations. Sound information processing leads to different types of activation, depending on the type of external stimulation.

During sensitive periods of development the perception of the auditory environment is shaped with binaural experiences leading to the formation of a variety of auditory processing aspects. This potential of plasticity depends on sound property and can be extended by many factors as well as hormonal changes. Due to age related changes this potential could decline over time [2].

In tracking binaural hearing development during sensitive period, it is essential to consider development of spatial hearing that provides a variety of sensory inputs from different sur-

rounding directions. It is also considered as a vital necessity in the protection from danger by identifying sound source direction, and in distinguishing multiple sound sources through spatial discrimination [3].

Spatial environment is exploited through localisation cues: Interaural time difference (ITD) and interaural level difference (ILD) in addition to monaural cues generated by the pinna head and torso defining the so-called Head Related Transfer Function (HRTF). In the case of Unilateral Hearing Loss (UHL), the balanced binaural cues are altered leading to a degradation in spatial processing, that varies according to different factors. This alteration can initiate a compensational reorganisation of central representation that overcomes spatial deficit. In order to understand the plastic mechanisms underlying monaural hearing, different studies tend to simulate UHL using monaural occlusion.

According to previous research it seems that the majority of studies and investigations that explored spatial adaptation after UHL are developed on non-human models compared to humans, as recent overviews on auditory processing consider an important amount of animals, as anatomical models and neurophysiological and computational models underlying auditory processing [2, 4, 5, 6].

These studies confirmed the remarkable capacity of the auditory system of animals to adapt to sensory stimulation. Neural plasticity is involved in different forms of hearing impairment. Different brain functions can change more or less permanently due to lack of input or alteration of these inputs, such as the processing of sensory information, or pain and motor functions. In the case of unilateral hearing loss, the alteration of binaural cues could have a severe impact on the capacity of localising sounds and segregating speech from noise. Patients suffering from unilateral hearing loss, does not only complain from localisation deficit and speech recognition, their deficit could also be extended to quality of life and psychological health. However, monaural deafness have variable impacts on patients spatial performances. while some patients present high spatial localisation deficits, others demonstrate near normal abilities, despite their hearing loss. These findings are an evidence of an existent adaptational strategies that are developed in these patients. The strategies are mainly related to the expression of brain plasticity that modifies cortical processing of information according

to the severity of impairment, in order to adapt to monaural listening conditions.

In addition, several studies explored the mechanisms accounting for sound localisation in monaural conditions. It has been shown that monaural spectral cues, such as the spectral filtering of the pinna and the head shadow effect, could contribute to the guidance of spatial information. Nevertheless, despite the alternative function of monaural cues, some patients does not present performant behavioral results, while in other patients we observed results identical to those reported in NHS. The behavioral and neural explanation of these variabilities in spatial performances in the population with similar hearing impairment remains unclear. Deeper investigations must take into account all the personal and behavioral characteristics of the patients in addition to the neural signature underlying this variable behavior between patients.

Without this adaptational plasticity, it would be difficult for the auditory cortex to be customized according to acoustical cues that are the basis of sound localisation and native language processing. Hearing loss, especially at an early age can consequently lead to the rewiring of connections and a modification in neuronal activity giving rise to impaired conditions such as tinnitus that is characterised by an experience of phantom sounds in the absence of any acoustic input [7]. Nonetheless, adaptational modification of neural circuits can provide efficient changes such as the case for experience-dependent learning after hearing loss.

However, our knowledge about human auditory processing are still quiet rudimentary compared to animals knowledge, although human behavioral and psychological approaches are more complex and sophisticated. Therefore, additional focus on the neural correlates underlying cortical adaptation in human auditory cortex seems timely and necessary. The challenge that is in our interest in this thesis is the integrative process that relies behind sound source localisation and the neurological processes underlying its mechanisms in normal hearing subjects and in patients suffering of unilateral or bilateral hearing loss [8].

Much of today auditory research are based on the earliest studies of auditory system function that were limited to experimental and analytical tools that were available at that time. The revolution in the experimental research started in the beginnings of 1930s where researchers

were able to record electrical brain activity and peripheral nerves activity. Wever and Bray were the first to start this revolution by recording cochlear nerve events potentials at this time, few years later Similarly Woolsey and walsl [9] improved the subsequent research on the auditory system.

The points of departure for the majority of the subsequent research on auditory processing started with the historic findings of Wever and Bray in 1930 on the cochlear nerve, followed by the findings on the auditory cortex adopted by Woolsey and Walsl in 1942 [9]. Afterwards, the interventions of micro-electrode recording appeared in the beginnings of 1940 with for example the work of Galambos and Davis [10], with also a long journey of quantitative investigations derived from experiments on single neurons neural encoding mechanisms at different levels of the auditory pathways.

Neuroimaging studies now offer the possibility to deeply investigate cortical reorganisation strategies. These techniques added importance to the understanding of the expression of neural plasticity by presenting the changes occurred in the processing of sounds. In this thesis we will be presenting our neuroimaging work, mainly based on the analyses of the Mismatch Negativity (MMN) to understand different brain activation to spatial change after hearing loss. Different neuroimaging signals could be used as marker of cortical functions. In our case, we suppose that the MMN, a component of auditory evoked potentials, could be a neural marker of the adaptational plasticity occurred in a population of unilateral hearing impairments.

This work will provide further knowledge about spatial performances and its relationship with the severity of hearing loss, speech and noise, sound perception in virtual reality environment and spatial discrimination at different positions in the horizontal space. Combined together, all these investigations will help to step further into the understanding of the spatial auditory behavior in humans. Thus, behavioral performances are accompanied with electrophysiological investigation. Neural findings are the cortical representation of behavioral manifestations that contribute in providing more evidence about cortical processing, that in our case, is the understanding of spatial adaptation after unilateral hearing loss.

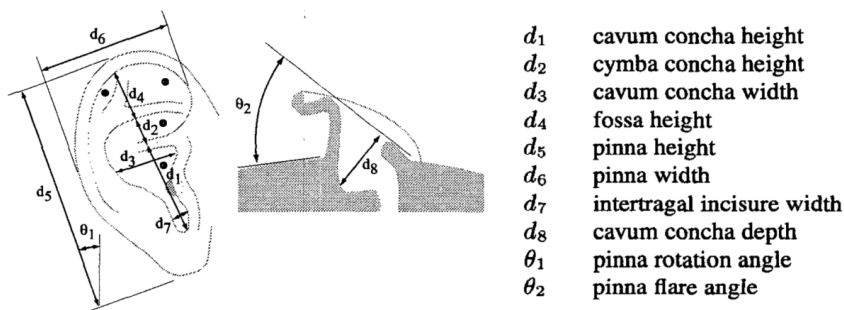
1.1 Anatomical and functional organisation of the auditory system from the periphery to the center

1.1.1 Anatomy of the peripheral auditory system

1- The Pinna.

The pinna is considered to be the first physical interference of the auditory system with a sound wave [11]. The directional characteristics of the pinna interfere in the detection of high frequencies [12] In species such as cats and bats, the directional pinna can lead to a variation of sound levels in the ear canal that may vary in a range of 20 dB or more between sound source direction that fall on or away from the acoustic axis of the pinna [13].

The geometric of the pinna are essential to estimate HRTF and individualise them to particular listeners in case the appropriate anthropometric measures were available [12]. We will focus in this section on the importance of the physical shape and geometric of the pinna that will be developed lately in chapter 2. The pinna dimensions are divided into 8 important dimensions in addition to two angles as shown in the figure below.



Algazi;2001

Figure 1.1: Anthropometric measurements of the pinna [14].

2- Ear Canal

The length of the ear canal is approximately 2.5 cm with an approximate diameter of 0.6 cm. [15].

3- Middle ear

The middle ear is divided into 4 main parts: The tympanic membrane, ossicles, middle ear muscles and the Eustachean tube.

3.1. Tympanic Membrane:

Terminating the ear canal, the tympanic membrane is slightly oval shaped with a thin membrane. It is cone-shaped, with an altitude of 2 mm with the apex pointed inward. The membrane is slightly concave if seen from the ear canal, and suspended by a bony ring under some amount of tension.

3.2. Ossicles

The ossicles are the middle ear bones. The three ossicles are suspended by different ligaments. The manubrium of the malleus is located at the apex of the tympanic membrane and the top of the malleus is suspended in the epitympanum. The incus is embedded in the inner fossa incudo of the malleus, and it is positioned in place with the help of the incudal ligament. The Malleus and the incus are fused together in a double rigid saddle joint. The stapes is the bones that moves towards the cochlea, its joint with the incus possess a high rigidity but also flexible to maintain piston like movements towards the cochlea that are induced due to the contraction of the stapedius muscle. Two stiff ligaments suspend the stapes in the oval window of the cochlea.

3.3. Middle-ear Muscles As already mentioned, to maintain a rigid yet flexible movements of the ossicles towards the cochlea, two small muscles interfere in the middle ear. The tensor tympani muscle that is extended between the malleus and the wall of the middle-ear cavity at the entrance of the eustachian tube. When this muscle contracts it pulls the manubrium to the inside which will lead to an inward displacement and stretching of the tympanic membrane. The second muscle is the smallest striate muscle of the body known as the stapedius muscle. The stapedius helps pulling the stapes in a perpendicular direction to the piston like motion and tilts it so it can rotate around the posterior ligament.

3.4. Eustachian Tube The Eustachian tube contains of a bony part called the protympanum mainly located next to the middle ear cavity. It also has a cartilaginous part that forms a

closed slit where it terminates in the nasopharynx (Fig. 1.6). The opening of the eustachian tube helps in maintaining the optimal pressure in the cavity of the middle ear that should be close to the ambient pressure.

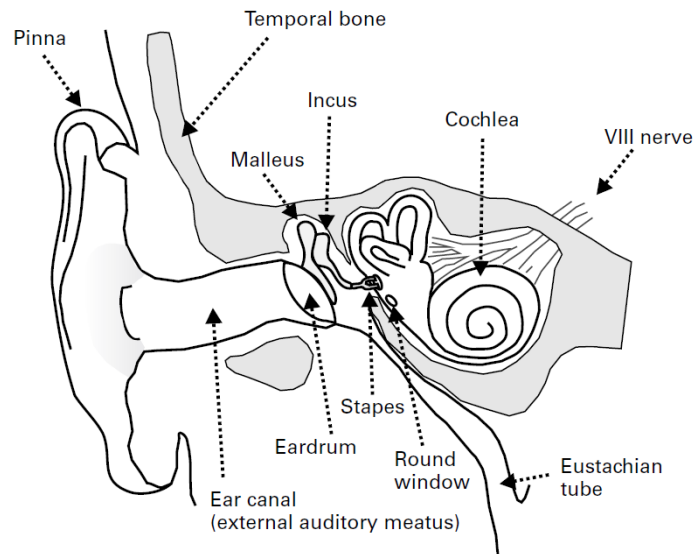


Figure 1.2: A cross-section of the side of the head, showing structures of the outer, middle, and inner ear [2].

5. Cochlea

The sensory organ of hearing is contained in the cochlea, it is a bony structure snail shape organ with little more than 2 and 1/2 turns. the cochlea contains three canals of fluids the scala vestibuli, the scala tympani, and the scala media. The scala media and the scala tympani are separated by the basilar membrane, and Reissner's membrane separates scala vestibuli from scala media. The fluid in scala tympani and scala vestibuli is rich in the ionic composition of sodium with low contents of potassium, however scala media's ionic composition is rich in potassium with low contents of sodium.

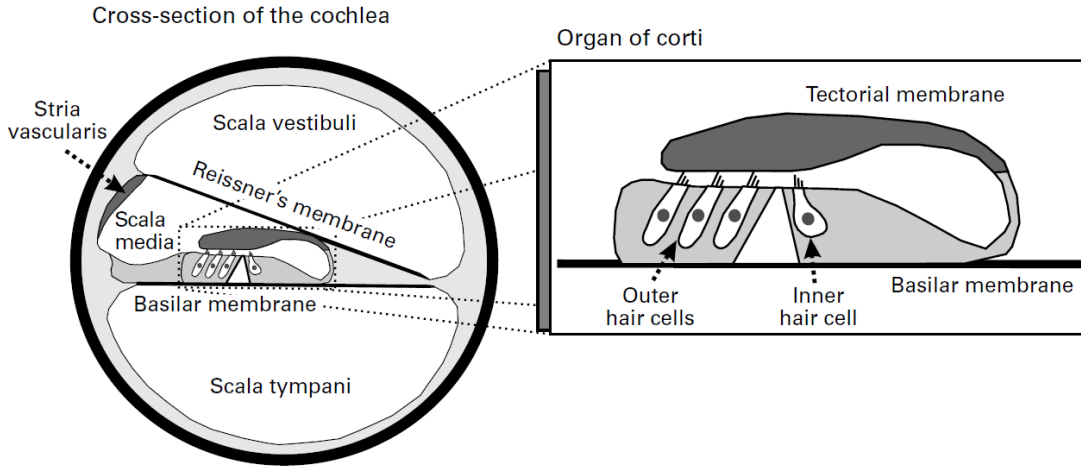


Figure 1.3: Cross-section of the cochlea, and schematic view of the organ of Corti [2].

The cochlea contains the hair cells that are organised in the basilar membrane in one row of inner hair cells and 3 to 5 rows of outer hair cells. The types of hair cells differs between the cochlea and the vestibular organ. the cochlear hair cells lack in a kilocinium. The type 1 auditory nerve fibers innervate the inner hair cells, while the outer hair cells are innervated by the types ii nerve fibers. The efferent nerve fibers terminates directly onto outer hair cells while other efferent fibers terminate on the dendrites of the type I fibers that innervate the inner hair cells.

1.1.2 Anatomical organisation of the ascending auditory pathways.

Ascending auditory pathways.

The ascending pathways of the auditory system is known to be more complex than other sensory nervous ascending pathways. Three main nuclei play an important role in fiber projections and their synaptic connections. After the electrical coding of the auditory information in the cochlea, the auditory nerve, emerging from the organ of corti to the cochlear nucleus extends into the different fibers at the three divisions of the cochlear nucleus. The

three fiber tracts will cross over to the opposite side and connect to the central nucleus of the contralateral inferior colliculus (ICC). Later on, the fibers connected to ICC are the projected to the medial geniculate body (MGB). The fibers projected from the MGB will generate the first connections with the primary auditory cortex (AI) and the posterior auditory field (PAF). These projections will lead to new connections between both hemispheres at different levels of the classical ascending auditory pathways. These types of fiber projections and connections are crucial for directional hearing. This anatomical hierarchy is the neural basis for an organised and parallel sensory processing that will lead to the normal and symmetrical auditory experience.

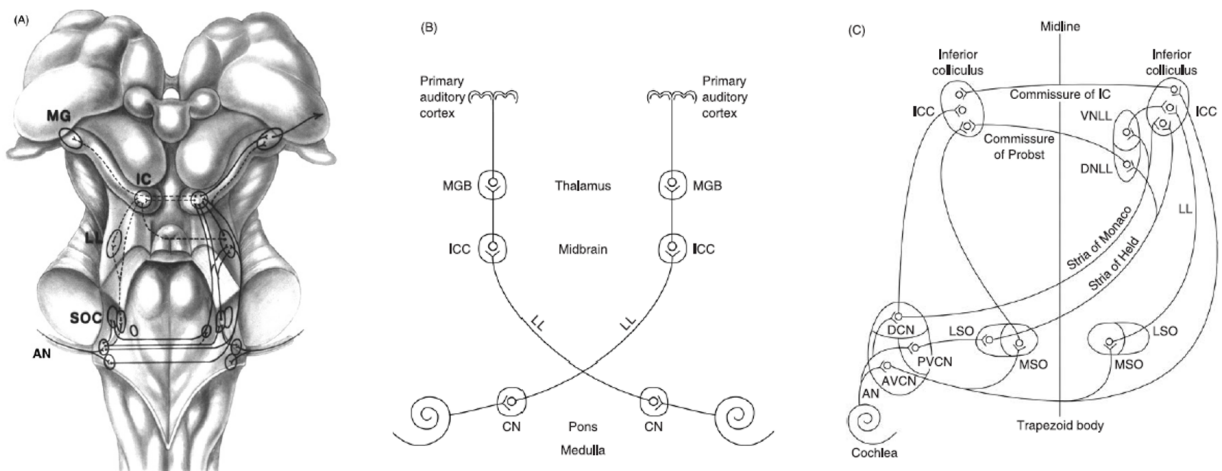


Figure 1.4: A) Schematic drawing of the anatomical locations of the ascending auditory pathways. (B) Schematic diagram showing the main nuclei and fiber tracts of the classical ascending auditory system pathways.(C) More detailed drawing of the ascending auditory pathways from the ear to the IC [16], [15].

3.1. Auditory Nerve.

The auditory nerve (AN) is one of the main contributors to auditory signal transmission with 30 000 fibers approximately. The auditory nerve is one part of the eighth cranial nerve (CN VIII) that also includes the vestibular nerve (superior and inferior). The AN has two types of nerve fibers the type I and type II, their cells are bipolar, with their bodies in the spiral ganglion that is located in the modular area of the cochlea [17]. The type I fibers terminates

their peripheral portion in the cochlear nucleus cells. This type of fibers carries the entire auditory information that emerges from the organ of Corti to higher levels of CNS. Type I nerve fibers are myelinated with a diameter of around is $2.5 \mu\text{m}$ [18] in the internal meatus of children. This diameter is approximately half that of the fibers of the AN in internal meatus when it is located in the osseous spiral lamina.

The diameter variation of the central portion of the AN in type I fibers is small, leading to a reduced velocity in signal transmission. Therefore, the amount of information arriving to the cochlear nucleus will reach its destination with very small time differences to ensure a high coherence in temporal resolution of nerve impulses arriving at the cochlear nucleus. This coherence resolution is found to be very important for complex sounds discrimination, for example, speech sound. this variation in cross section diameters and in signal transmission velocity increases with age [18]. This factor may explain age related hearing impairments that are not directly related to an increase in the pure tone threshold.

The outer spiral fibers, are the type II fibers that innervates outer hair cells. Only 1 percent of the fiber population is type II spiral fibers. the function of these fibers remain unknown and they are projected mostly to the dorsal cochlear nucleus (DCN). Most of the studies conducted to explore the morphology of the auditory nerve are based on animal models, mostly on cats. It remain unclear to which extend animal findings could be applicable on human. To our knowledge, the cell bodies of most of ganglion cells in human are unmyelinated with large variation between individuals [19]. Also the human spiral ganglion is found to be different from the animals according to most studies. The eighth cranial nerve in humans is longer. For example this cranial nerve in of around 0.8 cm in cats [20] while its about 2.5 cm in humans [21, 22], this is mainly related to the size of the head that is larger in human. Another aspect that contributes into the difference between human and animal models is the subarachnoidal space that is commonly used in auditory research. Its is larger in humans than in monkeys for example. Although this difference in size has not been given much attention, it may possess an influence considering the development of specific auditory disorders.

The eighth nerve is twisted like any other type of cranial nerve family. The auditory part

of the eighth nerve is located caudally with respect to the superior vestibular nerve in the nerve's central course [21, 23], dorsally in the internal auditory meatus and in its most peripheral portion it is located ventrally also with respect to the vestibular nerves. The myelinated auditory nerve fibers type I are covered with peripheral myelin that is generated in its peripheral course mainly by the Schwann cells. This peripheral myeline coverage changes to central myelin at the point just before leaving the auditory meatus. The myelin at this level is generated by the oligodendrocytes. The myelin transition between central and peripheral is called the Obersteiner-Redlich zone. Different aspects differs between peripheral and central portions of the nerve, and most of the structures that are supporting the peripheral portion are absent in the central ones [24]. The central portion of the auditory nerve is approximately 1 cm and its tissue is similar to brain tissue. This similarity of tissues has important implications that implies that auditory nerve can be at considerable injury risks during surgical interventions and manipulations in the are of the cerebello pontine angle.

3.2. Cochlear Nucleus.

The cochlear nucleus is located at the lower portion of the brainstem, in the junction between the medulla and the pons, known as the pontomedular junction. Each CN is located at the sam side of each ear from which itt receives the innervation. The cochlear nucleus is divided into three main parts: dorsal cochlear nucleus (DCN), the posterior ventral cochlear nucleus (PVCN), and anterior ventral nucleus (AVCN). The auditory nerve terminates at the CN site. Before it reaches the cochlear nucleus, the AN bifurcates into two branches. The first branch terminates in the AVCN while the second branch bifurcates again and terminates in ywo different sites, the PVCN and the DCN. Each auditory nerve fiber thus connects to all three divisions of the CN [25]. This anatomical construction represents the beginning of the parallel processing that is very complex yet very rich in the auditory system.

The CN is an important structure in the lower brainstem of small animals, while in humans this structure is comparatively small [26]. The fibers of the CN are projected to the contralateral inferior colliculus over three main fiber tracts. The stria of Monaco (SM), the stria of Held (SH) and the Trapezoid body (TB) (dorsal, intermediate, and ventral stria). The SM mainly originates from the DCN and the fibers from the PVCN projected in the SH

and the output emerging from the AVCN creates the TB. The lateral lemniscus (LL) is the structure formed after the crossing over of the three stria to the opposite side. The LL is also a fiber tract that projects to the central nucleus of the inferior colliculus (ICC).

However some of the fibers projected to the AVCN and the PVCN do not cross the midline, they stay on the same side instead ascending to the ipsilateral ICC. The fibers from the PVCN are projected to the dorsal nucleus of the LL (DNLL) where fibers trigger the ipsilateral ICC also. The ventral cochlear nucleus also delivers fibers to the facial motor nucleus and the trigeminal motor nucleus. This anatomical architecture plays an important role in the acoustic middle ear reflex.

Both sides of the cochlear nuclei are connected [27]. This connection the most peripheral between both sides of the ascending auditory pathways. However, the functional role of this peripheral connections remain unclear. Lastly, the CN collects inputs coming from the trigeminal somatosensory system [28, 29] as a part of the non-classical ascending auditory pathways.

3.3. Superior Olivary Complex.

Two main nuclei forms the superior olivary complex (SOC): the medial superior olivary complex (MSO) and the lateral superior olivary (LSO) nucleus. The fibers of the three striae SM, SH and TB project some collateral branches to the nuclei of the SOC, while other fibers are interrupted by some synaptic contacts in one of the SOC nuclei before contributing in the LL formation. The MSO obtain a projection of inputs from the CN of both sides. It is supposed that the first auditory information integration is initiated in the group nuclei of the SOC. These nuclei are implicated in the processing of directional hearing by the comparison of arrival time of neural activity emerging from both ears (in the MSO) and the intensity difference from (in the LSO).

one of the most complicated parts in the ascending auditory architecture is the SOC nuclei, with their largest variations between different mammal species. The anatomical organisation of the nuclei of the SOC in humans are different in many ways from those traditionally used in experimental investigations on animals such cats [26].

3.4. Lateral Lemniscus and its Nuclei.

Three stria contribute in the architecture of the LL emerging from the CN. The axons of the LL cross the midline and projecting to the ICC contralateral. The axon cells of the SOC also contributes to the LL. According to what has been concluded earlier, the fibers of the LL are extended from a variety of sources that leads to a variety of neuron orders (second, third and possibly fourth) and a domination of second order axons. Many collaterals of the LL terminates on neurons in nuclei of the SOC and on neurons in dorsal and ventral nuclei of the lateral lemniscus (DNLL and VNLL). The VNLL interrupts some fibers in the LL. In addition the originating axons of the LL that originates in specific types of cells such as octopus cells in the PVCN contralateraly, do not emerge directly to the ICC like some axons of the LL do, instead , they are interrupted in the VNLL. The DNLL obtain its input from the two ears and is implicated in binaural integration while the VNLL mainly collects input from the contralateral ears. Some of the axons that lead away from the DNLL cross to the opposite side as the commissure of Probst and connect to neurons of the ipsilateral ICC. Neurons in the CN also connect to the ipsilateral ICC.

3.5. Inferior Colliculus.

Located in the midbrain at the caudal level to the superior colliculus, the inferior colliculus (IC) is considered to be the midbrain relay nucleus where the entire information of the auditory ascending pathways is channeled. The IC consists of three main divisions, the central nucleus (ICC), the external nucleus (ICX) (also known as the lateral nucleus) and the dorsal cortex of the IC (DC). Inputs coming from the LL are then received by the ICC. The fibers of the LL are also interrupted by neurons in the ICC. The ICCs of both sides are connected with each other these connections are crucial for directional hearing that rely on binaural cues of time and intensity difference between both ears.

3.6. Medial Geniculate Body

All the fibers originating from the ICC are interrupted in the thalamic auditory relay nucleus also known as the medial geniculate body (MGB). The MGB has three distinct divisions: ventral; dorsal; and medial [30], [31]. The ventral division of the medial geniculate body includes the pars lateralis (LV) and the pars ovoidea (OV). The ICC projects inputs to the

ventral division. The branchium of the inferior colliculus (BIC) is the main output that terminates in the ventral part of the MGB, however, other parallel pathways also exist.

In 1961 Glambos showed that a sound could activate the auditory cortex even after a severe damage of the BIC [10]. The number of fibers of the BIC is ten times larger than that of the fibers of the auditory nerve with approximately 250 000 fiber. The divergence in fiber number is an indicator of the rich and extensive signal processing that is taking place in the auditory nervous system. The thalamic reticular nucleus (RE) also sends inputs to the ventral (MGB) [31], leading to an efficient control of the excitability of neurons generally in the MGB. The ICC of the ipsilateral probably also send inputs to the LV portion of the MGB. It is important to note that no connections exist between both MGBs of both sides.

3.7. Auditory Cerebral Cortex.

The abundant connections between cells in the auditory cortex with its complex structure maintain a high level neural processing of the big variety of auditory inputs. Until this date, researches succeeded in identifying different regions in the auditory cortex. The primary auditory cortex (AI) and the posterior auditory field (PAF) collect their inputs from fibers emerged from the ventral division of the MGB [32], [31] while the Anterior auditory field (AAF) receives its inputs from the PO division MGB.

However, the AI is not the terminal site of auditory information inputs, because the fiber tracts emerges from the AI and are projected to other areas in the auditory cortex in addition to the associative cortices where there is an integration of the auditory information with other sensory information coming from different parts of the CNS. Thus, there are important connections between both sides of the auditory cortices [33, 34]. As already mentioned before, the grand part of researches are based on animal models such as the cat, Guinea pig, rat, monkey especially in the description of the anatomy and physiology of the auditory cortex. For example, the auditory cortex is located on the surface of the cerebral cortex for the cats and the rats while in humans, its location is deeper in the superior portion of the temporal lobe at the transverse portion of the Heschl gyrus. This deep location make it invisible from the surface of the brain.

Despite the wide variety of investigations concerning anatomical structures of the AI, our

knowledge remains incomplete, thus, many investigators place different nomenclatures on the same parts of the auditory cortex in humans. Plus, there is a variation of the anatomical location of some components of the auditory cortex between individuals.

The axons of the MGB are connected with neurons in layers IV due to synaptic contacts. It has been found that an estimation of 5000 cortical neurons can be contacted by one afferent fiber coming from the thalamus. Plus, the axons in the cortex are horizontal and therefore are able to make inhibitory and excitatory connections with other functionally related neurons. The layers IV and V have the main output cells that are connected to cells in the MGB and in the IC. Based on studies in monkeys, these cells are able to integrate information from approximately 600 nearby cortical cells and they may also receive around 60 000 synapses. A very rich network is present between the primary auditory cortical areas and other similar areas [33, 35, 34]. It is very important to note that the connections that exist between subcortical structures and cortex cells, in addition to the connections within cortex cells are not "hard wired", which means that an expression of neural plasticity can implicate some resulting changes in these connection.

The layer III of neurons of AI are projected to the secondary auditory cortex (AII), to the posterior ectosylvian area (Ep) and to the contralateral AI [33, 35, 34]. The anterior auditory field (AAF) collects inputs from the MGB in its dorso-medial section. The neurons in the cortical auditory area respond only to sound information, however other neurons from other areas of the auditory cortex such as (AII, PAF, and AAF) are able to respond to other sensory modalities such as somatosensory or visual inputs. Therefore, neurons of these areas are able to receive inputs from other ascending sensory pathways.

The association cortices occupy a large part of the neocortex, while the primary and secondary auditory cortices conquer only a small portion of it. In addition, the associative cortices integrate information coming from divers sensory systems along with inputs from intrinsic sources in many areas off the CNS. These complex integrational abilities represent a high capacity of sensory information processing that is more important in the associative cortices than it is in the primary and secondary auditory cortices. The stream segregation, plays an important role also in this complex processing.

The two sides of ascending auditory pathways come in contact at the most peripheral level, specifically in the nuclei of the superior olivary complex (SOC). Inputs from both ears are sent through the neurons to the SOC, not to mention, the connections between the two cochlear nuclei also [27]. However, the exploration about the anatomy of the connection remain limited.

The Dorsal nucleus of lateral lemniscus (DNLL) of both sides are connected through the commissure of Probst, that also contains fibers from DNLL from one side that will be connected to the ICC on contralateral side. ICCs of both sides are also connected by the commissure of the inferior colliculus. Thus, auditory cerebral cortices of both sides communicate through a large fiber tract in the corpus callosum [36, 37]. The fiber tracts traveling in the posterior two thirds of the corpus callosum are responsible of this connection between both auditory cortices [38]. The crossing over of the AAF axons in more rostral compared to axons of AI and PAR and AII, that cross more caudally.

The connections present at the midbrain level and at the level of cerebral cortex between both two sides are the main contributors in the sound presentation and integration from one ear in auditory cortices at both sides. Some other connections can also provide auditory information to both sides such as the ipsilateral connections from the CN to IC. This bilateral representation of auditory inputs is the reason why the diagnosis of disorders affecting one side only can be challenging.

Parallel processing and stream segregation

During the processing of information in the nervous system the traveling in the auditory nerve is separated by different mechanisms. Two important aspects of this fundamental separation has been identified. First, the parallel processing: different population of neurons process the same information. Second, the stream segregation: different populations of neurons process different types of information. Investigator's first explorations of stream segregation was in the visual system, it was shown in other sensory systems in later researches.

a- Parallel Processing.

The branching of the ascending pathways are the basis of parallel processing, that begins at the periphery at the site of bifurcation of each auditory nerve fiber to connect to neurons in every part of the three main portions of the CN [30], [39]. Another sign of parallel processing is the large number of fiber tracts that connects the ICC with the MGB. These fiber tracts are around 10 times larger than fibers of the auditory nerve, meaning that information presenting a specific neural code is divided to different separate channels before reaching the cerebral cortex. The classical and non-classical ascending pathways are also a valid example of the parallel processing.

b- Stream Segregation.

Different studies reported that cell populations with common properties are grouped together anatomically while the cells processing different types of information are anatomically segregated [40, 41, 42]. The first studies to explore this kind of information processing by different population cells were in visual experiments. These studies reported two separated anatomical locations or two streams in the association cortices for spatial and object information [43, 44]. The locations found were named by "Where" and "what" streams. The dorsal portion of the cortex was found to be responsible of the processing of spatial information "Where stream" while the ventral part is responsible for recognizing objects "What stream".

The recent studies on stream segregation are more interested in the auditory cortex [45, 46, 47, 48]. The directional information was found to be processed in separate locations compared to the processing of object information. Most of the studies conducted on the rhesus monkey suggested that the processing of different kind of information takes place in the lateral belt of the auditory cortex because the neurons located in the anterior part of the belt is more responsive to complex sounds, for example, the specific communication sounds of some species (what) while neurons in the caudal part of the belt show more responsiveness to specific spatial aspects ("where") [46, 48, 49]. In macaques monkeys, it has been found that the neurons of the superior temporal gyrus is organized in two different regions with different functions. In the first region, the most rostral stream is more implicated in object information processing like the one carried by complex sounds for vocalization for instance. Nevertheless, the neurons located in more caudal portions are responsible of spatial information processing.

The directional information, or spatial information, is not strictly due to the location of a the receptor case, yet, it is the case for visual and somatosensory information. Spatial information however is emerged from information manipulation coming from both ears, and is more computational rather that surface receptor-related.

In speech perception a right ear advantage has been shown, meaning that the speech is better perceived in the right ear [50] however, there is no evidence reporting difference in the structure of both hemisphere with regard to identification of a speaker [51], this could be an indicator that speech perception and recognition are processed in different parts of the brain. In order to explore the anatomical locations of the processing related to different kinds of sound humans neuro-imaging techniques have been developed [52], showing a stronger activation in the medial section of the planum temporal in response to motion while stringer activation in the lateral portion of the planum was more related to frequency-modulation. These results suggested the presence of spatial and non spatial segregation of auditory information. This study also showed that the superior parietal cortex does not simply depend on the presence of acoustic cues of motion but also on the detection of the motion task. all these findings prove the dependence of processing streams from the type listening task. Extensive studies were interested in the psychoacoustic aspects of stream segregation [53], [54], the knowledge about stream segregation became very crucial in clinical research since it can be related to hearing impairment.

1.1.3 Anatomical organisation of descending auditory pathways.

Much less is known about the descending auditory pathways compared to the ascending pathways. It is known that these pathways are as rich as the ascending system [55, 31, 35] and have often been described as two distinct pathways: the cortico-fugal and the cortico-cochlear systems. The auditory cerebral cortex is the location where the most central portion of the cortico-fugal system is emerged, and the auditory cortex is the site of emergence of the cortico-cochlear system that is projected towards the cochlear nucleus and the cochlea. The two systems also have crossed and uncrossed pathways. The descending pathways emerging from the auditory cortices and projected to the thalamic sensory nuclei are known to be

very rich [31] reaching the auditory nuclei in the brainstem [35]. It seems more convenient to consider the descending pathways as reciprocal to ascending ones, instead of classifying them separately.

The primary auditory cortex, specifically layers V and VI are the origin site of a large descending fiber tract. The fiber tracts emerging from neurons of layer VI are uninterrupted, making synaptic connection with the neurons of the MGB, while neurons of layer V project fiber tracts to both MGB and IC [56, 31]. The projections descending to the IC arrive mainly to neurons in the ICX and DC [55, 57]. The layers V and VI may be considered as the reciprocal pathways of the ascending ones but they are still referred as separate descending auditory system.

The fibers tracts projected from the SOC arrive to the CN [58, 59], despite the extensive amount of efferent innervation received by the cochlea hair cells [60]. This system projecting fiber tracts from the soc to the cochlea is divided into two parts, the first part is mainly projected to the ipsilateral side of the cochlea and to the fibers traveling close to the fourth ventricle, the second part is projected contralateraly to the cochlea where the fibers travel deeply in the brainstem. The origin of the ipsilateral fibers is the lateral part of the SOC. and the origin of the contralateral fibers is the medial part of the SOC. These two systems project their fibers to hair cells in the cochlea, the fibers originating from LSO terminate on the afferent fibers of the inner hair cells while axons coming from the medial system mainly terminates on the cell bodies of outer hair cells.

1.2 Binaural auditory processing in human listeners.

The essential role of central auditory pathways is to parse auditory messages emerged from the two cochleae in the case where the function and integrity of both ears are normal. In order to understand the impact of hearing impairment on auditory integration, it is important to understand the mechanisms underlying this integration in the case of normal hearing.

The auditory nervous system, as shown in the previous section is very rich and complex anatomically compared to other sensory systems. Therefore, the processing of auditory information through this complex network can also be extensive and abundant. The complexity of this processing is also related to the fact that two parallel ascending pathways are working together, the classical and the non classical pathways. However the inter-connectivity between classical and non classical pathways in addition to the role of the descending pathways remain unclear until this date. However, it is supposed that the non-classical auditory system could be analogous to the pain pathways coming from the somatosensory system [15].

The understanding of different auditory impairments and the development of treatment and rehabilitation techniques is strongly related to the amount of knowledge and understanding of the aspects and functions of auditory nervous system. For example, the auditory brain stem implants and the introduction of cochlear implantation, made the anatomical and functional understanding of auditory nervous system a very crucial for clinical research. An important number of studies has investigated the coding of different types of sounds in the auditory nerve , and how this coding can vary or be modified during its travel from the neural axis towards the auditory cortex through the classical auditory pathways. It is important to note that, the biggest part of literature extensively focuses on the peripheral parts of the auditory pathways rather than central portions.

The studies of central physiology of the auditory cortex has mainly been investigated on animal models such as rat, guinea pig and cats. And the knowledge about the difference between these models and human model remain ambiguous. Therefore, little is known about the coding of information and its transformation across the non-classical ascending auditory pathways in addition to an ambiguity also in the knowledge of the resulting activation in

these pathways [61]. Thus, the neural activity of vast descending auditory pathways is still unclear, however, as already been mentioned, the peripheral parts seem to be more explored. In human listener, frequency coding is the most critical function for understanding speech. Nevertheless, frequency discrimination and its physiological basis has been studied extensively since it is a prominent feature in detecting and interpreting natural sounds. The representation of frequency and its contribution in speech understanding will be further developed in the second section of this chapter.

Speech in noise segregation and sound source detection are the main auditory functions. To be integrated naturally these functions depend on the famous mechanism of binaural integration. Binaural hearing plays an important role providing binaural cues for sound localisation and for optimising signal to noise ratio (SNR) for better speech in noise comprehension. The segregation of the speech through noise is facilitated due to three main mechanisms:

a- Head shadow.

The head plays the role of a physical obstacle creating a diffraction pattern of the sound, leading to a difference of SNR arriving at both ears. The binaural integration, due to head shadow effect, provides advantages by sheltering the ear projected towards a stimulus source from a noise emerging from the other side. For example, in the case where there are two competing sounds, one emitting a signal and the other one emitting a noise are placed at different locations, the SNR at the ear nearest to the sound is increased as the SNR of the noise is attenuated by the physical diffraction with the head. Consequently, a difference up to 15 dB between both ears may take place [62].

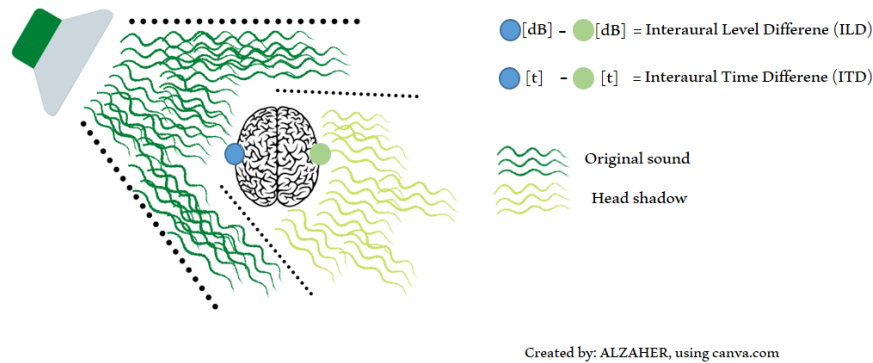


Figure 1.5: Illustration of the head shadow effect

b-Binaural summation (Redundancy).

The feeling of loudness emitted by a specific sound is related to the number of action potentials triggered by this sound while being integrated in the brain. This number can be higher when the sound is emitted from frontal positions where interaural differences are equal to zero, leading to an increase of the intensity of the sound up to 3 dB. The stimulation does not only sound louder, but the treatment of information is more sensitive to small differences. The small differences in loudness and in frequency improves with binaural redundancy, leading to an improve in spatial awareness or/and in speech intelligibility [62].

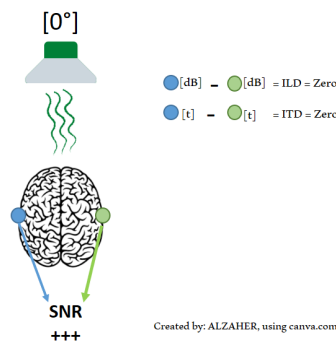


Figure 1.6: Illustration of the binaural summation

c- Binaural release from masking (Squelch effect).

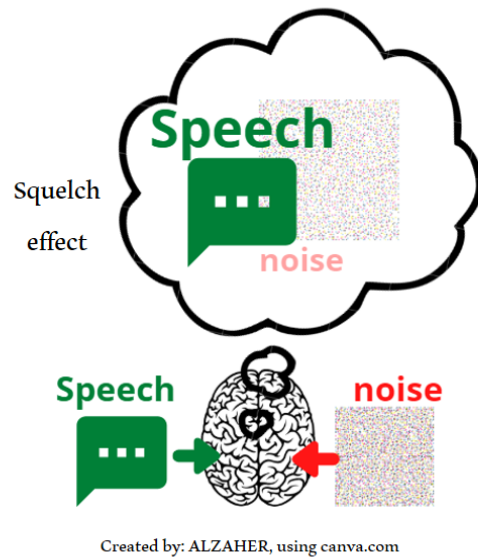


Figure 1.7: Illustration of the Squelch effect.

The spatial release from masking emerges to separate a target signal from a competing noise. It consists on adjusting the relative levels of a signal and a noise coming from two sources at the same location, in order to mask the target signal so when the noise source moves to a different place the target may become audible again (spatial release from masking) [62].

1.2.1 Binaural cues underlying spatial hearing in Mammals.

Our auditory system provide us with the capability of perceiving and interacting appropriately with surrounding stimuli, due to different sensory features, including spatial coordinates that are assigned to a specific object located in space. The localisation of acoustic information is achieved due to these sensory features also known as binaural cues.

Binaural cues are characterised by the processing of Interaural Time Difference (ITD) and Interaural Intensity Difference [63]. A sound emerging from one side of the head will reach the closer ear at first giving rise to a difference of time arrival between both ears (ITD). Thus, due to directional filtering properties of the external ear, and the shadowing effect of the head a difference in sound pressure level is produced between both ears (ILD). These cues

are illustrated by the waveform of the sound, which is both delayed and reduced in amplitude at the listener's far ear. Due to the symmetry of the ears according to the midsagittal plane, the ITD and ILD levels will reach zero value at the medial plan [2].

Both binaural cues are used by many mammals including humans to detect accurate positions of sound sources [64], [65]. It was also recognized, since the 19th century that ILDs becomes progressively small once the frequency of the stimulation is reduced, due to the increase of the wave length size according to the size of the head. These findings, in addition to other findings concerning the detection of lower frequency sounds locations led to the formalization of the Duplex Theory of sound localisation, suggesting that ILD are employed in the localisation of high frequency signals while Interaural Time differences are engaged in the detection of low frequency sounds [66].

The frequency specific modifications in the magnitude and phase of a signal, reaching the eardrum, are the result of the interaction between the environmental sound and the anthropometric dimensions of the head and the ears, known as the spectral cues. These features are also used for the detection of vertical located sounds. Sounds located in the cone of confusion are also being detected due to the contribution of the spectral cues in addition to binaural cues that are unable to detect these signals alone [64].

The spectral modifications that are largely generated by the pinna and the concha are known as the Head Related Transfer Function (HRTF). The spectral cues of localisation consist of notches in the sound spectrum at specific frequencies. As the location of a sound changes in elevation the frequency and magnitude of the notch changes [65].

As already explained, Mammals including humans, are able to discriminate sound changes up to 1 degree [64, 67]. Based on experimental studies using headphones, it has been reported that the human spatial hearing possesses an accuracy with thresholds that low at 10 microseconds for ITDs [68] or 1 to 2 dB of ILD when binaural clicks are presented [69]. The very high level of resolution that the ITD presents must be taken into consideration with the respect of the millisecond duration needed for a nerve to transmit action potentials to the brain [70].

The studies conducted by Steven and Newman [71] in 1934 confirmed the classical distinction of the duplex theory already established by Rayleigh. In their study, blindfolded listeners

were asked to report the location of a pure tone sound derived from a speaker at various frequencies. The sound sources were distributed between front and back. The lowest errors were reported for frequency tones below 2000Hz or above 6000Hz, while intermediate frequencies elicited the highest errors. These findings suggest the possibility of an incomplete representation of both cues over this range of frequencies (between 2000 and 5000Hz).

Headphone stimulation were used in some psycho-physical studies to determine the range of ITD detectors that are represented in the human brain. This study is based on the measurement of ITD discrimination thresholds and binaural unmasking. The findings reported a range of ITDs encoded that is considered to be roughly constant across the range of sound frequencies in less of 1500 Hz and set largely by the physiological range of around +/- 700 microseconds in humans, but with ITDs up to at least +/- 3000 microseconds explicitly encoded in each sound frequency band [69]. The experience of ITDs higher than the physiological range is also possible and can be presented over headphones, arising naturally when multiple sound sources interact and with the presence of acoustic reflections [11].

1.2.2 Stream segregation of auditory cues in the brainstem.

The first step, after the detection of binaural and monaural cues by neurons in the auditory system, is to transmit the information in the activity of nerve fibers. It has been shown that the firing rates of the fibers increases with the sound levels, which means that ILDs will be processed after a difference in the firing rates of afferent auditory information between left and right inputs. On the other hand, ITDs are processed due to differences in the temporal firing activity also coming from right and left ears.

As already shown in the section before, the auditory nerve fiber is divided into ascending branches that will form a solid connection with spherical and globular bushy cells at the AVCN, these cells are the gateway into the brainstem nuclei responsible of extracting the binaural cues. The descending branches on the other hand, will carry information to the DCN the suitable site to extract spectral cues.

In this section we will describe the processing of each of the spatial cues in the brain stem,

starting with the spectral cues.

Brainstem encoding of spectral cues:

The type IV neurons of the DCN are the principal neurons, and they are very sensitive to spectral shapes of sound stimulus. These neurons can be overall excited for broad band noise, however they can be strongly inhibited when there is a notch in the sound spectrum near the neurons characteristic frequencies. The inhibitory reaction to spectral notches is highly tuned for narrow frequency ranges, and therefore, DCN neurons will also be used to determine notch frequencies and not only spectral notches.

Studies conducted on cats showed this systematic dependency on notch frequency, that made small differences to the HRTF for low frequencies while at higher frequencies complex notches can be seen (above 7000 Hz for example). At frequencies around 10kHz the first notches can be seen and shifts to higher frequencies if the sound moves upward in space. Meaning that if a cat detects a first notch at 10 KHz in both ears this represents a sound coming straight ahead because it is the only location where 10 KHz notch diagonals of the right and left ear cross.

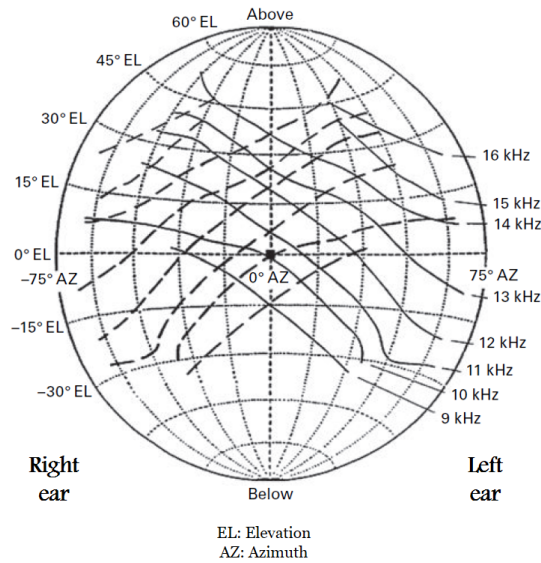


Figure 1.8: Grid of sound source directions in the frontal Hemifield of a cat. Diagonals (dashed and undashed) connect all source directions associated with the first notch frequencies in both ears.

Another example, if a first notch of 12KHz is introduced at the right ear and a 15KHz notch at the left ear, this is an indicator of a sound positioned at 35° in the vertical plane and at 30° in the left azimuth as the figure 1.5 show if you followed the fourth non dashed diagonal and the seventh dashed diagonal from the bottom to their crossing point.

The grid represented in the figure above provide a very neatly organized system for presenting spectral cues in the tonotopic organisation of the DCN. However, this arrangement of HRTF notches or peaks in cats have never been documented in other mammalian species. However, and even in the absence of a systematic pattern, the notch sensitivity of type IV neurons remain very useful in detecting the spectral cues and transmitting the input to the midbrain.

Brainstem encoding of interaural level differences.

The subtraction of sound intensities in both ears is usually performed by the lateral superior olive (LSO), in the superior olivary complex, where the neurons are more selective of high

frequencies. It appears that these neurons are excited when a sound is coming from the ipsilateral side of an ear, while it is inhibited from the contralateral side, therefore these neurons are called the IE neurons. Thus, an IE neuron in the LSO is less sensitive to sounds coming straight ahead where intensities are equal at both ears.

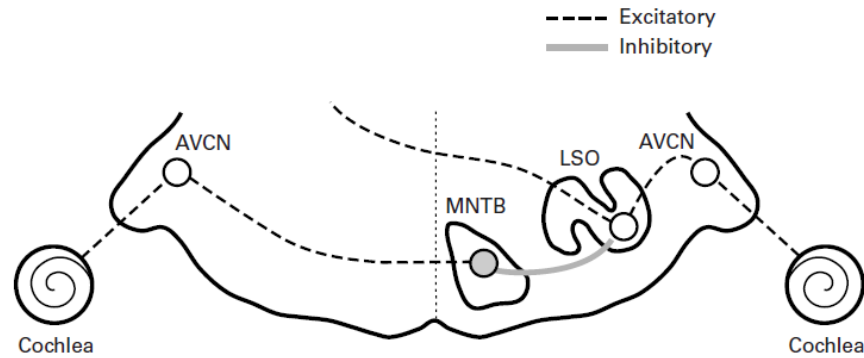


Figure 1.9: ILD processing pathway in the auditory brainstem. Artwork by Prof. Tom Yin [2].

In most cortical areas, sensory neurons classically prefer contralateral stimulations, unlike the IE neurons in the LSO. Therefore, in order to make spatial sensitivity of IE neurons conform with classical sensory representation, IE neurons send excitatory projections to the contralateral IC. As a response, the central auditory neurons will typically select contralateral stimuli. In addition, the output emerging from the LSO towards the midbrain does not cross entirely, nevertheless, the combination of excitatory and inhibitory projections will terminate on the ipsilateral side. The ipsilateral inhibition will also contribute to the contralateral selectivity in the spatial preferences of the IC neurons.

Brainstem encoding of interaural time differences.

The ITD cue consists of comparing the phases in left and right ear, that falls on neurons of the medial superior olive (MSO). These neurons happen to be more selective of low band frequencies contrarily to ILD neurons in the LSO. The excitatory inputs projected towards MSO are transmitted via monosynaptic connections of spherical bushy cells in the AVCN. In order to prevent a long traveling ITD-processing pathway, and contrary to classical synaptic

potential times courses, the fibers projection from the AN to the AVCN is yielded via the endbulbs of Held synapses. The endbulbs of Held are large and temporally precise synapses, at single presynaptic spike of an endbulb of Held synapses is sufficient to trigger one spike at the postsynaptic site of the bushy cell. Hence, bushy cells have high temporal precision that is higher than that of AN fibers from which they extract their inputs.

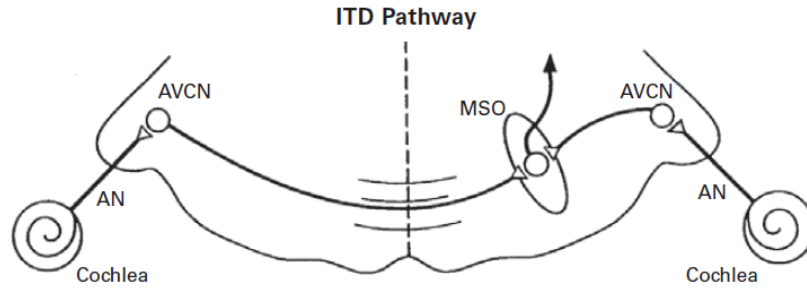


Figure 1.10: ITD processing pathway in the auditory brainstem. Artwork by Prof. Tom Yin [2].

It has been thought that MSO neurons carry out the interaural delay following a model known as the Jeffress model. In his theory, Jeffress proposed that temporal differences reaching both ears are represented as a "place" in an array of nerve cells. The theory of "place" cells that is referred to as the Jeffress model, is based on three essential assumptions: First, an arranged order of conduction times in the ascending fiber, second, the conversion of synchronised input into output spike rates into "coincidence detectors", third, spiking rates variation to form a neuronal "placemap" in the cell array [72].

The evidence of Jeffress place map is strong in birds of prey that are studied intensively due to the highly developed and exceptional localisation abilities such as in barn owls. This is mainly due to the ability of the barn owl to phase lock and use ITDs for high frequencies such as 9 KHz. However, the Jeffress-like ITD processing in mammals has been controversially discussed in the literature [73], [74]. It is known that phase locking in mammals is limited to around 3 to 4 KHz. In fact, there might be an important difference in ITD processing in birds versus in mammals that might perhaps reflect constraints from evolutionary history more than only arrangement considerations [75].

1.2.3 Sound source perception at different space dimensions.

i. Sound source detection in the horizontal space.

The duplex theory adopted by Lord Rayleigh, is mainly based on the notion that spatial information rely on ILDs for delivering high frequencies and on ITDs for low frequencies. In this section, we will explain more in details the implication of each of this cues in localizing sounds in the horizontal plane, based on different sound localisation experiments. In 1936 Steven and Newman [71] evaluated sound localisation using broadband stimulations such as clicks and noise bursts. Their experiment reported a clear frequency dependence to task performance. They found the highest error peak around 3000 Hz, that declined at higher or lower frequencies. This frequency dependency was also found in a study conducted by Sandel and colleagues in 1955 [76], who also reported low accuracies in range of 1500 to 3000 Hz. Concluding that at this range of frequencies, the sound is too high in frequency to provide temporal cues, with a long wavelength to provide convenient level differences.

On the other hand, minimal audible angle experiments conducted by Mills showed also highest MAAs for 3000 Hz, therefore, horizontal localisation seems to be very largely dependent and sensitive to interaural difference cues. In fact, the smallest thresholds for ILD tones are smaller than 1 dB [77, 78]. In addition, Middlebrooks reported high ILDs of 20 dB at 90° for the lowest frequency tested (4000 Hz), that increased to 35 dB for 10 KHz at the same position, proving that ILDs are proportional to the sine of the azimuthal angle. However, this ordered dependency of ILDs was not found in MAA for frequencies greater than 4000Hz and for azimuth greater than 30° [79].

The spatial dependence is also found for ITDs when treating the ears as two points in a rigid sphere, by determining geometrical differences of the paths towards the two points. The computation of geometric features give the following equation:

$$\gamma = (r/c)[\theta + \sin(\theta)] \quad (1.1)$$

γ : Interaural delay.

r: Radius of the sphere.

c: speed of the sound in air.

θ : Azimuthal angle of sound source in radians.

Based on this equation, Kuhnle made acoustical based analysis for the delay between the two points on the rigid sphere using a mannequin. He discovered that the interaural delay given by the equation corresponded well to the measured value for frequencies above 2000Hz. However, for frequencies below 500Hz the measured values are larger than those predicted by the equation. Meaning that the interaural delay is larger for lower frequencies, therefore, sensitivity is higher.

However, it is still quiet surprising why humans among other species, have difficulties detecting ITDs for higher frequencies while primates showed significant phase coding in their auditory nerve for frequencies up to 5000Hz especially for barn owls for example [80]. Nevertheless, listeners seem to be sensitive to envelopes of high frequencies as demonstrated for high pass and high frequency band pass transients [81, 78], bandpass noise [68, 82, 83], for sinusoidally amplitude-modulated (SAM) tones [84], and for two-tone complexes [85, 85]. The detection of interaural delay in a two tone envelope demand perhaps different mechanisms that those used by the barn owl and other species that have sensitive mechanisms to high frequency interaural delays.

ii. Sound source detection in the vertical space.

The pinna is considered to be a spatial cue that could disambiguate information about source location. In a study by Fisher and Freedman [86] that consisted on testing localisation performance of 8 loudspeakers positioned at 45° in elevation. They found that the performances after the occlusion of one ear did not potentially change. However, localisation performance was only affected when the listener was deprived from the reflections of the pinna after the insertion of 10cm tube by passing the pinna into the ear canal.

The pinna plays an important role in vertical localisation by creating echoes that lasts for few milliseconds and by producing multiple paths towards the ear canal, among these paths

there is a direct path and a reflection from the cavum concha of the pinna. This direct signal with a delayed version produces a comb filtered spectrum that contains characteristic pattern of peaks and notches. This direct path vary according to the elevation position, therefore, the spectral shape cues will vary in frequency with respect to the degree of elevation. These spectral shapes cues are often referred to as "monaural cues" since they do not require an interaural comparison.

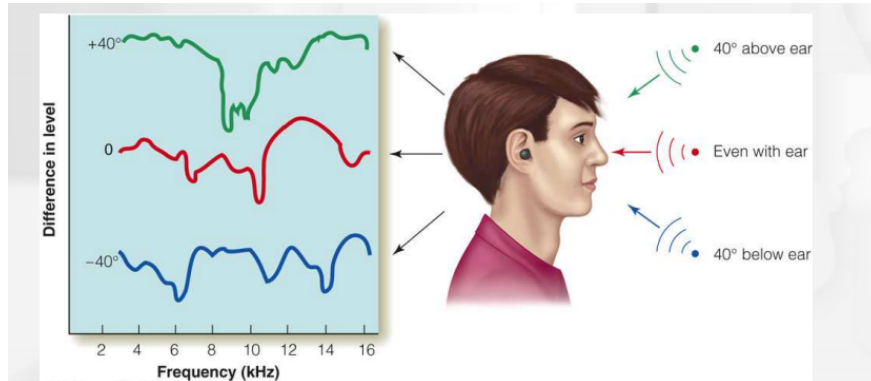


Figure 1.11: The influence of spectral cues on sound frequencies and intensities.

There has been a large debate about the requirement of high frequencies for accurate vertical localisation. Since the spectral shape cues are the main cues for vertical localisation, accurate performance is reported when broad band stimuli contained energy at high frequency. Butler [87] developed another concept called the "covert peak", when a specific frequency positioned at a specific location produces the greatest level.

The narrow band notches, are one of the most prominent features of the transfer function of the external ear. The features shift systematically in elevation according to the sound position. Thus, the spectral shapes seem to show a downward shift in frequency when the physical size of the subject increases. Meaning that the perception of elevation sources are also influenced by the spectral shape of the sound. Blauert in 1969 [88] tested this feature by recording noise sources in the front and in the back using in ear microphones. After the recording, he electronically modified each source to mimic the spectrum associated with the other source position. When he asked the subject to localise the new modified sound, the listener localised the source in the front as if it is coming from the back, proving that his

judgment on the source location was based on the source spectral features and not on its actual position.

To examine the spatial characters of the spectral notches, an experiment was conducted by Bloom in 1977 [89]. He set different sources at different elevation positions in the space, and he asked the listener to adjust the frequency of a sound to match one of the locations tested, by modifying the center frequency of a band reject filter. As a result, the center frequencies selected for each position correlated with the frequencies of the notches in the external ear transfer functions measured for stimuli located at corresponding elevations.

It is assumed that the interaural differences does not contribute in elevation perception in the medial plane, based on the assumption that the symmetry of both ears wouldn't produce interaural differences in the median. However, it has been shown in measurements by Searle that the ILD s in the median plane can extend to 10 dB and that ILDs can vary with sound elevations. Therefore, ILDs might contribute more than spectral shape cues in the elevation perception in the median plane, this assumption is confirmed when plugging one ear produced a reduction in the performance of elevation detection in the median plane [90, 91, 87].

iii. Sound source detection of distant sources (depth perception).

Little is known about the cues involved in depth perception and their efficiency. However, distance can be judged based on loudness cues. An experiment conducted by Holy and Therlow [92] consisted on positioning different sources ranged in distance from 32 to 64 feet. They sent a noise of 500 ms duration at each position, presented every ten seconds. The estimated responses of the subjects correlated with the actual positions only when the sound sources where at the side, the precision was reduced for sources positioned in the front of the listener.

It has been also shown that listeners are able to judge source depth in non-anechoic chambers compared to anechoic ones. The depth perception can be probably influenced by the reflections of the sound in specific listening environment. Like in the study of Mershon and

Bowers [93], when they reported significantly different estimations of sound distance of a wide-band noise when placed in a reverberant room. However, there are no systematic studies of the influences of direct/indirect ratio of sound energy on the perception of distance.

Key points

- **Binaural integration is the basic phenomenon underlying speech comprehension and sound localisation.**
- **Binaural integration is based on three main effects: Binaural Squelch, Binaural summation and Head Shadow.**
- **ITD and ILD also known as binaural cues are mainly involved in horizontal spatial localisation.**
- **Monaural cues are the spectral shape cues of the pinna that are used in vertical localisation.**

1.2.4 Spatial coding in the thalamo-cortical system.

Spatial discrimination VS source identification.

When we try to explore cortical areas involved in auditory spatial processing it is important to make a distinction between two main spatial auditory functions. It is known that spatial perception can be manifested behaviorally by either the accuracy of source identification usually assessed by the Root Mean Squared Error (RMSE), or by spatial discrimination assessed by Minimal Audible Angle (MAA) [94]. Despite the fact that both measures evaluate spatial auditory performance, these functions define different abilities. In one hand the

spatial discrimination is defined as the extent to which a subject is able to perceive two separate spatially distributed sounds in the azimuth, axis and its assessed with Minimal Audible Angle (MAA). On the other hand, localisation accuracy designate the measure of a deviated response from its original target position and its measured by the RMSE [77, 63, 95] (see chapter 2).

Many studies tend to evaluate spatial perception based on a simple localisation task assuming that RMSE for example, can be representative of the spatial capabilities of the subject. However, many studies suggest that the distinction between spatial localisation and spatial discrimination is important. Very little studies tried to compare these functions separately. Freigang for example aimed to compare behavioral spatial variation as a function of age by correlating age with spatial discrimination and spatial localisation. They found that RMS was not predictable with age. However MAA was more predictable and highly dependent on aging, consequently assuming that the effect of aging on spatial discrimination is much more important than its impact on localisation accuracy [63].

In 2010 Grieco Calub also evaluated both localisation accuracy and spatial discrimination in bilateral cochlear implanted children. He suggested that the experimental methods used for spatial discrimination, such as right-left discrimination provided limited information about sound sources identification (i.e. localisation accuracy), based on this assumption, Moore also suggested that both functions cannot be directly predictable from one another since the neural mechanisms underlying each skill may not be similar. The long debate of whether both skills are related led to an evidence that spatial discrimination emerges in the first 12 months of life, while source identification ability require longer binaural experience to be emerged [95].

The findings of Calub showed smaller MAA measures comparing to RMS thus he suggests that right-left discrimination ability is possibly acquired before source identification skill with children using sequential BICIs. His study reveals that spatial identification accuracy is expected to occur in children with good spatial discrimination, suggesting that spatial discrimination can be an indicator of spatial accuracy but not the opposite. Based on the previous debates it is likely assumed that the two functions depend on similar auditory

cortical structures due to an equivalent deficit after auditory cortical ablations [96, 97, 98, 99, 100, 101]. However, previous studies have also demonstrated that spatial selectivity of the auditory cortical neurons seem to be broader than the thresholds of relative localisation (MAA) [102, 103, 8, 104, 105, 106, 107].

Behavioral-lesion related studies applied on cats showed that unilateral lesions in the auditory cortex can produce deficits mainly limited to contralateral sound directions; this behavior has also been reported in ferrets and monkeys. In addition, unilateral lesion in the MGB also produces contralateral deficit in contralateral directions, leading to a conclusion that the entire thalamocortical system is necessary for spatial localisation. Jenkins and Merzenich also tried to test cat's ability to localize single clicks after the ablation of a defined unity of frequency bands in the A1. After the lesion, the contralateral deficit was only restricted to the frequencies deprived during the ablation, concluding that spatial coding can be carried out within frequency channels. However, such lesions did not affect the right-left discrimination abilities [96, 108, 99]. Jenkins in 1982 showed that after unilateral lesion of A1 cats were able to respond appropriately to a two choice task, however, this was not possible for more accurate localisation of sound sources. These results opened the possibility of asking whether these two functions (discrimination and localisation accuracy) possess the same or distinct cortical mechanisms [108].

Bilateral lesions affects also spatial accuracy and right left discrimination as shown on different types of animals: ferrets [99], monkeys [109] and cats [110, 96]. Strominger and Oesterreich in another study, tried to isolate the MGB from its collicular inputs using a bilateral section of the branchium of the IC in cats. This procedure led to a deficit in the right left discrimination task. On the other hands, bilateral forebrain lesions had no or minimal effect on spatial discrimination in other animals such as Rats after bilateral ablation of the MGB Kelly and Judge 1985). In addition, bilateral auditory cortex ablation did not show a significant impairment of spatial right left discrimination in bushbaby, hedgehog and opossum [109].

The responsiveness of neurons to azimuthal changes have also been roughly studied in the MGB and in A1. According to different studies conducted on cats by Eisenman he found

that the neurons of A1 and MGB responded similarly to azimuth change with maximal responsiveness of azimuth sensitive cells to contralateral locations (50%) or ipsilateral (25%) or midline (25%). These findings were different from those in the IC. In the IC the maximal responsiveness of the ILD sensitive cell is only present when the contralateral ear is more intense than the ipsilateral ear in the vast majority of high frequency ILD sensitive cells.

In the human model, the role of auditory cortex has been studied in patients with temporal lobe damage, however, the interpretation of its role was difficult because the types of lesions were frequently large and were never restricted only to the auditory cortex. Nevertheless, most of the findings were consistent with the results reported in animals.

To summarize, neural representation of acoustical environment has been studied through electrophysiological and behavioral experiments. They were able to show that in the thalamus and cortex, neurons are most sensitive to binaural cues, and sometimes neurons can be sensitive to direction information provided by monaural spectral cues. Although there is no evidence of systematic representation of azimuth, the findings suggest that high frequency sensitive neurons are more responsive to contralateral locations, and that neurons that are responsive to midline or ipsilateral locations mainly appear at the level of the thalamus. A direction coding transformation seems to be taking place between the midbrain and the thalamus. In the end, it is important to note that the responsiveness rate of cortical neurons is also affected by the context of the behavioral task implemented.

1.2.5 Speech and vocalisation processing at cortical fields.

The first one to suggest that speech processing is not symmetrical, and that the left hemisphere is capable of carrying out certain key speech processing compared to the right hemisphere, was Paul Broca (1824-1880). Broca stated that the left hemisphere is dominant for language in most, but not all individuals. Noting however, that right hemisphere cannot contribute to speech comprehension and production alone. Starting from Broca, and until this date, an extensive additional brain imaging evidence has helped improving our knowledge about the functional role of various areas involved in both production and comprehension of

speech.

In order to explore the cortical areas involved in speech comprehension, electro-cortical mapping experiments based on disruptive electrical stimulation of specific brain areas were conducted. The findings reported larger number of cortical activations when the task gets more complex. However, an acoustic phonetic task was not easily disrupted and electrical stimulation could only reliably interfere at a single specific spot of the superior temporal gyrus. Therefore, assuming that the phonological processing requires an extensive and complex degree of speech analysis involving large parts of the STG in addition to some sites at the Broca area in the frontal lobe. Plus, lexical semantic tasks seem to be also involved in more cortical areas, this has been proved after focal stimulation of the superior temporal sulcus (STS), STG, Broca's area and Wernicke's area, that lead to the disruption of lexical processing performances.

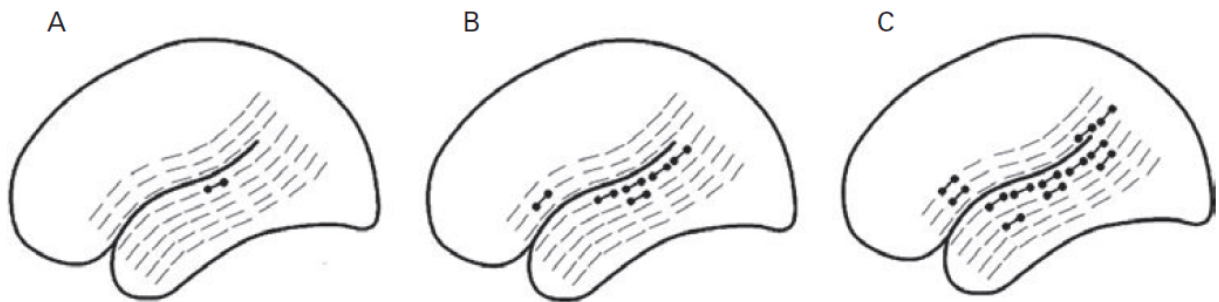


Figure 1.12: Disruptive functions after electrical stimulation at different brain areas. (A) Acoustic sites, (B) Phonological sites, (C) Lexical-Semantic sites. Photo from [2] reproduced from Boatman 2004 [111].

Cortical processing hierarchy is more organised according to "acoustic features" stimulus type, that does not reflect a precise temporal structure of the sound, however, it can reflect the time course of the stimulus. The average phoneme rate in human speech is approximately one every 20 ms. Engineer and colleagues in 2008, trained rats to distinguish syllables that differed in their onset (zad from sad for example). The rats learned easily the syllables that contained little energy at low frequencies, such as the response to /s/ where high frequency neurons responded in A1. This interplay between frequency sensitivity and acoustic char-

acteristics of the stimulus leads to each consonant having its own response pattern across the population of cortical neurons.

Anatomical observations in auditory cortical areas of the primate also suggested that the brain may be organised according to the dorsal and ventral processing streams. The dorsal stream is involved in identifying source locations, while ventral stream plays the lead in sound identification. Ventral stream run from PAC through the medial belt towards the STG and inferotemporal cortex, and from this site to the ventral prefrontal cortex (vPFC). As already mentioned, the ventral stream task consist on identifying different types of vocalisations and spoken words.

As we saw in this section, sound source identification and speech comprehension are two functions that involve complex phenomenons starting from the the first interference of the sound with the head and the pinna of both ears towards the ear canal, the cochlea, and then the AN, after the transformation of the acoustical information into electrical input, and its propagating through the ascending auditory pathways to be later integrated in cortical and subcortical areas. This extensive multistage processing is largely dependent on binaural type of information. The alteration of binaural integration may lead to devastating consequences effecting sound processing at higher stages according to the type and cause of the damage. The next section will develop the main alterations and consequences of hearing impairment, especially asymmetrical hearing loss, and its influence on cortical and subcotrical organisation in addition to the compensatory strategies adapted prior to the hearing loss.

1.3 Hearing Loss.

As we have seen in the previous section, the ear is presented in the auditory cortex by different populations of cortical units [112]. An extensive number of neuroimaging techniques aimed to explore the effect of bilateral versus unilateral stimulation on hemispheric activations. Evoked potential investigations and MEG studies found larger evoked response in a given hemisphere in binaural stimulation compared to contralateral or ipsilateral stimulation [113, 114, 115, 116]. Functional MRI anatomical explorations reported a crossing over of the

auditory pathways at the level of the brainstem, leading to an activation of the of contralateral hemispheres in the case of ipsilateral stimulation. However, when comparing findings from different neuroimaging techniques such as MEG, PET scan or fMRI it is important to note that these methods are based on different physical and physiological features. BOLD signals represent the focal level of hyperoxygenated blood in draining vessels, therefore, the spatial distribution of hyperoxygenation may not be sufficiently representative and parallel with activated neurons. However, electrophysiological studies possess the abilities to reflect neuronal activity at a very high temporal resolution, while its spatial representation remains limited [117, 118].

A variety of imaging studies aimed to explore brain activation and organisation after hearing loss. The accumulation of these neuro-imaging techniques helped the researchers to step into the nature of the hearing loss and its consequences according to the gravity of the deficit. In addition, a deficit in a peripheral or central features of the auditory system, was effective in understanding the main function of the feature in deficit. Disorders in the auditory functions can be detected through a decreased function or abnormal functions. The elevation of hearing threshold or decrements in speech discrimination designated by high Speech Reception Thresholds (SRT) are normally signs of decreased function. However, tinnitus, hyperacusis, distortion of sound or phono-phobia are considered to be abnormal functions. The following symptoms lead consequently to a modification in sound processing on the auditory nervous system.

The disorders of auditory system are subclassified into two categories: conductive hearing loss or sensorineural hearing loss. The conductive hearing loss is mainly caused by a dysfunction of the apparatus features conducting the sound to the cochlea while sensorineural hearing loss designate the pathologies directly related to the cochlea and the auditory nervous system. The distinction between peripheral and central causes of hearing loss can sometimes be blurred. Because, for instance, injuries affecting cochlear hair cells and therefore the function of the cochlea, can also be accompanied with auditory nervous system dysfunctions. A deficit in the neural processing of a sound can affect patients with conductive hearing loss. Therefore, the division of auditory disorders according to anatomical locations is no longer

valid.

Recently, it has become evident that auditory nervous system could go through systematic changes without any modification in the morphology. These changes occur as a consequence of neural plasticity expression, where specific auditory processing features can change permanently according to its activation. This designates the compensatory strategies adopted by the auditory system of a patient in order to adapt to the deficit.

Cortical reorganisation or experience related reorganisation is observed at different levels of the sensory system. In the auditory field, this plasticity was explored extensively in studies of experimentally induced frequency-specific peripheral hearing loss or complete monaural hearing loss. For example, it has been shown that frequency specific hearing loss could result in a change in the response properties of the neurons and in the activation of auditory pathways at cortical and subcortical levels [119, 120, 121, 122]. In this section, we will discuss the reorganisation process taking place in the case of monaural hearing or asymmetrical hearing loss and the cortical phenomenons underlying the adaptation to the new hearing conditions after hearing loss.

1.3.1 Behavioral manifestations of monaural hearing.

Although a broad number of researches confirm the impact of binaural cues deprivation on sound processing and its devastating repercussion on spatial perception, localizing sound sources in the space with a single ear is nonetheless, not impossible to achieve. A famous study conducted by Middlebrooks in 1998 [123] is one of the greatest evidence about the possible adaptation of a patient to new strategies to overcome monaural deficit. In his study, Middlebrooks attempted to assess localisation in the absence of interaural difference cues on two types of population. The first group was of Normal Hearing Subjects (NHS) group fitted monaurally with an earplug, the second group was patients with longstanding Unilateral Hearing Loss (UHL).

The results of this experiment reported a deficit in localisation performances in NHS when fitted with a monaural ear plug, where RMS increased of around 20° in monaural condition

compared to the binaural one. However, despite the high impact of monaural hearing on spatial localisation abilities in the control group, it seems to impact patients abilities in a less devastating manner compared to NHS (RMS patients: 36° vs 39° for monaural NHS). In contrast, three patients presented near-normal localisation measures compared to plugged controls on both hearing and impaired sides.

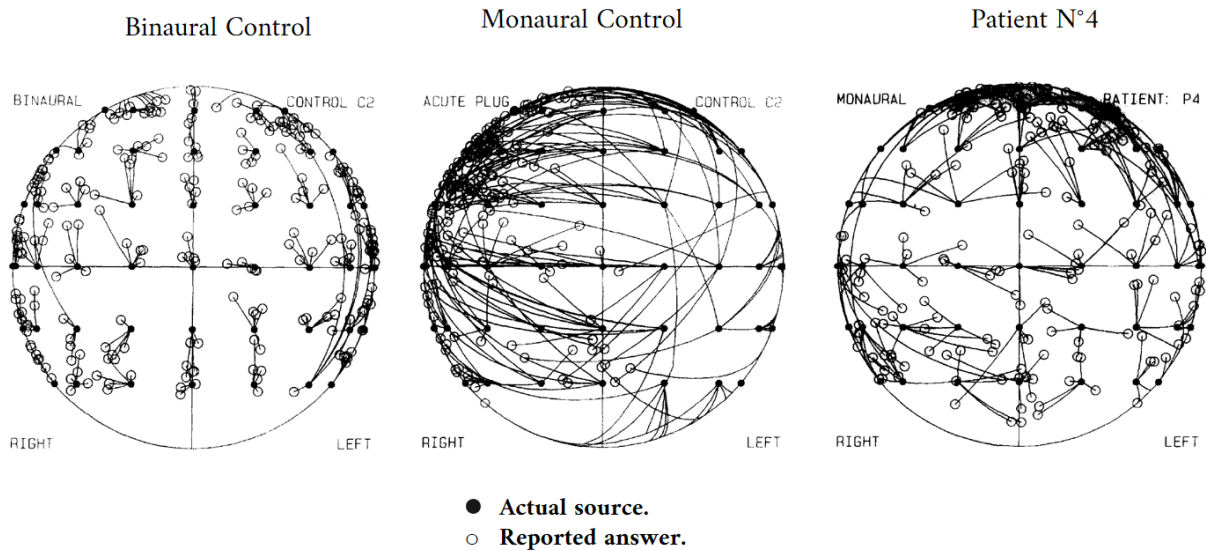


Figure 1.13: Participants performances at different space locations. The black dots represent the actual source and the white dots represent the answers reported by the participant. The left ear is the hearing ear.

As the figure 1.13 show, monaural controls tend to displace their localisation judgment towards the side of the hearing ear. Three of the patients included in this study showed little lateral bias compared to monaural control, and demonstrated accurate localisation precision as shown for patient 4 in the figure 1.13. One of those patients also noted that he recognised the sounds coming from the deaf side if they sounded "dull" or "muffed", meaning that localisation judgment under monaural condition can be learned, and those patients might benefit from formal localisation training.

Another theory suggests that the good monaural performers could be developing new localisation strategies that rely on monaural spectral shape cues for localisation. Although it is known that spectral cues are the cues of sound source elevation detection, it seems that they

can interfere when binaural cues fail to disambiguate sound location in azimuth. Oldfield and Parker [124], proved that even though binaural cues are the cues primarily responsible for determining azimuth sources, spectral shape cues, also known as monaural cues could contribute in azimuth localisation. However, this adaptation to monaural cues that is manifested on the behavioral level, is also manifested on neural level by cortical and subcortical reorganisations to overcome the binaural deficit.

The effect of chronic monaural occlusion was investigated in ferrets by King in 2000 [125], where he introduced monaural ear plugging for ferrets infants and for adult ferrets. They showed that ferrets that were raised with one occluded ear were able to perform as accurate as control ferrets in a horizontal sound localisation task, confirming the existence of compensation strategies adapted after earplug. Thus, they applied ear plugs for adult ferrets during seven months, and they were able to show an improvement in their auditory localisation after monaural occlusion, however this improvement did not reach the same level of performance as before the plug.

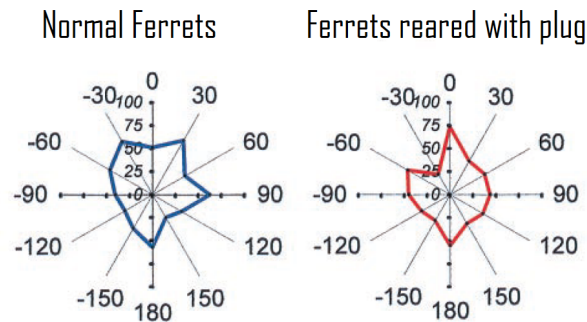


Figure 1.14: Sound localisation performances between normal ferrets and ferrets reared with monaural occlusion [125].

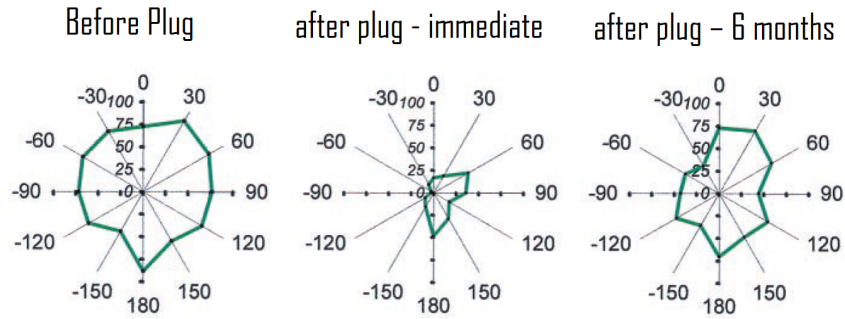


Figure 1.15: Adult ferrets, before and after monaural occlusion [125].

Next to absolute localisation, and in order to determine the aspect of spatial auditory features affected by monaural occlusion, King also investigated spatial discrimination abilities using Minimal Audible Angle (MAA) task. They found that monaural occlusion affected spatial discrimination in a different manner compared to absolute localisation. The long term monaural occlusion affected the ability of spatial discrimination in both infants and adults ferrets. However, they showed that ferrets that were raised with occluded ear, had better discrimination performances compared to adult ferrets [125].

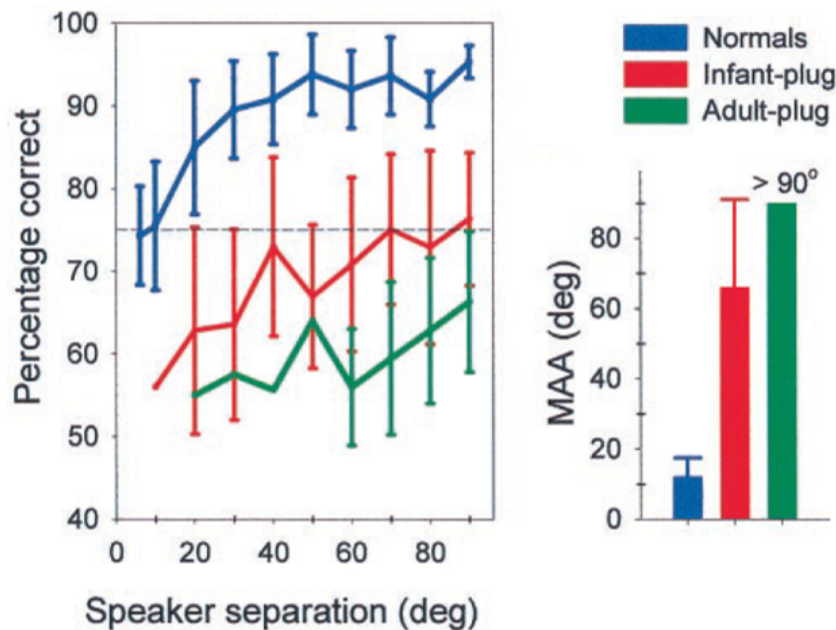


Figure 1.16: Variation of MAA performances between NH ferrets, adult ferrets with plug, and ferrets reared with plug.

It has been shown that adaptation to ear plugging could occur over time leading to an improve in spatial perception [126, 125]. After unilateral plugging, the plasticity takes place primarily due to the unchanged cues, in this case, the monaural spectral cues (review in [127]). This phenomenon is known as the re-weighting of spatial perception on monaural cues, it is more effective on high frequencies, and could therefore compensate the ILD cues. However, this compensation is far from perfect, because monaural cues cannot precisely detect spatial change similarly to binaural cues, therefore, the spatial location recovery after ear plug is limited. It is also important to note that spatial hearing can be reversed, for example, it has been shown, that normal localisation returned after one year of monaural hearing in ferrets [128].

Barn owls, on the other hand, develop specialized localisation abilities and specific frequency sensitivity that are helpful in prey hunting at night. These animals have high phase locking capacity in their auditory nerve [129]. This capacity provide the owls with an exceptional input for ITD, by highly and precisely detecting circuits that allows improving ITDs at very high acuity. It has been also shown that in young owls, after unilateral hearing loss, the binaural cues are rapidly remapped by increasing sensitivity to reduced inputs from the affected ear. Correspondingly, unilateral hearing loss in owls promotes compensatory remapping of binaural tuning in neurons within spatial brain maps [130]. The owl possess a unique ecological niche that provides it with particular abilities of binaural hearing with also an ordered topological map of ITD in the brainstem.

Mammals usually extract spatial inputs using a population of code from all binaurally sensitive neurons [3] and does not rely on an ordered topological map like in barn owl. This may be the reason behind the unique compensatory remapping in owls after unilateral hearing loss compared to mammals [131, 132, 133]. In mammals the weight of behavioral importance rely on the unchanged cues, i.e, monaural cues. Our knowledge about the mechanisms underlying this dependence is yet to be provided. This can however suggest that the compensatory remapping of binaural cues, normally adopted by owls after UHL, is not optimal for mammals. Although the present literature about the neural signature of space and its variation according to binaural cues alteration remain unclear. Different neuroimaging stud-

ies tried to explain cortical reorganisations prior to spatial deficits to further understand different activation patterns involved in these adaptational strategies [134].

1.3.2 Cortical and subcortical reorganisation in unilateral hearing loss.

Until this date, the longitudinal relationship between central reorganisation and behavioral performances remain unclear in the case of hearing impairment. It has however been reported that a unique plastic pattern can take place known as healthy side dominance in patients with acute UHL. In a study by Po Hung in 2012 [135] aiming to study the hemispheric asymmetry in patients with UHL and its implication in the prognosis of these patients using MEG to study the inter hemispheric differences in peak dipole on N100m to monaural tones. They reported healthy side dominance in N100m, and a pattern change according to the disease progress, concluding that central changes in terms of N100m can serve as predictor of unilateral sensorineural hearing loss progress.

Another investigation provided evidence of the presence of time course auditory plasticity. Ponton in 2001 [136], published a paper, where they compared experience related changes in the CNS using auditory evoked potentials of profound unilateral deaf teens and compared it with simulated monaural controls. They reported an increase in the inter-hemispheric cross correlation coefficients in the electrodes located over auditory cortical areas in patients with UHL compared to monaural controls. This result assumes that the asymmetrical pattern of cortical activation in normal cases, where the contralateral hemisphere is highly and early activated compared to ipsilateral side, is under substantial changes in the case of unilateral hearing loss, that presents more symmetrical and simultaneous activations.

In 2000 Bilecen [117] confirmed these substantial changes using fMRI. BOLD response is normally detected in contralateral auditory cortex when unilateral acoustic stimulation is elicited, however, in his experiment on a subject with sudden hearing loss after cochlear nerve resection, he reported a progress in the bilateral cortical BOLD signal in response to unilateral stimulation over a period of 12 months. Bilenen traced the time course of the

compensatory reorganisation after the cochlear nerve resection. Before the resection, the patient showed normal contralateral bold response in the primary auditory cortex. After 5 weeks of the resection of the cochlear nerve, the stimulation of the intact ear elicited stronger contralateral activation in addition to ipsilateral response. Twelve months later the bilateral BOLD response was progressively balanced.

Many studies explained that in normal cases, auditory pathways are projected contralaterally but also ipsilaterally to the side of acoustical stimulation through uncrossed pathways, leading to a strong contralateral activation and a weak ipsilateral one [117, 134, 136, 135, 133]. In the case of unilateral hearing loss, the ipsilateral projections that are usually suppressed, are dis-inhibited once contralateral inhibitory inputs are altered. The time course needed for reorganisation is almost around 12 months in humans, according to Bilecen [117], which was consistent with the findings for animal experimental lesions. The bilateral cortical activation appears to play an interesting role in spatial encoding, which might also explain the near normal localisation performances found by Middlebrooks in 1998 [123]. However, the process underlying this putative dis-inhibition and its exact mechanisms remain unknown, and the biologic significance of compensatory ipsilateral cortical recruitment remains to be elucidated.

The change in the blood oxygenation level dependent in the plane of the superior temporal gyrus after acoustic stimulation was also investigated by Scheffler and Bilecen [118], on five monaural deaf patients. The acoustic stimulation was either monaural for each ear a part, or binaural. As expected, NHS revealed a lateralisation response towards contralateral hemisphere in monaural stimulation. The left and right hemispheric responses ratios were 3.4 and 5.2 after monaural stimulation, this ratio is balanced in the case of binaural stimulation. When the cortical activation volumes were calculated, their addition in the case of monaural stimulation, was 30 % smaller than the overall activation during the binaural stimulation, indicating a neural facilitation (explained later) in auditory pathways. However, the lateralisation ratio of patients with UHL after monaural stimulation between left and right was around 1.3 towards the contralateral hemisphere, which indicates a near symmetrical activation, comparable to the findings in normal binaural stimulation. This is one of the

indicators of adaptational strategies reflecting auditory cortical plasticity in patients after UHL.

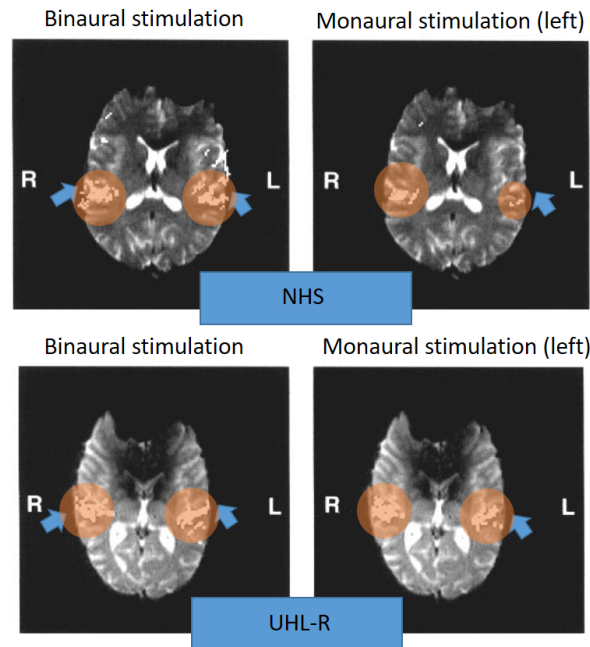


Figure 1.17: Example of cortical responses upon binaural and monaural stimulation in one healthy volunteer and one UHL-R. The binaural stimulation in both subjects show bitemporal activation. Monaural stimulation of the left ear in the healthy subject enhanced right hemisphere activation, however, for patients with right UHL, stimulation of the healthy ear lead to bi-temporal activation. Image from [118].

Burton also investigated cortical activations using fMRI in core, belt, and parabelt auditory cortex in adults with normal hearing (NH) and unilateral hearing loss (UHL) [137]. NHS underwent a simulation of monaural hearing loss using an ear plug, and received stimulation on the side matching the intact ear in UHL. A contralateral response was noted in several auditory cortical fields in NHS regardless of the side of stimulated ear (Right or Left). For patients, when the right ear (unaffected ear) was stimulated, a larger ipsilateral response was noted in core and belt compared to NHS. However, when the left ear was stimulated this ipsilateral response was only shown in the posterior core of auditory cortical fields (ACFs). Meaning that the rest of ipsilateral ACFs that were not activated might have greater resilience against the reduced crossed inputs coming from the deaf ear (right ear).

Nonetheless, regions located postero-lateral to core and belt had higher activation in NHS compared to UHL regardless of the side of the ear. It is important to note that UHL influences the activation of ACFs but is also dependent of the side of affected ear.

In order to further understand the integrative alteration of binaural inputs and its impact on cortical reorganisation, it is important to investigate the disrupted binaural integration on animal models. Single unit recordings is an interesting approach to study the extent of fusion between two sides inputs compared to monaural input. Binaural interaction takes place in the single neurons. In 1977 Imig [138] classified neurons responses to simulations in different categories according to their activation pattern: facilitation, suppression and occlusion. The facilitation or summation is characterized by high response volume when both ears are stimulated equally, compared to the summation of two responses to separate monaural stimulation of each ear apart. Suppression characterises neurons that fire less during equivalent binaural stimulation compared to monaural stimulation of a single ear. Occlusion or monaural responses characterises the neurons that does not fit in the class of suppression or summation. These neurons fire with no attending change in their firing rate between binaural or monaural stimulation.

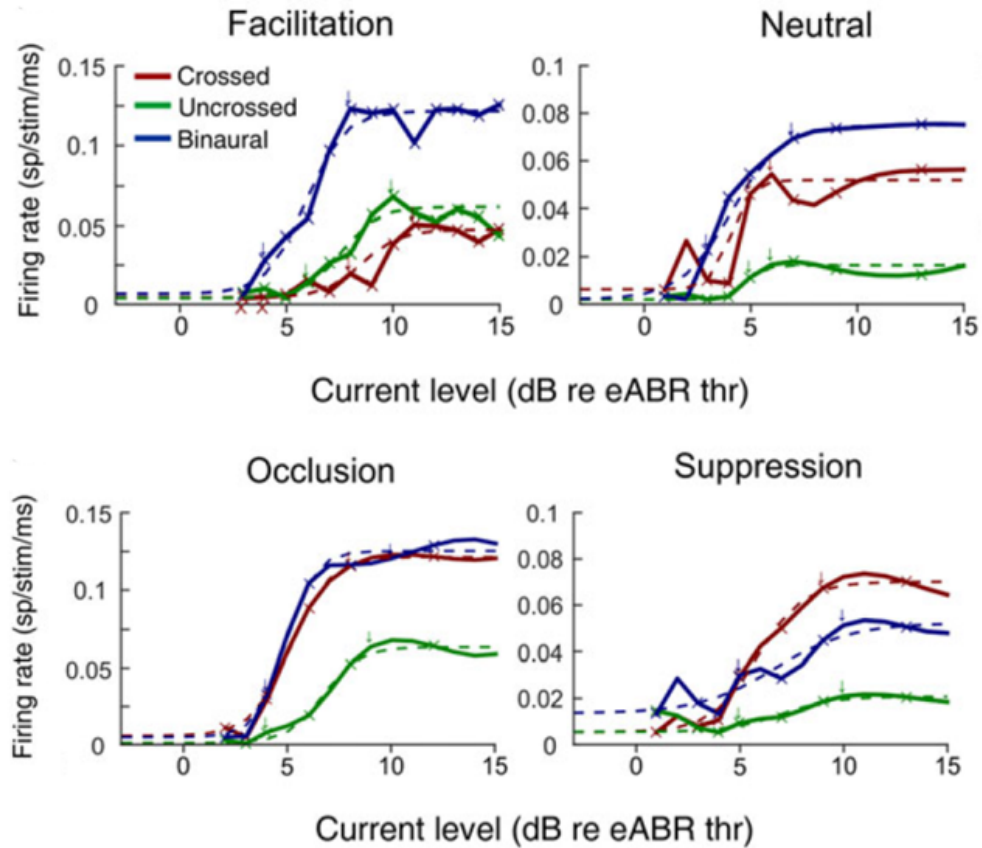


Figure 1.18: Example of binaural response classification in normal hearing cats. Figure from [133].

This approach has been investigated in cats with congenital single sided deafness by Tillein in 2010 [133], he reported a severely weakened binaural computations in the PAC, the facilitation process was nearly absent in the cats, which reflects a reduced computation of binaural inputs (figure 1.18).

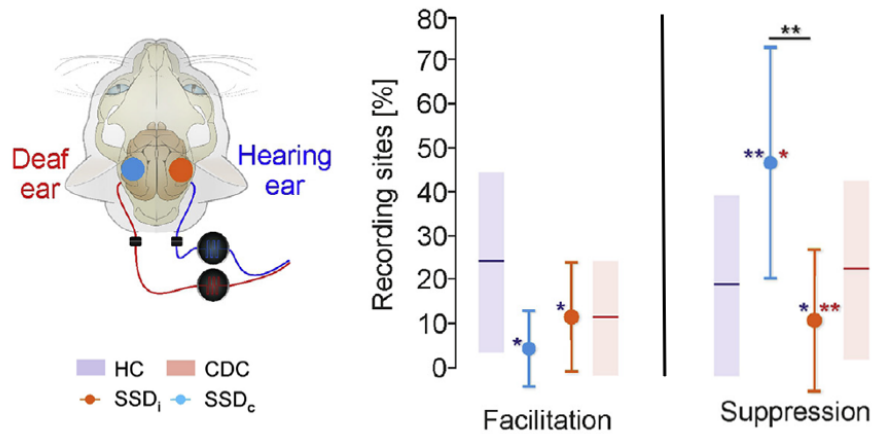


Figure 1.19: Significant decrease of binaural facilitation in both hemispheres of single sided deaf cats. Increased suppression in the contralateral side compared to the ipsilateral side where it was significantly reduced. HC: Hearing Controls. CDC: Congenitally Deaf Cats. SSD_i: Hemisphere ipsilateral to the hearing ear. SSD_c: Hemisphere contralateral to the hearing ear. Figure from [133].

In addition to the weakened facilitation, the single unit recordings also reported a diminishing of the binaural suppression that was replaced by binaural excitation in the hemisphere ipsilateral to the hearing ear. Thus stronger suppression was reported in the contralateral hemisphere, this is mainly due to common inhibitory pathways for both ears. Therefore, when one side input is absent (from the deaf side), the pathway is boosted and inhibition is facilitated [133, 139, 140, 141, 142]. The latter finding conclude that alteration of binaural integration is manifested not only by a reduced facilitation, but also by the reduction of inhibition from the side of the unaffected ear, and boosted inhibition from the deaf side.

Taken together, the previous literature about cortical activation pattern changes after unilateral hearing loss confirms that the brain undergo a multistage developmental changes that aim to enhance processing using the hearing ear to compensate the deficit generated by the affected ear.

1.3.3 Differential effect of the side of hearing loss.

In the previous section, we explored the consequences of unilateral deafness on cortical activation patterns, noticing that a differential adaptational pattern takes place according to the side of the affected ear. Different experiments aimed to assess the effect of left side deafness compared to right side. In 1998 Scheffler and Bilecen [118] studied hemispheric differences using fMRI, although his experiment was based only on 5 patients, he was able to report more interhemispheric symmetry when the patient suffered from left unilateral deafness, compared to right deafness. These findings were also consistent with Khosla in 2003 [143] where he found evidence that in the case of left unilateral deafness, the stimulation of the unaffected ear (right ear) evoked equal activation pattern at both hemispheres for clicks, whereas right unilateral deafness, showed classical contralateral activation, suggesting that compensatory plasticity does not take place in right hearing loss as it does after left hearing loss. Hartvig in 1989 [144] also reported poorer sensitivity to verbal subsets in unilateral right deafness compared to the left deaf patients.

When Burton in 2012 [137] studied the activation magnitude in core belt and parabelt on NHS and patients with UHL, he reported varying lateralisation asymmetry according to auditory subdivision and the side of deaf ear. Woods and colleagues explored acoustically activated regions and classified it onto average gyral and sulcal landmarks to relate different auditory cortical fields to the Te subdivisions [145], [146]. The corresponding cortical fields for each Te subdivision are represented in the figure below.

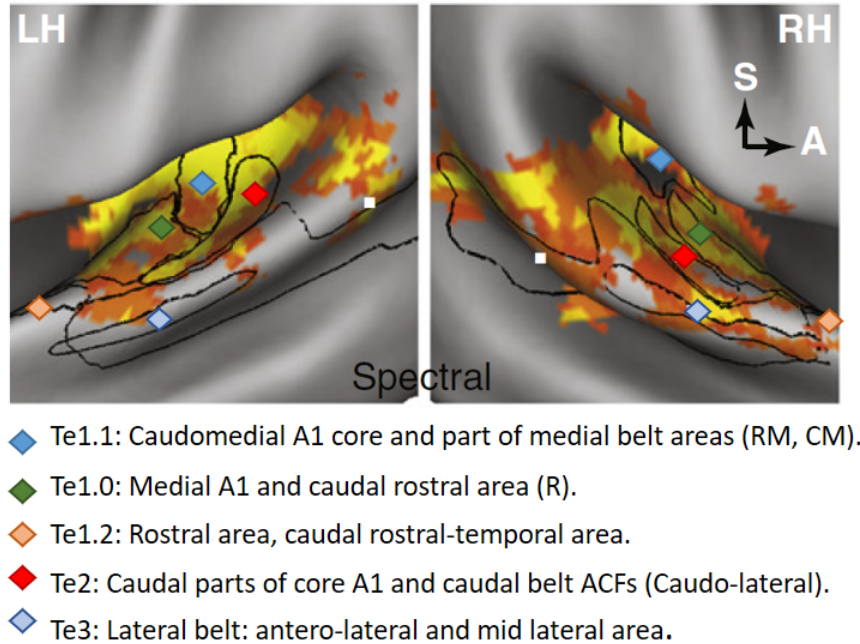


Figure 1.20: Right and left hemisphere maps representing the distribution of auditory cortical fields Te1.0, Te1.1, Te1.2, Te2, Te3 in a NHS. Figure from [137].

Accordingly, Burton [137] stimulated the unaffected ear of each patient using random spectrogram sound (RSS). The BOLD signal magnitudes across ranges of interest (ROI), revealed different lateralisation effects. The comparisons between hearing groups (UHL and NH), and stimulated side (right ear or left ear) are presented in the figure below (1.20). The NHS, similarly to previous studies, a RE (right ear) stimulation lead to a large contralateral (left) response in almost all ROI. It is important to note that response to left ear stimulation, elicited larger responses in Te2 and Te3 in the right hemisphere, compared to the left hemisphere after right ear stimulation. However, this activation was controversial in Te1.0 and Te1.1, where, RE stimulation elicited larger responses in the contralateral hemisphere (left), compared to ipsilateral hemisphere (right) after left ear stimulation. As we presented in figure 1.20, Te1.0 and Te1.1 represents the caudal and medial areas of A1 in addition to rostral areas. These areas are more activated in the left hemisphere after right ear stimulation, compared to the right hemisphere after left ear stimulation.

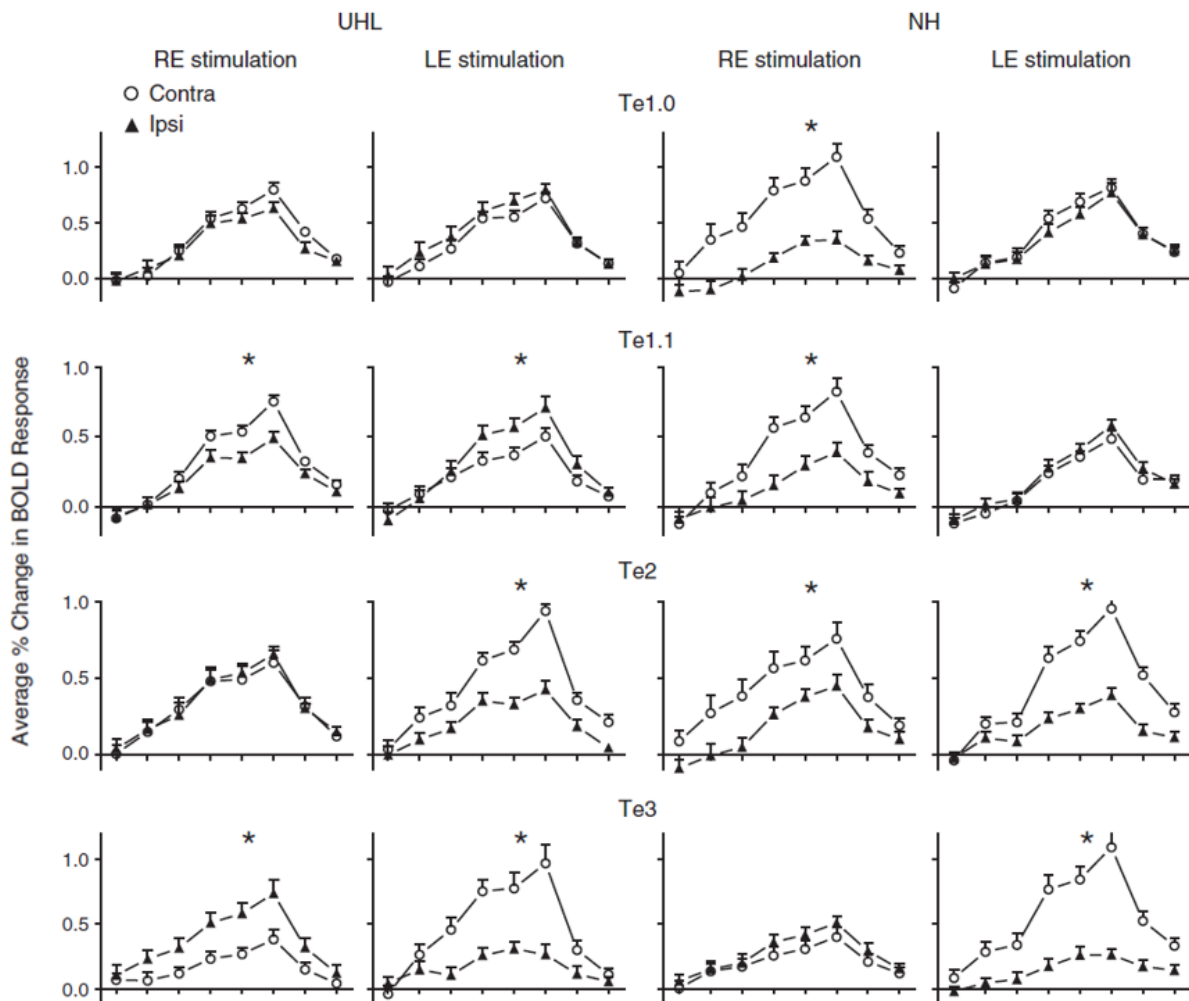


Figure 1.21: Comparisons of variable BOLD response magnitudes between right and left ear simulations for UHL and NHS, in different ranges of interest in the auditory cortex.

The lateralisation varied between patients with left and right UHL also according to the subdivisions and as a function of hearing side. The responses in Te1.1 were larger in the left hemisphere after right ear stimulation. And were still present at the left hemisphere after left ear stimulation, suggesting an ipsilateral activation parallel to contralateral one, but not in the same magnitude. This result is consistent with previous hypothesis of Khosla [143] concerning the left dominant hemisphere for providing "cortical processes of spoken language perception and production".

Richter in 2009 [147] aimed to assess hemispheric specificity using spatial Mismatch Negativ-

ity (MMN) on 15 NHS at different locations in the horizontal space, covering the semi-circular frontal fields from 90° to the right towards 90° to the left. The positions of deviants and standards are illustrated in the figure below (1.22).

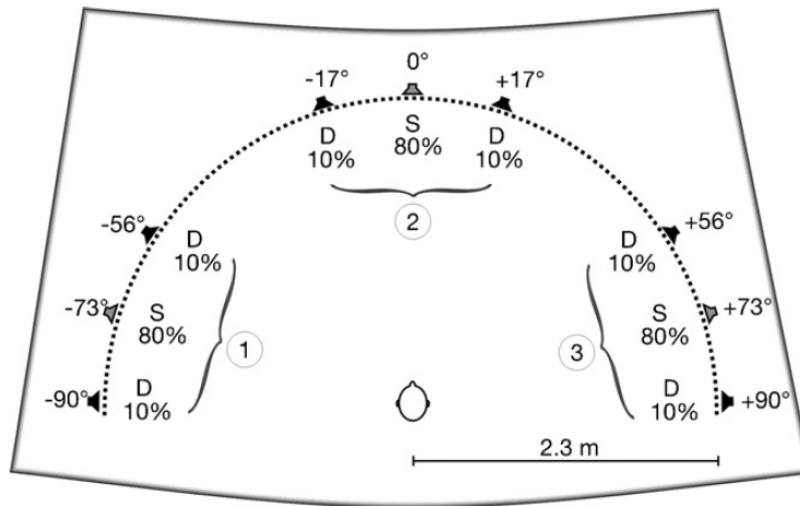


Figure 1.22: Speakers arrangement. S: standard, D: deviant.

The analyses of the EEG data revealed MMN responses that varied as a function of horizontal position and electrode side sites (right or left). Richter aimed to measure the MMN amplitudes evoked in the left and right hemisphere at 3 electrodes sites from each side (F3, FC1 and FC5 for the left and F4, FC2 and FC6 for the right).

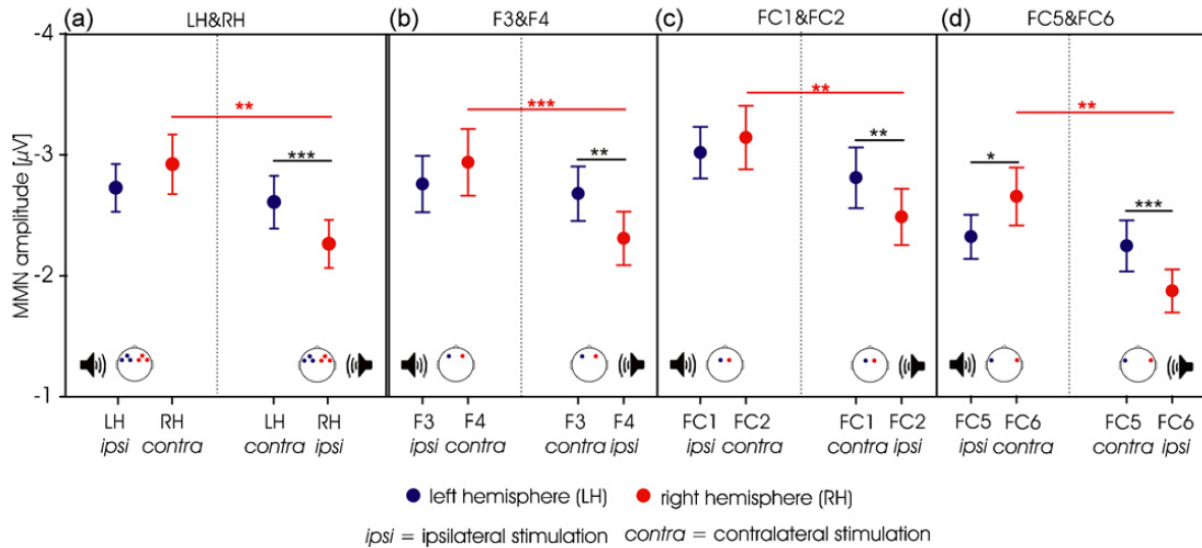


Figure 1.23: MMN amplitudes variation as a function of electrode site and side.

As shown in the figure above, the most prominent interhemispheric difference was at the lateral electrode sites (FC5,FC6) where left side stimulation induced higher MMN amplitudes in the contralateral and ipsilateral side, compared to right ear stimulation. However the other electrodes sites, frontal (F3, F4), and medial (FC1, FC2) did not show, high interhemispheric difference. The study of Richter reveal a controversial result compared to previous free field localisation studies, that suggest right hemisphere specialisation in space perception. However, in MMN studies, it is important to take into consideration that the MMN experimental design is not an absolute localisation, it is nonetheless, a sound source discrimination task that involves spatial attention and working memory, instead of voluntary localisation task.

As it has been discussed, it seems that hemispheric specialisation depend mostly on the type of processed information. While some studies refer to the left hemisphere as more specialised in speech processing and language production [143, 118, 117, 137], right hemisphere seem more likely to interfere in active auditory space processing , [148, 149, 150].

As we presented in this section, our auditory cortex is able to adapt to new space presentations after the alteration of binaural localisation cues. However, adaptation and compensatory strategies seem to vary as a function of the onset of the incident. Congenital unilateral

hearing loss, seem to develop more solid strategies, that appears behaviorally equal to normal hearing. While later hearing loss could have different impacts on behavioral spatial performances. Some patients presented high adaptation, to monaural spectral cues, yet, not totally matching normal hearing abilities. The studies presented in this section, have added further insights to our knowledge about different dynamics underlying cortical adaptation.

As we already mentioned in the beginning of this chapter, our thesis aimed to step further into the nature of this spatial adaption. We tend in this project to assess different spatial features from the absolute localisation, to spatial discrimination by correlating behavioral measures with the neural signature represented by auditory Evoked Responses (AEP), the MMN. This ERP component is currently used as a marker of different functions involved in spatial perception, such as attention and working memory. It reflects the ability of the auditory system to detect minor changes in a physical properties of a sound. These physical properties can be designated by the frequency, intensity duration or even spatial position of a sound. In our study we aim to change the spatial position of a stimuli, this will help us to explore the spatial MMN, that will reveal the variation of sound discrimination abilities between different types of population by analyzing its amplitude, latency and scalp distribution. Thus, we will try to correlate the findings with our behavioral measures that aimed to asses sound localisation in the same populations. All this will be discussed further in the upcoming chapters.

Key points

- **Animals reared in monaural hearing conditions are able to reach near normal localisation performances.**
- **Patients with UHL are able to adapt to monaural spatial deficit due to cortical reorganisation.**
- **Cortical reorganisation is manifested by ipsilateral activation of auditory cortex of patients with UHL.**

Chapter 2

Spatial Localisation Accuracy and Spatial Discrimination in Normal Hearing Subjects and Hearing Impaired Patients.

Binaural hearing plays a critical and important role in the perception of spatial information, by enhancing sensitivity to small differences in the intensity and the arrival time of a sound, consequently improving the localisation and discrimination abilities of sound sources for NHS [151]. This integrative phenomenon, based on the processing of ITD and ILD depends also on the sound frequencies and the HRTF of the listener [71]. Based on psycho-acoustic researches, humans preferentially rely on their ITD as localisation cue for sounds inferior to 6 kHz while ILD interfere as a cue for higher frequencies [152]. Not to mention the cutoff zone between 1.5 and 2.5 kHz where threshold of localisation accuracy reports local maximum, i.e. non of both interaural cues can be interfered efficiently to localise sounds inside this cutoff [81]. However, as already mentioned in the introduction of this thesis, binaural cues are the main cues for spatial perception that aids orientation, communication in noisy environments and discrimination of multiple sound sources. These skills are significantly reduced after hearing impairment, due to a deficit in the basic parameters of auditory processing consequently

leading to the alteration of symmetrical spatial analyses of a sound [153].

Two important aspects of auditory spatial processing have been studied intensively: localisation accuracy, that is often evaluated via sound source identification task i.e. absolute localisation task [154] and spatial discrimination i.e. the ability to detect differences or deviations in spatial locations of two neighbouring sounds, usually measured using a paradigm called the Minimal Audible Angle (MAA) [77].

The existing studies on spatial hearing skills does not always report behavioral measures that are reliable to perceptual categories, especially the ones conducted in children [153]. For instance the identification of source location is a term that have been used alternately in some studies employing absolute localisation tasks and not MAAs, like studies evaluating left right discrimination without a reference stimulus position [155]. However, recent researches agreed that absolute localisation and spatial discrimination (MAA) are two distinct tasks that are also processed at different stages of the auditory pathways [150].

Despite the distinct processing pathways, absolute localisation and spatial discrimination possess a possible interrelation since the noticeable change in the perception of a specific sound source location may represent the basics of spatial discrimination. However, studies on human and animal models showed that a precise acoustic discrimination with very low MAA values cannot always be an indicator of high absolute localisation performances and vice versa [95, 156]. Therefore assessing both phenomenons of spatial hearing (absolute localisation and discrimination) will help in understanding the development of sensory performances that takes place on a cortical level especially the assessments after the alteration of binaural cues in the case of UHL.

In the case of sensorineural hearing loss the ability to detect these differences is affected, causing a deficit in the perception and the analysis of the frequency and temporal features of a specific sound [157]. One of the first evaluation of sound source perception in monaural listening conditions was attempted by Olfield and Parker in 1986, where they fitted NHS with a monaural ear plug. The ear plug consequently led to a lateralisation of the responses towards the side of the unplugged ear. Olfield and Parker called this phenomenon ‘effective compression of auditory space onto the side of the unoccluded ear’ [124]. Later on, Butler

and colleagues reported an error increase in the azimuth due to the monaural experience [87]. These studies used stimulus locations that were only located in the hearing hemisphere. On the other hand, Middelbrooks showed a significant increase of localisation errors that was even more conspicuous when stimuli were presented on the occluded side of the ear. This lateralisation observed in both cases (occluded and non occluded sides) is mainly due to the alteration of interaural balance of time and intensity after the intervention of a unilateral ear plug [8].

Despite several evidence reported in the literature showing a decrease in spatial hearing after hearing impairment, some benefits of this integration seem to be well preserved in patients diagnosed with symmetrical hearing loss or BHL [158]. Noble and Gatehouse [151] showed that participants suffering from BHL had better spatial location performances and spatial discrimination abilities when they were compared to patients with asymmetrical or unilateral hearing loss.

However, in 1993 Middlebrooks proved that some patients with monaural deafness were able to demonstrate high performances in spatial localisation that were more accurate than NHS in monaural listening condition [159], these findings are an important behavioral evidence of the presumed compensational strategies that takes place after UHL, probably related to reorganisation at cortical and sub-cortical levels. Auditory spatial performance seem to evolve after UHL due to the adaptational spatial mechanisms that compensate altered binaural integration.

The alteration of binaural integration in UHL cases does not only influence spatial auditory performances. Binaural effects are also important for speech comprehension in noisy environments. Speech perception is established due to three main effects: the binaural summation, the release from masking also known as Squelch effect and the head shadow effect. In addition to their extensive role in spatial localisation, the integration of ITD and ILD cues is also essential for segregating speech in diverse hearing environments or "Cocktail Party".

The access to ILDs and ITDs is disrupted in patients with UHL, consequently, binaural advantages for speech recognition in the presence of competing noise are also altered. Monaural listening conditions, especially in early auditory development, can result in slower speech and

language development, educational deficit and social and behavioral changes that could affect the listeners life quality. A study conducted by Vannson in 2015 [160] aimed to correlate Speech Reception Thresholds (SRT) and quality of life in patients with acquired UHL. Vannson suggested that the level of recognition of a speech that is spatially separated from the noise have an important impact on the quality of life, reporting a reduced quality of life in patients with UHL with higher PTA thresholds in the deaf ear.

Nonetheless, clinical PTA thresholds, used to measure the level of hearing loss of a patient are not sensitive enough to predict SNR loss especially in environments with competing noise [161]. Patients with UHL present difficulties in segregating speech in noisy environments, this requires higher SRTs for better speech understanding [162]. Thus, speech segregation performances does not seem to improve as effectively as spatial auditory performances after UHL.

This chapter contains two main sections:

The first section will focus on behavioral observations by measuring the absolute localisation performance for NHS, UHL and BHL groups and correlate the obtained measures with the PTA thresholds of the patients groups. In addition, we will be evaluating speech recognition performances in different noisy conditions. The aim of this study is to find a relationship between absolute localisation performance using localisation task and level of hearing loss using pure tone audiometry, in addition to the evaluation of the interrelation between the spatial perception and the speech in noise segregation using the French Matrix test.

The second section will evaluate sound source discrimination abilities, using different simulated spatial recordings of head related transfer functions. Spatial discrimination will be assessed by the MAA at different reference positions in the horizontal plane using headphones instead of a free field setup. In addition to the investigation of spatial discrimination, the aim of this experiment is to check the feasibility of such evaluation using simulated HRTF in headphones as a clinical alternative of a complex and time consuming free field design.

To resume, this chapter will evaluate the behavioral measures of different auditory spatial aspects (absolute localisation and spatial discrimination) in different auditory conditions:

Monaural, Binaural, UHL, BHL, in order to find a relationship between these different measures and our findings in the electrophysiological experiment, that will be discussed in the next chapter. We want to check whether the ERP that represents spatial change detection i.e. the MMN, can be used as a neural marker of plasticity and spatial adaptation in hearing impaired patients.

2.1 Sound source localisation and speech in noise perception.

The absolute localisation of a sound source include several binaural strategies that are affected in monaural conditions as demonstrated in patients with unilateral deafness. However, many studies were able to prove that the spatial localisation is possible even after the deprivation of normal binaural hearing and using a single ear [86]. In this section we will compare localisation errors of patients with UHL, with RMS errors of NHS in both binaural and monaural listening conditions.

We will conduct a simulation of the monaural hearing loss by occluding the entrance of the ear canal. We should note that plugs that have been used in the literature can produce 30 to 40 dB of attenuation. Therefore the stimulation of the occluded ear with a sound that is superior to 40 dB will not affect the temporal cues but will only alter the ILD cues. Plus it seems to be critical to conduct a spatial localisation test with sensational levels lower than 40 dB especially when these performances will be compared to a population of patients with variable hearing loss levels [86].

In 1986 Oldfield and Parker [124] tried to compare monaural localisation in 2 dimension: Vertical versus horizontal. The absolute error of monaural localisation in vertical space was only a few degrees greater than the binaural condition (3°), however, when it comes to horizontal spatial location the monaural absolute error increased up to about 20° to 30° after monaural plug. Such result confirms the contribution of ITDs and ILDs to horizontal localisation while monaural spectral shapes are the cues to resolve elevation localisation

[124].

Certainly, auditory system appears to favor binaural cues over spectral shape cues for azimuth localisation. Still, studies showed that single ear localisation in the azimuth can be achieved using monaural spectral cues. However, we should mention that in these studies the sound was presented from only a few of the many potential loudspeaker locations, and that the speaker locations were visible, which may affect the judgment of the listener. Therefore different aspects should be taken into consideration when building the experimental design of the sound localisation task.

The investigation of sound source localisation depends on many factors and different experimental designs. The free field investigations are able to evaluate the ability of the listener to identify the direction of the sound source. As already mentioned in previous chapters, ITDs are more sensitive to lower frequencies (below 1500 Hz), while ILDs are sensitive to higher frequencies. The frequency band of the sound used should be an indicator of the implication of one of these cues more than the other [163, 164].

In addition, accuracy in sound-source identification can also be affected by the characteristics of the testing environment, such as the loudspeaker array, the amount of separation between each speaker, the gating of the stimulus to be localized, and the noise conditions in the room. For example, the localisation accuracy with slow onset is found to be significantly higher in absorbent than in reverberant test rooms [165, 166]. In rooms with reflecting surfaces, pure tones with abrupt onsets or offsets are more easily localized than those with longer rise/decay times [167]. Performance may also be affected by the presence of background noise, depending on the signal-to-noise ratio and noise location relative to the speaker [168, 169].

It is very crucial to decide the accurate method for presenting a stimulus to a subject and to choose the convenient acquisition modality that can accurately reflect sound localisation abilities [170]. Therefore the experimental design and stimuli type selection, should be taken into consideration when evaluating every type of behavioral performances. When it comes to sound localisation performances, many investigations were conducted using different types of presentations of the stimuli and stimuli acquisition across many years, including, verbal

feedback response, drawing sound direction, pointing with a laser pointer, pointing with the nose, chest or finger or also responding using sophisticated computer interfaces.

We will describe the sound localisation and the speech in noise experiments conducted in the free field in different hearing condition. These experiments had different objectives:

- Compare absolute localisation errors and speech reception threshold variation between NHS in binaural condition and after the introduction of a 39 dB ear plug.
- Analyse localisation accuracies and speech intelligibility for patients with UHL and compare the results to NHS in monaural condition.
- Study the effect of symmetrical hearing loss on sound source localisation in the free field localisation task and compare it to normal and monaural hearing situations.

2.1.1 Materials and methods.

Subjects.

Three groups of participants took part in the behavioral study, 20 NHS (9 women, 11 men), 21 UHL (11 women, 9 men) and 14 BHL (9 women, 5 men). The NHS group underwent two conditions of testing, the first was a binaural condition with both ears intact. The second condition was a simulation of monaural situation using monaural ear plug of an attenuation of 36 db in addition to anti-noise headset on top of the ear with an attenuation of also 37 dB, the addition of both attenuation was around 39 dB. All participants underwent audiometric testing by measuring pure tone audiometric thresholds using a GN otometrics Madsen Itera 2 Audiometer and TDH-39 headphones at the octave frequencies ranging from 250 to 8000 Hz, results of the PTA in patients with UHL and BHL are presented in the figures 2.3 and 2.4. The study was approved by the ethics committee of the University Hospital of Toulouse Purpan.

The audiometric testing was conducted in an anechoic, sound attenuated room, NHS were rejected if they had a pure tone average threshold of more than 15 dB at one of the 6 frequencies. The audiometric testing revealed a pure tone average thresholds ranging between

40 dB and Cophosis in the poorer ear of patients with UHL, and an average of 40 dB of hearing loss for patients with BHL.

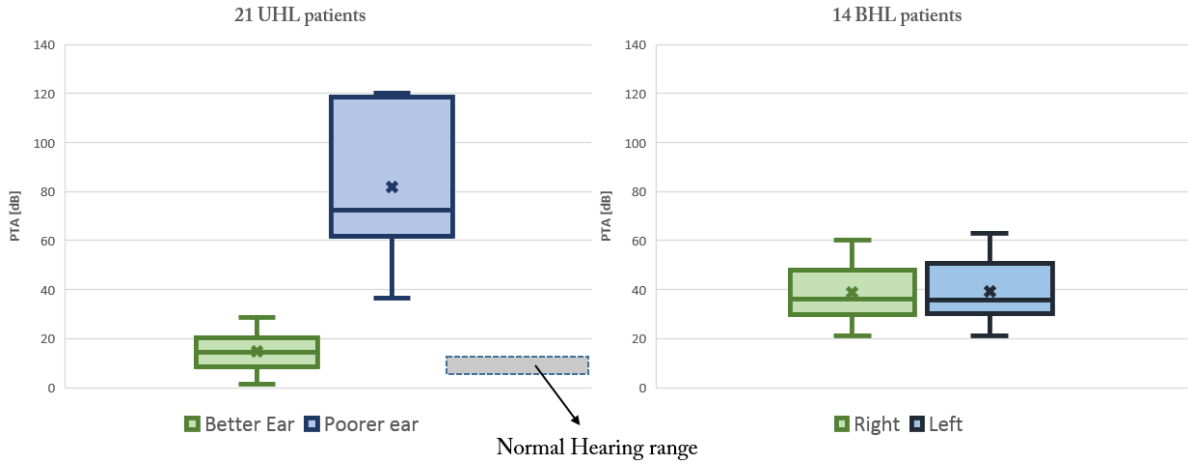


Figure 2.1: *Pure tone average thresholds for patients with UHL and patients with BHL, with normal PTA level equivalent to 10 dB in the NHS population.*

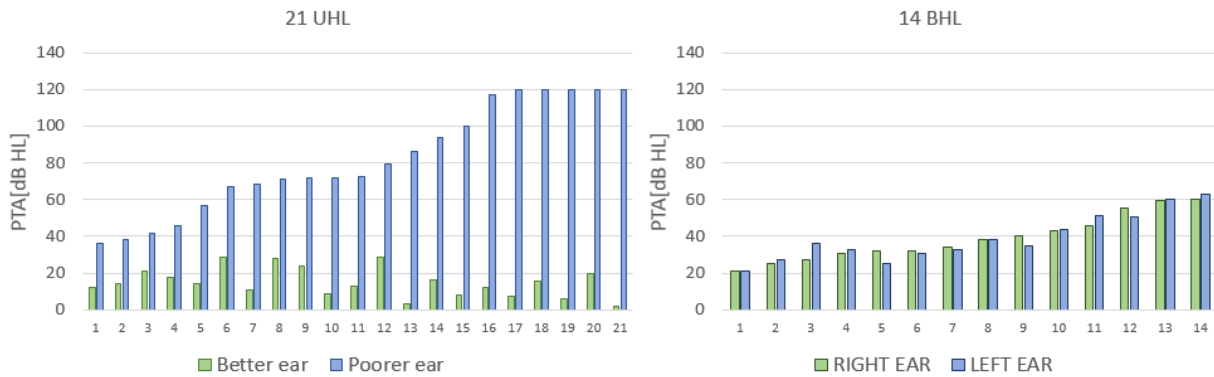


Figure 2.2: *Pure tone average thresholds for patients with BHL and UHL. Patients with UHL present normal hearing level in the hearing ear compared to the deaf ear. Patient with BHL had symmetrical hearing loss in right and left ears.*

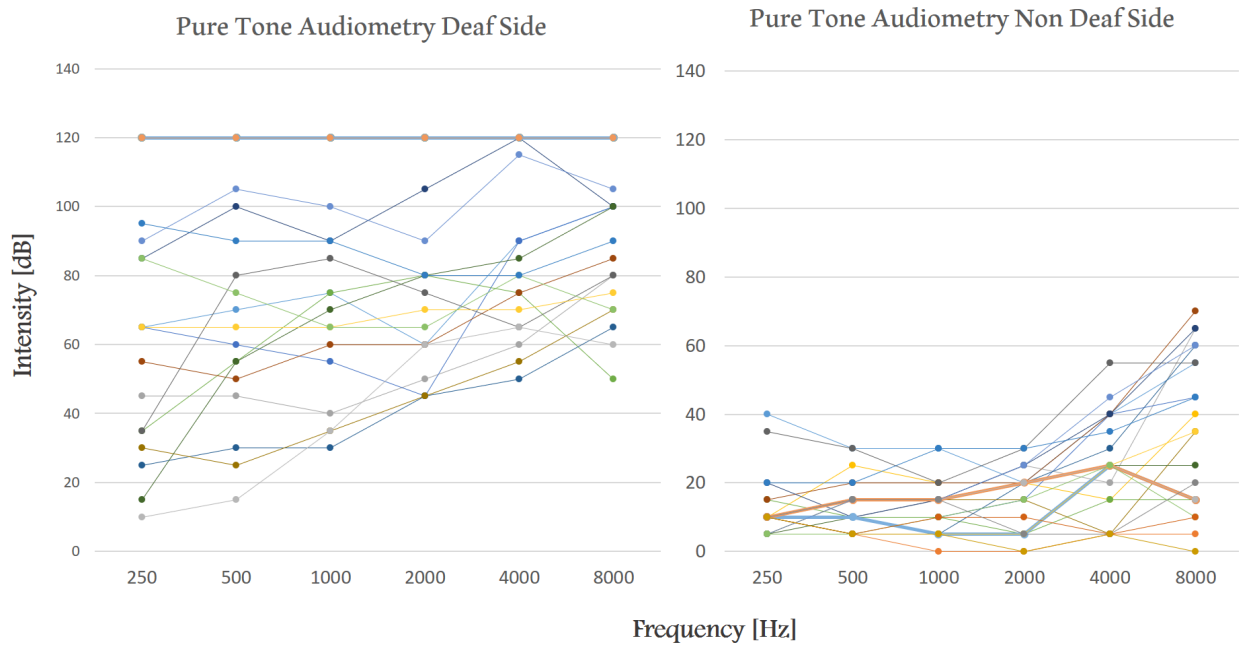


Figure 2.3: Pure tone average thresholds of 21 patients with UHL at the 6 frequencies from 250 Hz to 8000 Hz in the impaired ear and in the healthy ear.

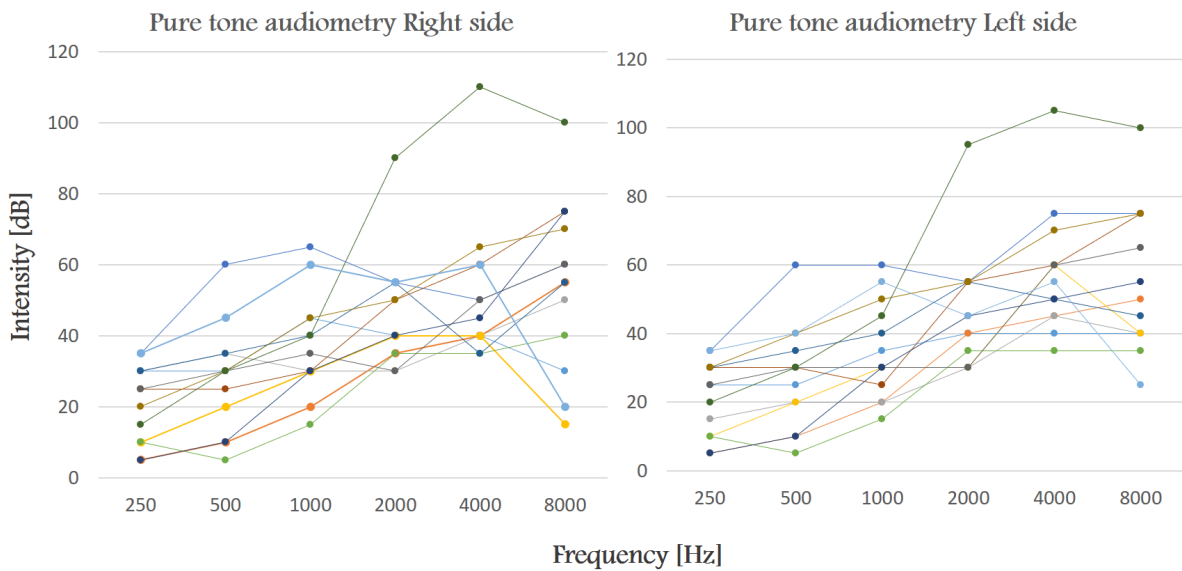


Figure 2.4: Pure tone average thresholds of 14 patients with BHL at the 6 frequencies from 250 Hz to 8000 Hz in the left and right ears.

Information about the age, sex, duration of deafness, PTA of each patient and SSQ score in

both UHL and BHL groups are represented in the tables below 2.1 and 2.2. It is important to note that the data in the table are organised according to the RMS score of the patients. DS: stands for Deaf Side, HS: stands for Hearing Side.

N	Age	Gender	Side	PTA-DS	PTA-HS	RMS	Duration	Etiology	SSQ
1	71	M	L	41.5	21	6.08	2014	Trauma	-
2	65	F	R	36.5	12	8.2	2004	Ch. otitis	3.9
3	63	F	R	46	17.5	15.2	2018	Unknown	-
4	37	M	L	67	28.5	17.8	2012	Trauma	1
5	69	M	R	65.5	14.5	21.1	2015	Unknown	5.3
6	57	F	L	100.5	8.5	21.5	2017	Ch. otitis	4.6
7	41	F	R	71	28	24.4	2018	Unknown	-
8	69	M	R	72.5	12.5	26.15	2019	Menier	9.75
9	40	F	L	72.5	9	27.2	2015	Unknown	3.66
10	25	M	L	68.8	11	28.05	2012	Cholesteatom	6.1
11	25	F	R	86	3.5	28.05	2006	Unknown	5.75
12	48	F	L	C	15.5	30.7	Cong	Cong	9.46
13	81	F	L	79.5	28.5	30.9	2018	Sudden	6
14	49	F	R	38	14.5	31.2	2017	Unknown	2.6
15	68	F	L	C	20.5	32.2	Cong	Sudden	5.41
16	35	M	R	C	7	37.8	2010	Unknown	6.37
17	67	F	R	93.8	16.3	40.3	2016	Unknown	3.1
18	25	M	R	C	1.5	62.5	2010	Trauma	6.16
19	67	M	L	72	32.5	60.6	2008	Unknown	5.08
20	44	M	R	C	6	44.2	Cong	Cong	3
21	57	F	L	C	12	79.8	Cong	Cong	1.6
Mean(SD)				82.2 (29)	14.7 (8)	32.1 (18)			5 (2)

Table 2.1: Demographic information of the 21 patients with UHL. PTA-DS: Pure tone audiometry in the deaf side. PTA-HS: Pure tone audiometry in the healthy side. RMS: Root mean square errors. SSQ: Speech, Spatial and Quality of hearing scale, "C" stands for cophosis.

N	Age	Gender	PTA-R	PTA-L	RMS	Duration	SSQ
1	68	F	22.5	21	11.8	2014	7.25
2	32	M	55.5	50.5	12.2	2013	4
3	82	F	30.5	32.5	13.6	2017	8.9
4	59	F	34	33.5	14.6	2010	5.9
5	54	M	32	31	15.2	2016	6.32
6	58	F	40	35	17.2	2016	4.16
7	70	F	60	63	17.5	2008	4.91
8	62	M	27	36.5	17.8	2016	6.83
9	50	F	43	43.5	24.2	2003	3.91
10	68	F	59.5	60	32.8	2003	4.55
11	77	F	45.5	51.5	34.4	2015	5.9
12	67	F	24.5	27.5	34.4	2016	8.03
13	80	F	38	38.5	63.9	2019	7.25
14	69	F	32	25.5	-	2014	3.08
Mean(SD)			38.8(12.5)	39.2(12.7)	20(10)		5.7(1.7)

Table 2.2: *Demographic information of the 14 patients with BHL. PTA-R: Pure tone audiometry in the right ear. PTA-L: Pure tone audiometry in the left ear. RMS: Root mean square errors. SSQ: Speech, Spatial and Quality of hearing scale.*

Experimental Design of sound localisation task.

The experimental setup of sound localisation task consisted of 12 loudspeaker distributed in a semicircular array, with a separation of 15° between each speaker. Participants were seated in the center of the semi circular array of a 1m radius, with a tablet in their hands. The tablet showed an image of the 12 loudspeaker in the semicircle and participants were instructed to point/select the speaker position that corresponded to the sound location detected. One of the main difficulties in this experiment was to eliminate any visual cue that the participant can rely on, however, it was not practical to put a computer screen in the front of the participant to report his answer since we did not want objects to interfere between the sound waves coming from the speakers toward the subject’s ears. The optimal solution was to use Prism glasses, that permitted to reflect the screen of the tablet as shown in the figure

2.5.a. The only visual feedback that participants were able to perceive was the presentation of the 12 speaker arrays on the 2 dimensional tablet screen, the glasses were beneficial not only for masking any other visual environment but also to prevent the participants from bending his head to look at the screen and report the answer.

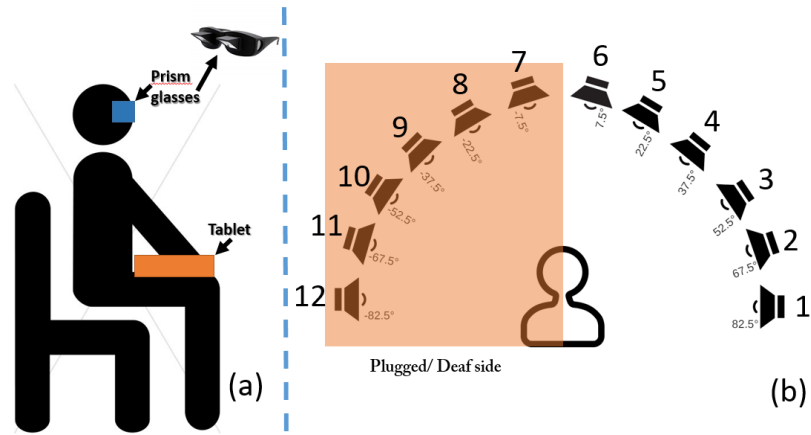


Figure 2.5: *Experimental design and speaker positions. (a) Subject seated on a chair in the center of the room wearing prism glasses with a tablet for sound source pointing. (b) Semi circular speaker array of 12 loudspeakers with 15° of separation.*

The speaker distribution was from 1 to 12 as illustrated in the figure 2.5.b. The first speaker corresponded to the position 82.5°, representing the first position tested from the side of the non-plugged/non-deaf ear for the monaural condition. The central azimuth is considered to be the 0° in front of the subject. The masked side (plugged/deaf), was designated in this study, by the negative angles from the 7th to the 12th speaker (-7.5° to -82.5°).

Acoustic Stimulation and repetition.

The sound used was a low frequency Gaussian noise burst band pass filtered between 300 and 1200 Hz. The reason behind the selection of this particular band noise was to be compatible with the EEG study (upcoming Chapter).

Before the task, participants underwent a training session where they were instructed to listen to the stimulation displacing in the 12 speakers with a feedback on their tablet to familiarize them with the stimulus position. The subjects listened to one preview that

contained one back and forth sound displacement among the 12 speakers. Participants were asked to listen carefully to the stimulation and report its position by pressing on one of the 12 loudspeakers illustrated on the tablet. Twenty four simulations were randomly played among the 12 azimuth positions, with the occurrence of two simulations per position. The end of the 24th answer marked the end of the experiment.

Computation of the absolute errors:

A response error is the difference between the angle reported by the participant in the task and the actual localisation of the stimulus.

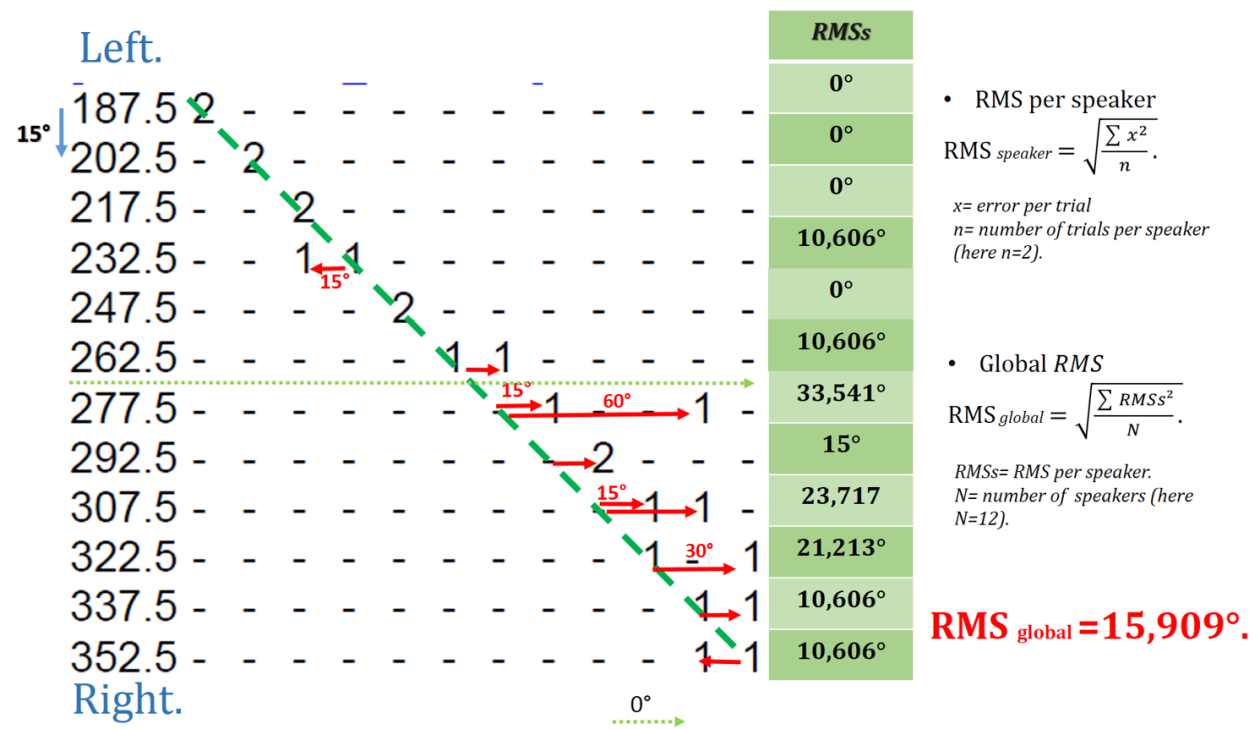


Figure 2.6: Example of single speaker RMS and global RMS calculation for one subject. RMS per speaker is the Root Mean Square Error of the errors at each position. Global RMS is the Root Mean Square Error of the RMS per speaker among the 12 speakers.

In the figure above we give an example of how the RMS is calculated in a NHS subject. The RMS at a single position for a single subject is designated by the root of sum squared errors of each trial, divided by the total number of trials (st a single position). The global RMS is designated by the root of the sum squared RMS at each position divided by 12. The absolute

error of the group was obtained by averaging the all individual RMS of each subject.

Experimental Design of the french matrix test.

The Fr Matrix is a test that aims to evaluate the ability of a participant to understand specific words in variable noise levels and noise directions. It contains 50 words that are selected based on their phonetic content, representing the phonetic distribution of the French Language. The 50 words are divided as follow: 10 names, 10 verbs, 10 numeral, 10 object and 10 colors [171].

	<i>Name</i>	<i>Verb</i>	<i>Numeral</i>	<i>Object</i>	<i>Color</i>
1	Agnès	achète	deux	anneaux	blancs
2	Charlotte	attrape	trois	ballons	bleus
3	Emile	demande	cinq	classeurs	bruns
4	Etienne	déplace	six	crayons	gris
5	Eugène	dessine	sept	jetons	jaunes
6	Félix	propose	huit	livres	mauves
7	Jean-Luc	ramasse	neuf	pions	noirs
8	Julien	ramène	onze	piquets	roses
9	Michel	reprend	douze	rubans	rouges
10	Sophie	voudrait	quinze	vélos	verts

Figure 2.7: The Fr Matrix 50 words set.

A five word sentence is sufficient to prevent repetitions of sentences during the experiment. Therefore, to avoid memory based responses. An IBM PC running the Oldenburg Measurement Application software and a high quality 24 bit sound card were used (www. ho- orteck.de) to generate the sentences via loudspeakers and amplifier (Studio Lab, SLB sat 200). The speech level was fixed at 65 dB SPL and remained unchanged during the whole experiment. The competing noise varied following the adaptive procedure suggested by Jansen et al. to obtain the SNR for 50 correct word recognition (SNR50) [171].

The subject was instructed to listen carefully to the sentence by keeping the head straight and to repeated the words that he was able to perceive. The experimenter note on the PC,

the recognisable words by the participant. The noise level of the next trial changed according to the number of recognised words in the previous trial. The speech and noise were presented in three different conditions in a sound attenuated room. In each condition participant had to repeat a list of 20 sentences.

Room Setup:

The test was conducted in a sound attenuated room in the university hospital of Purpan. Three loudspeakers were placed at the following three positions -60° , 0° and 60° at a distance of 1.30 m from the center of the room with an elevation of 1.12 m from the floor. The participant was seated in the center of the room facing the central loudspeaker. The spatial positioning of the speakers at the respective angles -60° , 0° and 60° is conducted by previous studies suggesting that these positions aided in reducing the head shadow effect compared to more peripheral positions ($\pm 90^\circ$) in addition to the maximisation of the binaural squelch effect [172]. This configuration is able to create different SNRs at the left and the right ear of the participant when noise and speech are separated in one speaker each inducing a benefit of about 8 dB at the ear receiving a speech and a loss of 8 dB at the ear receiving the noise, leading to an attentional shift towards the speaker emitting the higher SNR [172].

Conditions description:

The three conditions varied in the speaker position of the emitted speech and noise in order to test the implication of 3 binaural effects: binaural summation, head shadow and the Squelch effect.

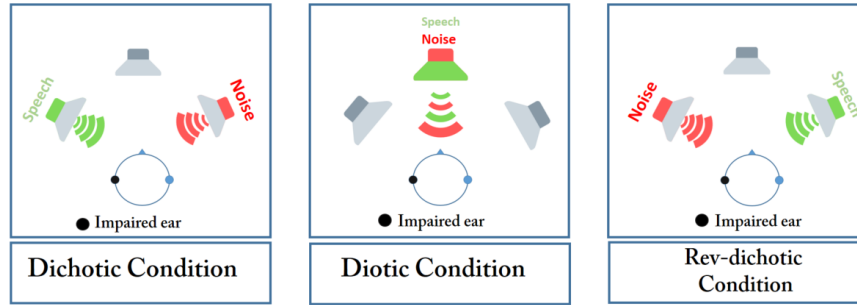


Figure 2.8: *The 3 conditions of FR Matrix testing procedure. Dichotic condition, speech is emitted towards the impaired ear. Diotic condition, speech is emitted with the noise from the central speaker. Reversed dichotic condition, speech is emitted towards the better ear.*

Condition 1, the dichotic condition: The sentence and the noise were dissociated, the noise was emitted from the loudspeaker ipsilateral to the healthy ear. The speech was emitted from the loudspeaker ipsilateral to the deaf ear. This condition evaluates the head shadow effect in addition to the Squelch effect.

Condition 2, the diotic condition: The speech and noise were both emitted from the same central speaker. This condition evaluated the binaural summation effect.

Condition 3, the reversed dichotic condition: The speech and noise were dissociated, the noise was emitted from the loudspeaker ipsilateral to the deaf ear. The sentence was emitted from the loudspeaker ipsilateral to the healthy ear. This condition evaluated the same effects as the first condition.

Data analyses

Different modalities of analysis were applied on the acquired data. First we analysed the variation of sound localisation performances among the three groups. Then we divided the UHL population according to their PTA to moderate and severe UHL in order to check the variation of performances accordingly and to test the impact of hearing loss on spatial performances and speech in noise performance.

Statistical analysis:

Due to the abnormal distribution of the data, the analysis of sound localisation and speech

in noise performances were conducted using a non parametric repeated measure design in R using the LMe4 package as an alternative of the ANOVA repeated measure, followed by post-hoc comparisons between group means.

We conducted a comparison between the different groups according to the global RMS in addition to the interaction between the group and the absolute error obtained. The same repeated measure design was applied on the data per position per group, followed by a post-hoc comparison to check for differences between group means.

2.1.2 Results.

Global group RMS comparison :

The repeated measure design applied for the group comparison with two factors (group and speaker position). The analysis revealed an effect of the group ($p < 0,001$) and the speaker position ($p < 0,001$), in addition to an interaction between group and position ($p < 0,001$). The NHS were consistently accurate in localisation at all position with a maximum error of 17° . Their averaged average RMS error was equal to $13,4^\circ$. After the introduction of the ear plug, the average RMS error significantly increased of about 20° , reporting a global error equal to $33,3^\circ$ ($p < 0,001$).

The average RMS errors of UHL group was equal to $27,2^\circ$ and almost 5° less than the errors for NHS with ear plug despite the average hearing loss of the UHL population (81,8 dB) that is approximately two times superior to the plug attenuation (39 dB). Patients with BHL who had an average symmetrical hearing loss of (39 dB), showed near normal localisation errors, with an average RMS equal to $15,4^\circ$, only 3° larger than errors in NHS. The $15,4^\circ$ errors can suggest that the maximum error deviation reported by patients with BHL was of only one speaker.

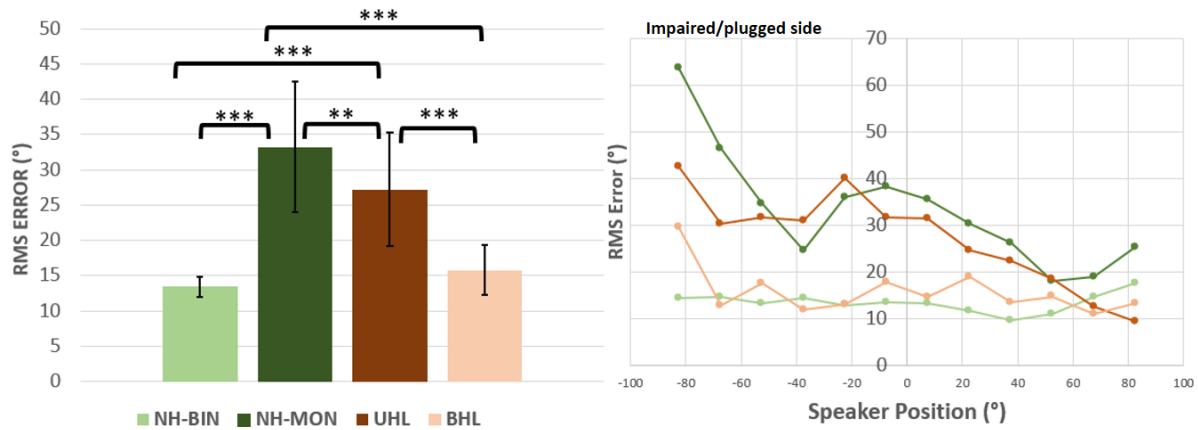


Figure 2.9: *Right: Histogrammes presenting the average and the standard deviation of the global RMS errors for the 4 groups. Left: Average RMS error at each azimuthal position for the 12 positions in the 4 groups.*

Variation of RMS with the azimuth location:

The post-hoc comparison was also conducted between speaker positions for each group. The average RMS of NHS did not show any significant variation among the 12 positions in the azimuth. However, after the occlusion of one ear, the errors significantly increased at the side of the plugged ear. The increase of the errors was progressive with respect to the deviation from the side of the unoccluded ear. This linear increase is an evidence of the lateralisation of the answers towards the direction the unplugged field. The highest localisation errors were reported at the peripheral sides of the plugged ear.

Patients with UHL had smaller localisation errors compared to NHS in monaural condition (in the positions 1,2,4,5,6,7,10,11,12), especially at the peripheral position of the better ear. At this side, they reported the smallest localisation error of 9.5° at 82.5° compared to NHS (13.4°), BHL (17.6°) and NHS-mon (25.4°). Similarly to the group analysis, BHL patient showed near NHS performances with no variation of localisation errors among azimuthal positions.

RMS distribution according to PTA:

Given the inter individual variability of sound localisation errors in the 21 patients with UHL, it was interesting to check if the pure audiometry can be a reliable tool that can explain this behavioral change in sound localisation. The UHL group of 21 patients was divided according to the median PTA in the poorer ear obtained across the 21 subjects. The median PTA found in the poorer ear of our UHL population was equal to 72.5 dB. Therefore, UHL group was divided between patients with mild to moderate UHL who had PTA threshold in the poorer ear that were inferior to 72.5 and patients with severe UHL, with PTAs superior to the group median.

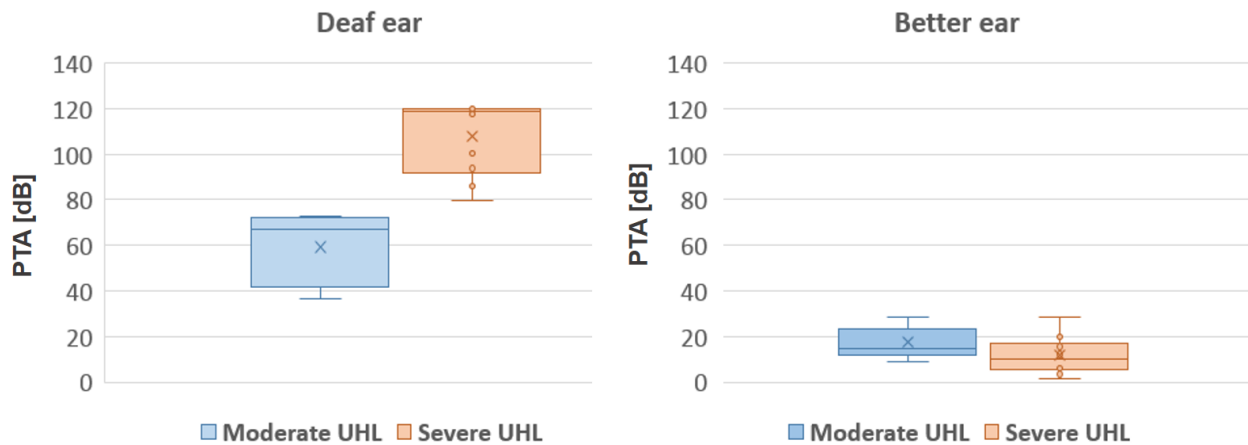


Figure 2.10: *Pure tone average thresholds after the division of the UHL group according to the median with a cutoff of 72 dB in the deaf ear. Patients with a PTA inferior to 72 dB were considered as moderate UHL, patients with a PTA superior to 72 dB were considered as severe UHL.*

As the box plots show, the UHL population was divided into 11 mild to moderate UHL with an average PTA of 59 dB in the deaf ear and 10 severe UHL with an average PTA of 107 dB. It is also important to note that for computational purposes we considered 120 dB the level of hearing loss for patients presenting a Cochlosclerosis. The mild to moderate UHL group, had 5 left deafness, 6 right deafness, while the severe UHL group had 5 left deafness and 5

right deafness.

The repeated measure design was applied using the lme4 package in R for the comparison between the 4 groups: NHS, NHS-MON, Mild to moderate UHL and severe UHL. The analyses was followed by a post-hoc comparison between groups means. To further examine the relationship between pure tone audiometry and localisation errors Pearson's ranks correlation was applied on the individual RMS of patients with UHL versus (VS) the differential PTA level between both ears (delta PTA) and the correlation between the PTA at the deaf ear versus the RMS only at the 6 positions ipsilateral to the deaf ear (RMS AVERAGED).

The results for the localisation performances are illustrated in the figure below. In the previous experiment we showed that patients with UHL had better performances compared to NHS with acute monaural plug. After the division of the UHL population between mild to moderate and severe deafness, new interesting result is obtained concerning the spatial capacities of those patients.

The repeated measure design applied on the data showed a group effect ($p < 0,001$), a position effect ($p < 0,001$) and interaction between group and position ($p < 0,001$). After the division according to PTA, the moderate UHL group showed smaller average RMS errors (19°) compared to the severe group (36°) and to NHS in monaural condition (33°). However the difference between NHS and patients with mild to moderate UHL is still presents, with 6° higher errors for moderate UHL compared to NHS. It is important to note that mild to moderate UHL had better accuracies than patients with severe UHL, with an average RMS error increasing from 19° in moderate UHL to 36° for severe UHL. Thus, the 17° difference between moderate and severe UHL is an evidence of the hearing loss impact on the auditory spatial capacities of the patients.

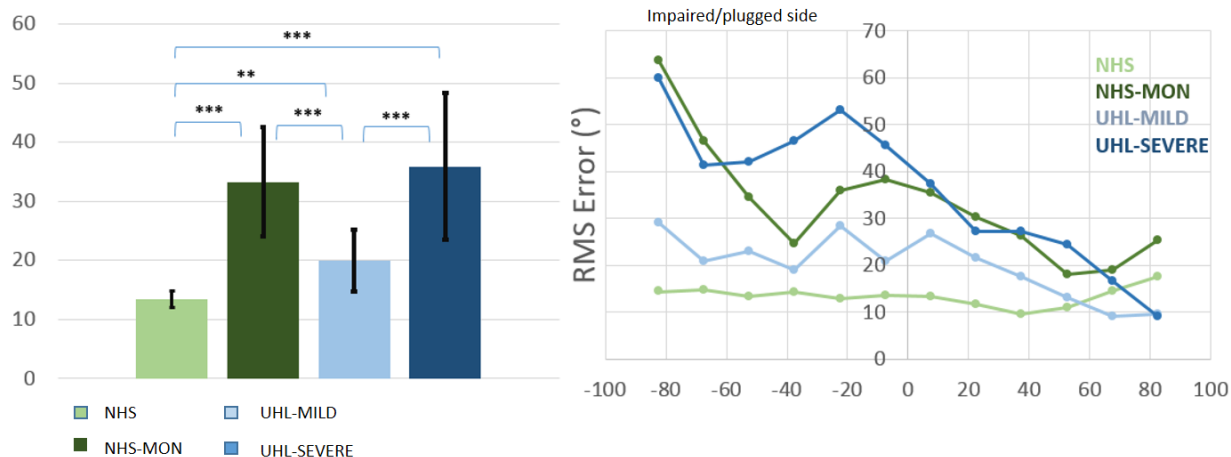


Figure 2.11: *Right: Histogrammes presenting the average and the standard deviation of the global RMS errors for the new 4 groups. Left: Average RMS error at each azimuthal position for the 12 positions in the new 4 groups.*

We also conducted a post hoc comparison between the group means at each of the 12 positions in the azimuth. We didn't find any significant differences between RMS scores at the peripheral position speaker position from the side of the unplugged/non impaired field. However errors started to progressively increase with the deviation towards the plugged/impaired field for the 3 populations: severe and moderate UHL and Monaural NHS. The increase of the errors began to be significant starting position 4 ($37,5^\circ$), between NHS-MON and NH-BIN only, this difference remained significant at position 5 ($22,5^\circ$). When the sound reached position 6 ($7,5^\circ$) another significant result appeared between NHS-BIN and patients with severe UHL. These significant differences increased progressively at position 7 ($-7,5^\circ$) in addition to differences between NHS-MON and moderate UHL ($p < 0,05$). These differences were progressively increasing until position 12 ($-82,5^\circ$), where they reached the highest differences between NHS-BIN and NH-mon ($p < 0,001$), NH-BIN and severe UHL ($p < 0,001$), NHS-MON and moderate UHL ($p < 0,001$) and between moderate and severe UHL ($p < 0,001$).

Furthermore, after the observation of data variation prior to the group division, we decided to test the correlation between the RMS errors at the masked hemifield and the PTA in the deaf ear of the 21 patients with UHL. The RMS error of the subject at the masked

hemifield was calculated by averaging the RMS of the 6 positions from the midline towards the periphery of the deaf ear. We also checked for a possible relationship between the patients behavioral localisation and life quality by correlating average RMS to SSQ scores. The data of the different correlations are presented in the figure below.

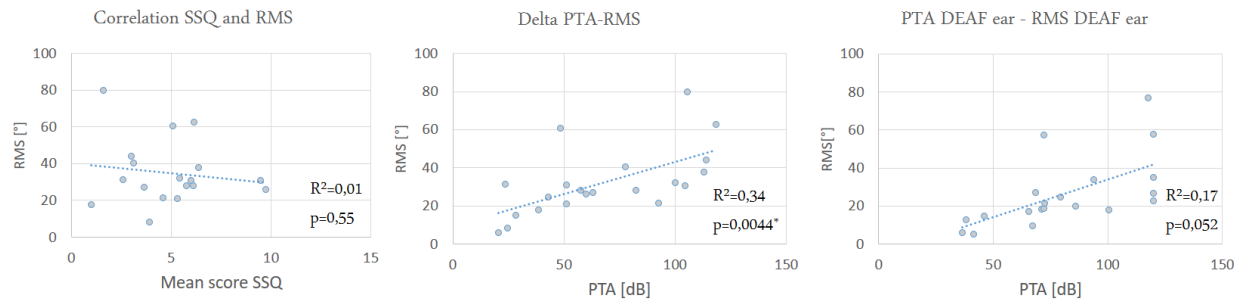


Figure 2.12: *Right: Correlation between the score of SSQ and the global localisation errors (RMS), Middle: Correlation between the hearing loss asymmetry (Delta PTA) and the global localisation errors (RMS), Left: Correlation between the hearing loss level in the deaf ear (PTA deaf ear) and the localisation errors from the side of the deaf ear (RMS deaf ear).*

Pearson correlation coefficient revealed a positive linear relationship between Delta-PTA and average RMS, but no correlation was found between the PTA and the average RMS in the deaf ear, thus, no correlation was found between average RMS scores and SSQ individual average.

Results of the Speech in Noise (SPIN) evaluation.

The linear model showed a strong effect of the group and the condition ($p<0,001$), and an interaction between them ($p<0,001$).

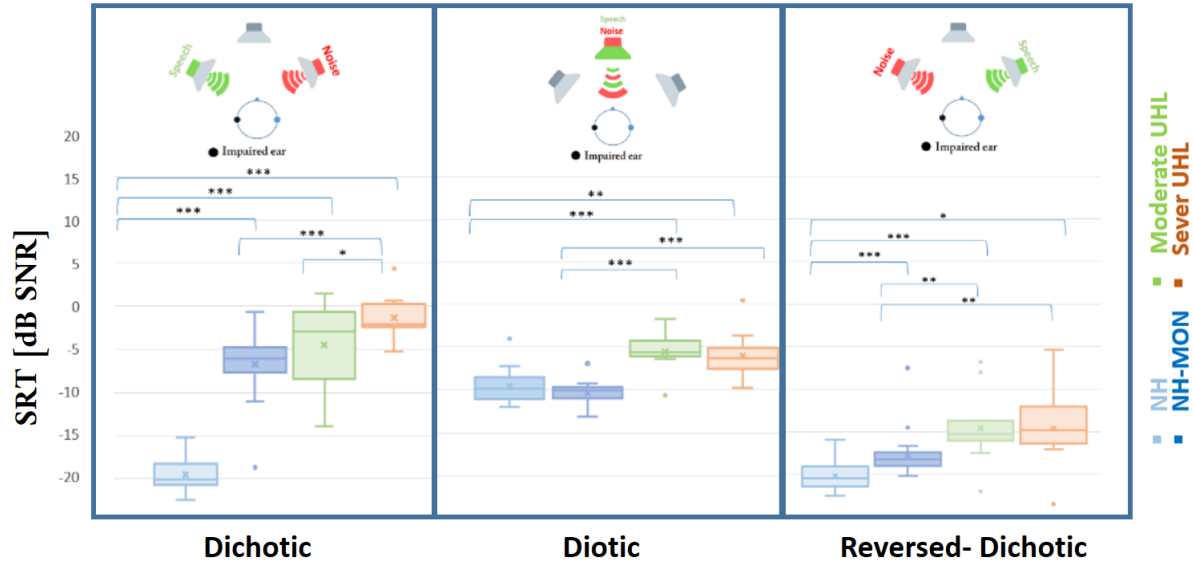


Figure 2.13: *Speech Reception Thresholds of NHS in binaural and monaural conditions and patients with mild to moderate unilateral hearing loss in the three stimulation conditions: Dichotic, Diotic and Revesed Dichotic.*

In the dichotic condition, speech was emitted at the ipsilateral side of the impaired/plugged ear. We observed different speech reception thresholds between the groups. NHS in binaural condition had better abilities to understand speech compared to the three other groups since no ear plug is introduced. patients with UHL and NHS with ear plug showed poorer abilities to subtract the sentence from the noise. However, patients with mild to moderate UHL showed better SRT compared to patients with severe UHL ($p < 0,05$).

In the diotic condition, the speech and the noise both emitted from the same central loud-speaker. When the sound and noise are combined the ability of NHS to understand was poorer than the condition where both speech and noise were emitted separately. However, the SRT decreased for the other 3 groups compared to the previous condition due to the deviation of the speech to the central position rather than the side of the plugged ear. NHS (bin and mon) showed smaller SRTs than both UHL groups with no significant difference between severe and moderate UHL.

When the speech was emitted in the ipsilateral side of the unimpaired/unplugged ear, we

noticed a decrease in the SRT for the 4 groups. However the differences between NHS and UHL were still present, in addition to the difference between NH-BIN and NH-MON.

2.1.3 Discussion of the section:

This study provides further evidence about spatial localisation performances on different levels. First, we elaborated the variation of localisation performances in monaural *simulated or impaired* situations. We also investigated the impact of altered binaural cues on the strategies adapted by the subjects to localise sounds. Second, we stepped further in the nature of the relationship between pure tone audiometry and localisation errors, and the possible adaptational mechanisms that are involved in spatial perception after hearing loss. Third, we explored the variation of speech intelligibility performances for each group according to the stimulation condition.

a- Relationship between spatial performances and pure tone audiometry.

It is known that some patients with UHL may partially compensate unilateral deficit by improving the use of their monaural cues, however, there is no clear evidence about the relationship between the severity of the unilateral deficit and the extent of intervention of the spectral shape cues that mainly depend on the head and pinna dimensions [104]. Thus, patients with UHL are able to learn how to lateralise sounds by detecting the sounds perceived louder when it is coming from the hearing side, this strategy does not only depend on the hearing level of the better ear, but also on the asymmetry of hearing level between both ears (delta PTA), that was found to be correlated in our case. Nonetheless, we found lower average RMS scores in patients with mild to moderate UHL compared to NH-mon despite their average hearing loss (60 dB), that was higher compared to the plug used. The better precision in patients with mild to moderate UHL compared to NHS-mon is an evidence of the occurrence of spatial adaptation, especially in this study where patients with UHL were older than our NHS group (NHS, age range between 19-30 years old/ UHL, age range between 35-71 years old).

The importance of delta PTA or hearing symmetry seem to be an important issue in spatial auditory perception. In the first section of this chapter, symmetrical hearing loss patients (BHL) reported near normal localisation errors despite the level of the hearing loss (39 dB). This disruption of the access to ILD and ITD in the UHL can be a function of the severity of the case. However, a study conducted by Byrne and Noble [173] aimed to assess sound localisation abilities of symmetrical hearing loss patients by dividing them into two groups according to their PTA. Patients with BHL who had hearing loss inferior to 50 dB rated their localisation to be poorer than NHS, while patients who had higher hearing loss levels (50 dB), reported poorer localisation abilities compared to the moderate BHL. This study confirmed that the degree of localisation difficulty is also related to the severity of the hearing loss, concluding that the binaural asymmetry is not the only detrimental factor.

The effects of hearing loss on localisation differs also between horizontal and vertical space. Localisation abilities in the azimuth deteriorates with the increase of the hearing loss at frequencies below 1500 Hz. The studies conducted by Noble et al. in 1994 showed a correlation between horizontal localisation and hearing level at 500 Hz and 1000 Hz [174, 175]. The findings of Noble are therefore consistent with the theory that low frequencies are more important in detecting ITD cues and that higher frequencies ranging from 1500 to 4000 Hz are more important for detecting ILD cues. Noble also concluded that for patients with mild to moderate sensorineural hearing loss (less than 50 dB), horizontal localisation seem to be slightly impaired, while more severe hearing loss (superior to 50 dB) leads to greater spatial localisation disruption. These findings are consistent with our results, where patients with mild to moderate UHL presented less average RMS errors compared to severe UHL. On the other hand, patients with BHL who had an average hearing loss of 39 dB did not suffer from an alteration of their localisation abilities.

The etiologies of hearing loss are also variable especially in the UHL group, and the PTA did not vary accordingly. Thus we did not find a correlation between average RMS scores and age or duration of deafness. In our investigation, the delta PTA was the only factor that is affecting the average RMS compared to other factors such as age, duration of hearing, and etiologies.

b- Relationship between speech recognition and pure tone audiometry.

This study also tried to observe the variation of SRT according in each group division. The diotic condition reflects the binaural summation effect, it is clear that patients with UHL were unable to process the combined speech and noise properly in this condition, however, this reduction in the performances was not present in the monaural NHS who showed normal SRTs. In addition, the ability to extract speech from noise, in this position did not vary according to the PTA of the patients where the SRTs of both severe and moderate UHL were similar.

The reason NHS-mon were better in recognising speech in noise compared to patients with UHL - which was contradictory with what we found in the localisation study - can be explained in two ways: first, the monaural spectral cues are compensational cues used by patients with UHL to improve precision in spatial source detection, yet, it seems that these cues does not have the same implication in extracting speech from noise. Second, the ear plug used to simulate the monaural condition in NHS of 39 dB attenuation is able to suppress low frequencies such as the low frequency band noise that we used in the sound localisation experiment, however, it is not enough to mask higher frequencies, mainly frequencies that represents consonants, therefore, NHS in monaural condition were still able to perceive consonants with high frequencies in their plugged ear better than patients with UHL.

In the dichotic condition, where speech is ipsilateral to the impaired/plugged ear, patients showed inability to benefit from squelch effect to extract the speech. Thus, the head was a physical obstacle in front of the speech propagation towards the better ear. Yet, patients with mild to moderate UHL presented lower SRTs than severe UHL, this can be explained by the better ability for patients with less hearing loss in the deaf ear to separate the speech coming toward the deaf ear and masking the competing noise at the side of better ear. The results are consistent with the findings of Vannson 2017 [176] who observed a correlation between PTA and SNR50 obtained at the poorer ear proving that UHL subjects possess lower abilities to discriminate speech coming towards the deaf ear when the PTA is higher. The deficit of selecting speech from noise is less severe in the reversed dichotic condition,

where the speech is emitted towards the good ear. No difference between severe and mild to moderate UHL was found in this case. Thus, Vannson 2017, did not observe a relationship when PTA versus SNR50 were assessed alone [176].

A study conducted by Bronkhorst and Plomp (1989) tried to assess the relationship between PTA and SRT in quiet and in noise, they reported a correlation between SRT in quiet and PTA, but not for SRT in noise [177]. In our case, the only condition that can reflect the relationship between PTA and SRT is the dichotic condition, where the ability to understand speech emitted toward the deaf ear, depends on the level of hearing loss in this ear. In this specific case the PTA in the poorer ear can be predictive of the speech in noise difficulties, however these findings are not enough to conclude a relationship between SRT and average RMS errors despite the correlation found between PTA and average RMS in the previous section. Indeed, plastic reorganizations and more symmetrical activation are observed at the level of the auditory cortex after UHL [117, 178, 136]. Some patients with UHL seem to benefit more from monaural spectral cues for sound localisation but not for speech in noise segregation.

c- Spatial adaptation to monaural situations.

Although the contribution of monaural spectral cues to localisation in elevation is well documented [104, 8, 79], the role of these cues in horizontal localisation is more difficult to demonstrate. Consistent with previous studies, all of our control subjects, when rendered with monaural earplug, showed an increase in their localisation errors with a tendency to project localisation judgements towards the open ear (lateralisation), nonetheless, UHL had better localisation performances compared to simulated monaural hearing conditions despite the level of hearing loss (60 dB).

Middlebrooks reported the same behavior when NHS were fitted with a monaural earplug , corrupting the interaural cues. Subjects consistently displaced their responses towards the side of the hearing ear as a consequence of the binaural imbalance caused by the unilateral ear plug. This typical lateral displacement appeared to be less severe for patients with UHL who had monaural hearing for a more important amount of time. These results were also

found in fMRI studies on animal models with unilateral hearing loss, where results reported functional reorganisation at the cortical and subcortical levels [178].

Also studies have shown that the significant improve of spatial accuracies in some patients with UHL maybe due to different adaptational factors including : their ability to improve the utility of their spectral cues, their ability to distinguish between louder intensities coming from the hearing side and therefore facilitating their lateralisation. Nonetheless, these studies were mostly conducted on patients with congenital deafness in one ear, while our study examines listeners with with different etiologies of hearing loss (Only 4 patients had congenital unilateral deafness). To a better understanding of our behavioral observation it is important to explain the relationship between central plastic changes and the clinical presentations of spatial hearing impairment.

Therefore, in our discussion, we need to step further in the findings related to the compensatory strategies adapted by monaural listeners after binaural deprivation. First of all, when it comes to horizontal localisation, a series of observation conducted by Lord Rayleigh should be taken into account. Rayleigh accounted horizontal localisation in terms of ILD, by the amount of head shadowing that is strongly related to the wavelength of the sound and its interaction with the head dimensions. Concluding that at higher frequencies the shadow amounts to a difference of about 35 dB between two ears if a sound was coming from a source located at the side [8]. However, at lower frequencies possessing more important phases, that can be larger than head dimensions as computed by Rayleigh, the ILDs induced are negligible.

Rayleigh concluded that the sensitivity to phases declines progressively with higher frequencies, with an upper frequency of around 770 Hz in one of his experiments. In our case, the band noise used was filtered between 300 and 1200 Hz. We therefore suggest that the spatial information is mainly delivered from ITDs rather than ILDs. Thus, the contribution of monaural spectral shape cues seem to be effective in monaural listening for patients with UHL compared to NHS-mon, suggesting the spatial adaptation to monaural can be learned over time [8].

d- Cortical changes after hearing impairment.

In our population, patients with UHL, experienced binaural hearing in the past (except for 2 patients where the date of hearing loss onset in childhood is unclear), as a consequence of their unilateral deprivation, the central auditory pathways underwent related changes in the activation pattern even with late onset deafness. In fact, evidence from animal models of experimentally induced frequency specific hearing loss is responsible of changing the response properties of the neurons at both cortical and subcortical levels. Usually, due to the deprivation of normal peripheral input, the tonotopically organized areas of the auditory cortex often become responsive to intact adjacent frequencies [179], these changes in the activations of central auditory pathways are suggested to be more important when this modification of sensory experience is derived soon after birth [180].

In addition, experience related cortical and subcortical changes have also been reported in the adult brain of mammals including humans [181]. It is known that our central auditory system includes afferents that are cortically projected to the ipsilateral side of the stimulated ear as well as afferents that cross the midline at the brainstem level to be projected on the contralateral cortex. It is also known that the contralateral projections contains greater number of nerve fibers representing more direct pathways with fewer synapses to the cortex compared to the ipsilateral pathways [182]. This leads to stronger and lower activation thresholds in the contralateral auditory pathways after monaural stimulation. However this normally observed asymmetrical activation is altered after unilateral deafness. Animals with unilateral deafness have larger responses and lower activity thresholds in the ipsilateral hemisphere with minor activation in the contralateral side. These changes are observed at the subcortical level, at the auditory nuclei such as the inferior colliculus [183], as well as at the auditory cortex [184]. It have been suggested that the loss of inhibitory process can be an additional cause to the increase of ipsilateral activity [185].

In humans, cortical changes following unilateral hearing loss is consistent with the previous findings. After experimentally induced unilateral hearing in non mammals, MEG studies on adult onset profound hearing loss showed an increase in the ipsilateral cortical areas of the stimulated ear [186]. Scheffler in 1998 [118] compared the patterns of cortical activation

after unilateral deafness using fMRI concluding more symmetrical cortical activations for patients with UHL compared to NHS [118].

For the BHL group, auditory spatial performances are different. Despite their hearing loss, patients with BHL preserved the capacity of localising sounds almost as good as NHS-BIN. The findings were consistent with many studies that aimed to compare unilateral hearing aid fitting with bilateral fitting. Noble and Gatehouse showed better spatial abilities in sound localisation and discrimination for symmetrical hearing loss patients after bilateral hearing aid compared to unilateral hearing aid. Other studies also confirmed that bilateral aid fitting is expected to offer more advantages due to more balanced binaural hearing functions [173]. This substantial advantage is not occurred only for sound localisation, but for speech in noise segregation also [151].

🔑 Key points

- Increased localisation errors in NHS-mon after the introduction of an ear plug, errors were significantly higher than the ones reported by the 21 UHL patients.
- Patients with symmetrical hearing loss did not show significant increase of their localization errors compared to NHS.
- Speech in noise performances were different between severe and moderate UHL in dichotic condition only.
- Speech in noise performances were reduced in NHS after the introduction of an ear plug in dichotic and reversed dichotic conditions.

2.2 Sound source discrimination assessed using Minimal Audible Angles in headphones

During childhood, the sizes of head and body changes slowly causing a change in the head related transfer function (HRTF), that also influences ITD and ILD cues. These changes were observed in studies on developing ferrets. Reared ferrets showed spatial response fields in some neurons of the auditory cortex that were present due to modifications of filtering processes of the pinna and the body [187]. The auditory system of a growing ferret is continuously remapping the relation between binaural cues and spatial locations of sounds in his environment. This can also be called the re-calibration of acoustic space [187].

Spatial discrimination, is the ability of listeners to discriminate between two adjacent sound sources, it is measured using a paradigm known as the minimum audible angle. In 1958 Mills was the first to develop the MAA paradigm in order to evaluate and measure the sound localisation accuracy of human listeners. The MAA paradigm was used to investigate sound localisation in the horizontal plane [188] and also on the vertical plane [189].

The MAA paradigm involves two neighbouring sounds, the first sound is emitted from a standard position (STD) and the second sound (deviant (DEV)) is elicited from a neighbouring location or from the same location as the standard. In the MAA task participants are asked to listen to both consecutive sounds (STD and DEV), and judge whether the second sound is coming from the same position as the standard or from a different position. This method is mainly used to compare localisation accuracies at different positions in the azimuth, as a tool to evaluate the spatial resolution among the acoustic space.

Sound source discrimination was examined in details by Heffner starting 1973, who studied the hearing and sound localisation abilities of animals, especially mammals. Heffner originally assumed that the animals are usually exposed to a selective pressure to accurately localize sounds, that depends on the sound localisation cues mainly generated by their head and pinna. Heffner was able to show that spatial discrimination appears to improve with respect to the functional head size, with a MAA of 1° to 2° for humans and elephants, 5° for cats, and 12° for Norway rats [190].

However, Heffner found later on that MAA is much larger for horses and cattle (25° and 30°), concluding that a large functional head size does not provide better spatial discrimination [190]. Heffner discovered later, that spatial discrimination was closely correlated with the size of an animal's field of best vision, specifically, the narrower an animal's field of best vision, the better is the spatial discrimination ability [110]. Overall, mammalian MAAs range from about 1° for humans and elephants to nearly 30° for cattle, 33° for mice, and 180° for subterranean species. In human, it is known that infants up to 18 month of age can detect sound shifts of about 10° from the midline, and that this accuracy of detection decreases at more lateral positions [191], in addition, different studies showed better MAA for low frequency noise and for frontal positions.

In a clinical environment, testing a patient's sound source discrimination and localisation abilities in his/her surrounding environment can be technically demanding and time consuming when it is performed in free field. Since the pioneer work of Wightman and Kistler, 1989 [163], it is possible to simulate a free-field presentation over headphones using the measurement of the two transfer functions between a position in the 3D space and the two eardrums (HRTF). Not to mention a direct binaural recording of the free field using in-ear microphones [192], HRTF can be measured either on humans or artificial heads. And now a collection of human and artificial HRTFs data were made available online (<https://www.sofaconventions.org>).

Different methods were developed to measure sound localisation abilities, such as measuring the perceived sound event direction compared to the auditory event direction, the difference being the localisation blur [64] and the minimum audible angle (MAA) which is an angular threshold measuring the smallest audible difference in angle between two sound sources positions [164]. Although many studies on sound localisation and spatial discrimination use free field setups [193, 163, 194, 195, 196, 197, 198, 199]. Further, Wang et al. have developed a method for HRTF individualization and showed that individualized HRTF were more reliable in sound localisation than standard HRTFs derived from the KEMAR artificial head [200]. Finally, it has been shown that source localisation can be enhanced with individualized HRTF [201] as well as moving sources [202]. Simulated enhanced pinna improved MAA for

both normal and impaired hearing participants with up to 10° of improvement [203]. MAA of less than 5° were measured on (NHS) with human HRTFs by Cai et al. (2015) [204]. A mean MAA of 7° - 11° was found by Wersényi (2007) [205] with NHS with a set of HRTFs coming from an earlier measurement using a “good localizer” subject [206]. Despite this literature, a consistent comparison between the available techniques, including recent advances with artificial heads [196], remains needed regarding the measurement of MAA.

From a clinical perspective, sound localisation is strongly impaired in diverse populations of deaf patients, especially in those with unilateral or asymmetrical hearing loss (UHL and AHL). In these cases, the loss of binaural cues affects also speech in noise processing, leading to a severe alteration of quality of life. However, audiogram alone failed to predict accurately the subjective handicap of UHL/AHL patients while spatial auditory processing correlated with the hearing thresholds and the quality of life evaluation [160]. Most clinical studies focused on sound localisation using Root Mean Square (RMS) error and percentage of correct identification of sound sources, but only few assessed sound source discrimination using MAA. These observations highlight the necessity to develop rapid and accurate protocols to assess the spatial discrimination skills of patient with hearing loss, an objective that could be obtained using MAA evaluation through HRTF datasets.

2.2.1 Definition.

The head related transfer function is characterized by the interaction between a sound wave and the human anatomical head structure. The morphological measurements of the human head and pinna play a significant role in defining his individual HRTF, therefore, a simulated HRTF via headphone cannot be perceived similarly between individuals with different morphological measurements of the head and the pinna.

Nowadays, different HRTF datasets can be used as a tool to investigate sound localisation performances. Some of these datasets are available to use for free, such as the CIPIC dataset of individualized HRTF [14], in addition to non individualized HRTF sets like the recorded HRTFS of the Kemar dummy Head [207] or the Neuman Ku100 mannequin that is known

for his high spatial recording resolution [208].

The recording conditions of a specific HRTF set is very crucial for its efficiency, the chambers used for recording play the most significant role. Usually, HRTFs are measured in anechoic chambers that reduces the influence of the room, which binds the measurement to a specific location. In addition, a high spatial resolution of recordings is essential in order to enable a dynamic virtual environment with head movements. Despite the detailed measurement considerations in recording HRTF sets, sound localisation investigations using headphones remained difficult to conduct, especially with the non-individualised HRTF sets, that presents high front/back confusions and high localisation errors.

However, it has been shown that better localisation performances were provided by individualized HRTF data with lower front/back confusion compared to HRTFs recorded with artificial mannequins [201], yet, the measurements of these HRTF datasets require enormous technical effort [209]. Still, these individualised HRTFs can always be estimated by the anthropometric shapes of the torso, ear and head geometry, these measures can be quantified without the use of special rooms and sophisticated acoustic equipment.

2.2.2 Recording design of HRTF datasets

KEMAR HRTF recording design:

The extensive set of the KEMAR (Knowles Electronics Mannequin for Acoustics Research) dummy HRTFs is measured in MIT lab anechoic chamber. The anthropometric measures of the neck, shoulder, chest breadth and the distance from the shoulder to the ear were considered in the design of this dummy. The KEMAR had two different pinna shapes, the right pinna was “normal” and the left pinna was a “large red model pinna” which resulted with two complete sets of symmetrical HRTF.

The spherical space around KEMAR contained 710 location samples varying according to the elevation in a range between -40° and 90° . At each elevation position, the KEMAR was mounted on a motorized turntable rotating accurately at any azimuth position. The rotating turntable maintained an equal step increment in the azimuth completing a full rotation of

360° with a 5° step size of increment at 0° of elevation.

The measurements of each position were sampled using a Realistic Optimum Pro7 loudspeaker placed at 1.4 meter of distance from the dummy ear. The physical analyses of near-field HRTF Data conducted by Bungart et al. showed a significant increase in the ILDs for KEMAR as well as an increase in the low pass filtering when the sound source is closer to the head. For post processing, check Bill Gardner and Keith Martin 1994.

KU100 HRTF design:

The impulse responses of KU100 were measured in an anechoic chamber of the acoustic Lab at TH Koln, with a room dimensions of 4.5m *11.7m * 2.30m (W*D*H) and a low cut off frequency of about 200 Hz. The loudspeaker used as a sound source was a Gethain RL906 with a two way coaxial design and flat on axis. This speaker allowed HRTFs measuring in an almost full audible frequency range. The sounds were captured following two spatial sampling grids: Circular grid with steps of 1° in the horizontal plane (figure 2.14) and Lebedev grid with 2702 points, which made KU100 one of the few HRTFs that covers all spherical positions.

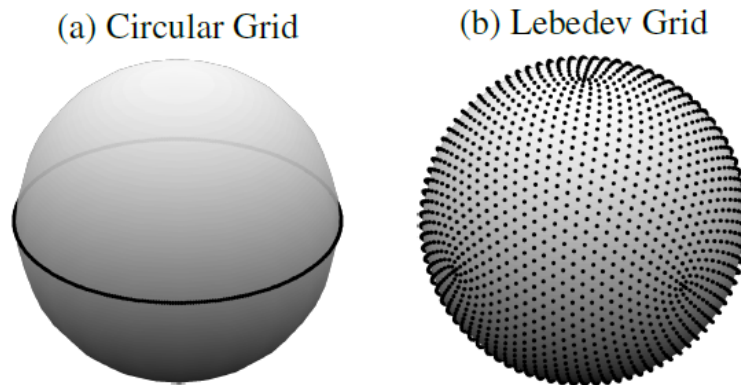


Figure 2.14: The configuration of the grids used in the recordings using KU100 HRTF.

In order to get a precise positioning of the KU100 dummy, a Varisphear measuring system was used for each spatial sampling position and for capturing different head related impulse responses (HRIR). In this setup nine HRIR were measured: five sound source distances were measured in the circular grid whereas only four distances (0.5 m, 0.75 m, 1.00 m, 1.50 m) were captured for Lebedev grid that covered a full spherical grid of 2702 positions.

Measurements of individualized HRTF:

The HRTFs can also be recorded on human instead of mannequin, it is known as individualized HRTFS. The setup used for the measurement of this type of HRTF was designed by the institute of the technical acoustics (ITA) using multiple loudspeakers for a higher sampling resolution, with microphones positioned inside the ear canal. 64 loudspeaker were aligned in a vertical semicircular arch with a radius of 1,2 meter starting from an angle of 1.5° to 160° with a step of 2.5° . The subject is aligned on a turntable using a cross laser to set every position, the sampling of the HRTF was a spherical sampling, the turntable rotated 360° with a step of 5° for each sampling position.

The anthropometric dimensions of the head and ear of the 48 individuals were measured in MRI scans and three dimensional ear models. The head dimensions extracted from the

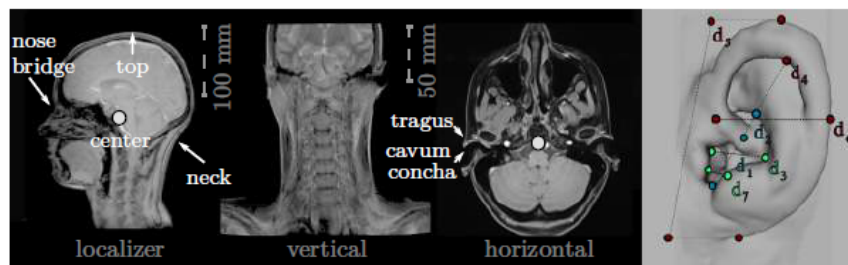


Figure 2.15: The 12 head dimensions implicated in the bestmatching of the individualised HRTF.

different segmentation in the MRI Scan generated 12 dimension: W (Targus and center), df (Nose Bridge to center), db (neck and center), h (top and center) in addition to 8 pinna dimensions presented in the photo. These 12 dimensions were used as a selection criterion of the adequate individualized HRTF for each participant.

Key points

- **Spatial environment can be simulated using pre-recorded HRTF.**
- **Pre-recorded HRTF can be registered on humans: individualised HRTF, or on mannequins such as Kemar and KU100.**
- **Kemar dummy head was recorded in 1993, with a resolution of 5° between recorded sounds in the horizontal plane.**
- **Ku100 dummy head was recorded in 2004, with a resolution of 1° between recorded sounds in a spheric grid.**

2.2.3 Materials and methods:

Subjects

25 participants aged between 18 and 25 took part in this study after an audio metrical evaluation that showed a normal and symmetrical pure tone thresholds between 250 and 8000 Hz for all participants.

HRTF datasets and sound stimulation

Four types of HRTF datasets were used in this experiment: 2 datasets extracted from two mannequins: Kemar and KU100 in addition to 2 dataset extracted from a set of 48 individualized HRTF by calculating the bestmatch anthropometric measures (section below). Each dataset comprised a number of sound that reflects different spatial locations. The acoustic stimulation used in this paradigm was a low frequency Gaussian noise burst band pass filtered between 300 and 1200 HZ of 100 ms duration including 10 ms of fade in and 10 ms of fade out. We tested the performances of the subject using the 4 HRTF sounds at three reference positions: 0° (front), 50° (left), 180° (back).

Bestmatching

For each subject we measured 12 dimensions of the head and the ear, these measures were later compared with the dimensions in each of the 48 individualized HRTF in the dataset. The best match was calculated by finding the minimal distance between the participants dimensions and one of the 48 datasets measures. This distance was calculated in a multidimensional Euclidean space where each dimension represented one of the 12 anthropometric measures.

Two approaches were used to match each subject to a specific individualized HRTF. In one approach we selected the HRTF that matched the 12 dimensions of the head and pinna of the participant (Total Best match) and in other approach we selected the HRTF that matched only the 6 dimensions of the head (Partial Best match). The reason behind these two types of selection is to investigate the extent of implication of the pinna in the sound source detection performance. Assuming that the total best match HRTF was the one that could reveal the most accurate results, we decided to test the MAA using this dataset in 3 different conditions: one binaural condition and two simulated monaural conditions. In the simulated monaural conditions, the level of the sound was digitally attenuated to around 39 dB, either at the opposite side of the reference position (TBM MON1) or at the same side of the reference position (TBM MON2). In total, we tested the performances using 6 datasets: Kemar, KU100, TBM Bin, TBM Mon1, TBM Mon2 and PBM. Each dataset is tested at 3 reference positions 0° , 50° et 180° .

Experimental design

Before each stimulation block, participants underwent a training procedure. The training served to familiarize the subjects with the positions of the sound in the headphones. During the training, participants were asked to listen to the sounds in the positions arranged in a semicircular array and to associate the stimulation source with the angular position indicated on the screen. The paradigm involved two source locations: one standard (S) that corresponds to the reference position (0° or 50° or 180°) and one deviant (D). Subjects were asked to distinguish between the two signals (S and D) coming from different or same angular positions, by pressing “1” for different angular positions and “0” for the same angular

position.

In the beginning of the experiment, the deviant sound (D) was presented with a disparity of 50° to the left of the reference position (S). The spatial disparity varied as a function of the answers of the participant. In the case of a false response, the disparity was increased by one step of 5° . If three consecutive responses were “false” the deviant returned to the initial position. In the case where all the responses were “correct” the procedure restarted from the beginning. Each listener completed the test after 36 trials.

2.2.4 Data analyses

The MAA of each subject was calculated by averaging the angle positions where participants reported no difference in the sound (positions that correspond to the button press “0”). The average of all the angles was then subtracted from the reference position to obtain the minimal audible angle of the participant. All subject’s MAA were averaged afterwards to obtain the MAA per group for each HRTF at each reference position. In order to select the most accurate dataset and the spatial reference with the best performances, we used a repeated measure design implemented in R (package LMe4) with two factors: dataset and reference. This design permitted to check the global effect of each factor. To further specify the differences, post-hoc comparisons and Wilcoxon test were applied.

2.2.5 Results

As already mentioned, the following statistical analysis was based on the mean value of the trials at which the subject pressed the button “zero”. The repeated measure design yielded a significant reference position (STD) main effect ($p < 0,001$) and a significant dataset effect ($p < 0,001$) as well as an interaction between reference position and dataset ($p < 0,05$).

Variation of MAA with the HRTF dataset.

Post-hoc comparison confirmed larger MAAs using KEMAR dataset compared to KU100, TBM and PBM respectively ($p < 0,001$; $p < 0,05$; $p < 0,01$). Also when we compared the MAA

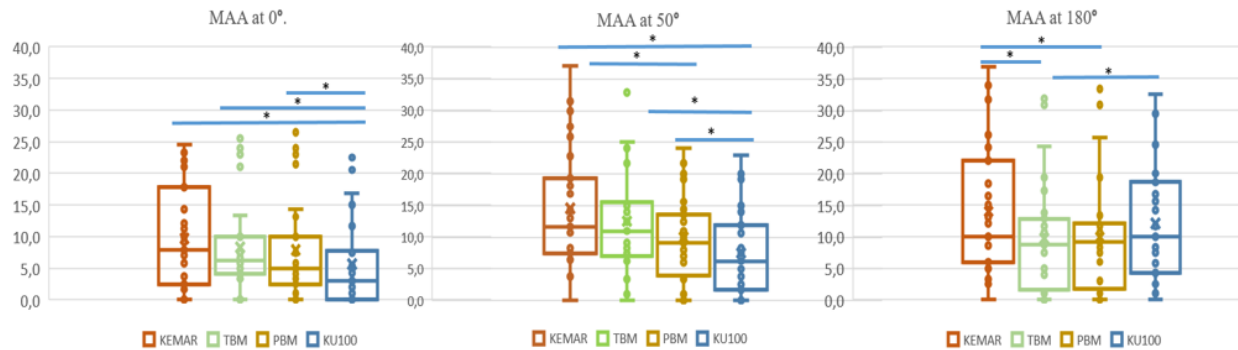


Figure 2.16: *Minimal Audible Angle (MAA) scores using the 4 HRTF (KU100, Kemar, TBM and PBM) at the three reference positions (central 0°, lateral 50° and posterior 180°)*

means using the dataset at each reference position, KU100 showed smaller MAAs than Kemar in the front and lateral position respectively ($p < 0,05$ frontal; $p < 0,001$ lateral) in addition to smaller MAAs using KU100 compared to TBM in the lateral position ($p < 0,05$).

We applied a Wilcoxon rank sum test to verify the mean differences within the datasets at all the reference positions. The values of MAA performances using this statistical test at the central position, showed the smallest MAA using KU100 set compared to the three other HRTF sets (KEMAR: $p < 0,01$; /TBM: $p < 0,05$; /PBM: $p < 0,05$). The testing using KU100 set showed also the smallest MAA in the lateral position at 50° with an angle of 7,5° that was significantly smaller than the MAAs using KEMAR ($p < 0,001$), TBM ($p < 0,01$) and PBM ($p < 0,05$).

The box plots at 50° showed a big interindividual variability of the performances for KEMAR set with the largest mean of MAA 14,5° compared to KU100 (7,5°; $p < 0,001$), and PBM (10°; $p < 0,005$) but not to TBM (12,6°; $p < 0,05$). This large variability between participants performances using kemar is also noticed when the MAAs were tested from the back at 180°, with the largest MAA using Kemar (14°), that was significantly different than TBM (9,7°; $p < 0,005$), and PBM (9,9°; $p < 0,01$) but not different than KU100 (12,1°; $p = 0,22$). TBM and PBM showed the smallest MAAs when the participants received the stimulation at 180° (9,7° and 9,9°), compared to KU100 and KEMAR (12,1° and 14°), with no significant difference

between TBM and PBM at the three azimuth positions.

Variation of MAA with the spatial reference.

Concerning the variation of the MAA values according to the reference position, post-hoc comparison showed a significantly smaller MAAs at the central position compared to the MAAs in the back ($p < 0,001$) and compared to MAAs in the lateral space ($p < 0,001$). KU100

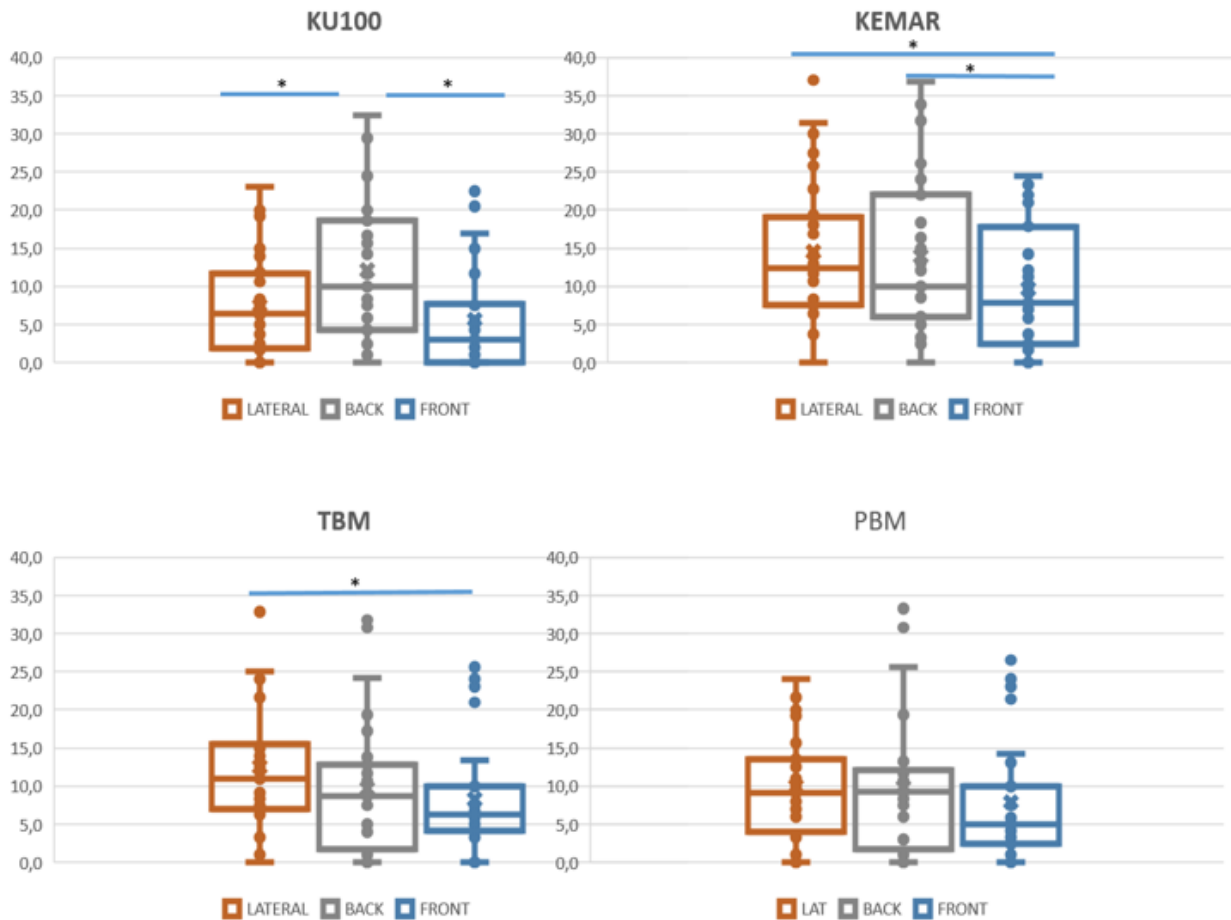


Figure 2.17: *Minimal Audible Angle (MAA) scores using the 4 HRTF (KU100, KEMAR, TBM and PBM) at the three reference positions (central 0°, lateral 50° and posterior 180°)*

showed the smallest MAA at 0° compared to the back ($p < 0,001$), with also smaller MAAs at 50° compared to 180° ($p < 0,005$). These results are confirmed with the Wilcoxon rank sum test that revealed the same front/back confusion with a larger MAA at 180° (12,1° ; $p < 0,001$) and the smallest MAA at 0° (5,6°). The MAA using KU100 at 180° was also significantly

more important than the MAA in the lateral position ($7,5^\circ$ VS $12,1^\circ$; $p < 0,001$), although the findings between lateral and front did not show any significance. Kemar also showed the smallest MAA at 0° compared to the lateral and the back using post hoc comparison ($p < 0,05$; $p < 0,05$). Wilcoxon test found the similar front/back confusion ($9,7^\circ$ vs 14° ; $p = 8,027$), in addition to a difference between the front and the lateral performances ($p < 0,05$) with smaller angles at 0° rather than at 50° ($9,7^\circ$ vs $14,5^\circ$). However the TBM set did not show similar results, no difference between front and back performances, but a slightly higher MAA in the lateral position than in the front ($8,3^\circ$ vs $12,6^\circ$; $p < 0,05$). These findings are also not significant when we tested the differences between positions for the PBM set.

Binaural VS Monaural Performances with the TBM dataset.

The repeated measure design showed an effect of the condition on the variation of the performances but no effect of the reference position, in addition to a significantly higher MAAs at both monaural conditions compared with the binaural ($p < 0,001$ for both monaural conditions) with no difference between the two monaural conditions.

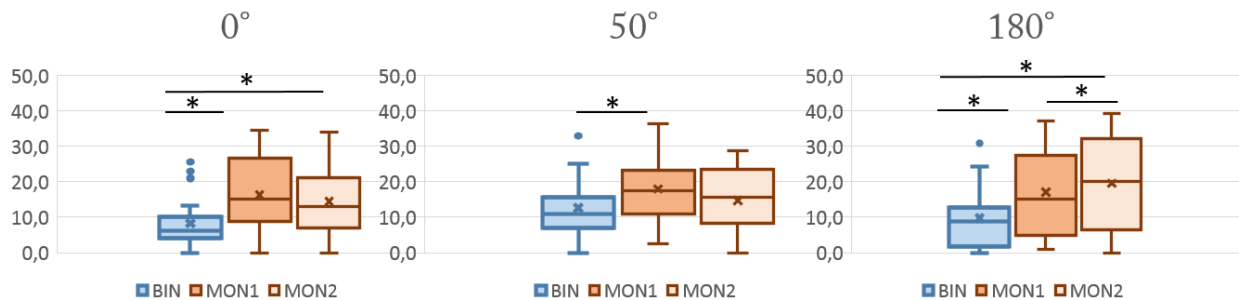


Figure 2.18: *Minimal Audible Angle (MAA) scores using the Total Best Match (TBM) at the three reference positions (central 0° , lateral 50° and posterior 180°) in binaural condition, monaural condition 1 and monaural condition 2*

The Wilcoxon rank sum test showed significant difference between the binaural and the monaural1 in the three azimuth positions, with higher MAA in MON1. At 0° MAA increased in MON2 (MAA= $14,4^\circ$, $p < 0,001$). When we changed the side of attenuation, the MAA remained higher than binaural MAA ($16,4^\circ$; $p < 0,001$); with no difference between the two monaural conditions. At a more lateral position (50°) the significance between binaural

and mon 1 was still present ($p < 0,001$), however in mon2 this difference with the binaural condition is no longer significant. When the stimulation was at 180° MAAs in both monaural conditions were significantly higher than the binaural condition ($p < 0,001$), in addition TBM set showed a more important MAA in monaural 2 rather than in monaural 1 ($p < 0,05$).

2.2.6 Discussion of the section.

This study had two main objectives. The first aim was to build a simple, easy to use, setup with no technical difficulties, to accurately evaluate the ability of subjects to discriminate sounds in the space using headphones, and to use this setup, for clinical investigations with patients. The second objective was to find the best simulated HRTF set that represents accurately spatial discrimination abilities in free field, to be also administered in the future investigations as one of the assessment tools classically used with patients.

The measures of MAA with headphones collected in this study revealed contrasted results according to the type of HRTF used as well as the reference position. At both 0° (front) and 50° (lateral) reference positions, the artificial head KU100 produced not only the smallest MAAs compared to the two individualized HRTFs and the KEMAR artificial head, but also the closest to normal values reported in previous free field studies for NHS such as 1° for 750 Hz pure tones [77] or 1° for 400 Hz click train [210]. Indeed, the smallest MAA are obtained in free field at the central position with average RMS errors equal to 5° for young adults and 10° for older adults [63] these values are compatible with those obtained in the present study. The other analogy with free fields MAA evaluation is that in our comparative study, MAA increases with increasing distances from the center.

Such observation has been classically reported in free field studies [211, 63] as well as in HRTF studies [204]. For example, Richter 2013 showed an increase of the MAA from $6,9^\circ$ at lateral positions to $7,2^\circ$ at more peripheral positions (90°). In the present study the discrimination accuracy reported at 180° (back), using the KU100 did not show more precise measures than those reported using individualized HRTF, and both artificial heads showed large inter individual variability in performances. Our findings suggests that the need for individualized

HRTFs rather than standard HRTFs obtained on artificial heads is more critical for rear source positions than for front and lateral positions. This is coherent with previous findings showing poorer localisation abilities for rear sources compared to the frontal space [64].

In addition, larger MAAs were reported in monaural condition than in binaural condition, confirming the important contribution of interaural differences of intensity in the perception of source position. These findings were coherent with the ones found in patients with UHL in the study of Cai 2015 where averaged MAAs revealed significantly smaller errors for NHS ($4,88^\circ$) than for asymmetrical hearing loss patients ($13,6^\circ$ left, $10,3^\circ$ right). Finally, despite the fact that our results show larger MAAs than those measured in free field in previous studies [64], our results confirm that MAA can be measured efficiently with headphones using HRTF simulation in both binaural and monaural conditions. The MAA values reported in this study were approximately 2° larger than the values reported in free-fields when it comes from front localisation [63, 211], however, this evaluation is accurate enough with respect to our clinical application aim. In addition, evaluating the MAA at two different positions (centre and periphery) takes less than 10mn which can be easily included in a clinical evaluation. To conclude, this comparative study clearly shows the feasibility of using such MAA evaluation for patients with hearing loss. Testing MAA with KU100 dataset provided reliable evaluation of sound source discrimination of NHS as well as simulated hearing loss cases, therefore, this HRTF can be adapted easily to clinical evaluations practiced routinely in ENT departments.

Relationship between spatial accuracy and spatial discrimination.

Different studies tried to explore the relationship between sound localisation assessed by RMSE and spatial discrimination assessed by the MAA. For instance, Kuhnle in 2013 tried to study the effect of signal frequencies on spatial localisation (spatial accuracy) and spatial discrimination [153], the study suggested an interrelationship between these two features of spatial hearing. However, the correlation was significant only in limited sets of stimulus conditions. In addition Kuhnle found an effect of the age on the spatial source discrimination abilities, but not on sound localisation accuracy suggesting that the two hearing skills are

distinct, and cannot be predicted depending on each other. Additional studies have been conducted by Grieco-Calub and Litovsky in 2010 [95], where they tested both spatial localisation and discrimination on NH children and bilateral cochlear implants. Their findings did not show any correlation between spatial discrimination and sound localisation accuracy. Hence, this study reported large variability in average RMS errors, even in children with accurate spatial discrimination. This interpretation suggests that poor spatial discrimination could be a predictor of poor localisation accuracy, nonetheless, better or worst spatial accuracy cannot predict spatial discrimination performances.

The MAA study that we conducted showed a progressive increase of the MAA according to the reference position. NHS had better accuracies in the front compared to the lateral. A better central performance is only presented in the spatial discrimination task, while in the sound localisation test, no variation of the performances over the 12 spatial positions was noted for NHS in their binaural condition. In addition, differential cortical activation patterns have been documented in several studies for absolute localisation versus discrimination. Frontal and parietal cortices seem to play the prominent role in representing localisation processes [212, 213, 214], whereas superior temporal regions seem to be predominantly involved on the spatial discrimination level [215, 216].

According to Zatorre 2002, cortical activation differed in that the right inferior parietal cortex was activated in tasks that employed absolute localisation, but not in tasks where spatial discrimination was required [214], in addition Spierer et al. suggested that superior temporal regions play a crucial role in the refinement of spatial discrimination. The same authors furthermore stressed the importance of interactions between temporal and parietal regions for the transformation of spatial positions into coordinate systems (spatial maps) necessary for absolute localisation judgments [216].

Several studies attempted to find correlation between the physiological mechanisms and anatomical reorganization underlying auditory functions [217, 218, 219]. Studies also tried ablation methods to further understand the effect of removal of specific brain tissues on animal behavior [97, 108, 220]. In addition, a series of studies on patients with lesions located in the brainstem demonstrated a correlation between the location of the lesion and

the poorer performance of binaural tasks. Furthermore, patients with lesions in the inferior colliculus and lateral lemniscus showed deficit in sound source lateralization, although the results did not affirm the relation between the side of the lesion and the performances when sounds are presented in the contralateral hemifield. The inferior colliculus contains arrays of neurons that are sensitive to ITD and ILD providing a coding mechanism for source localisation in space [221]. Lesion studies suggested that the ability of animals to localize sounds in space is impaired after unilateral lesions in the dorsal midbrain, including the inferior colliculus and dorsal nucleus of the lateral lemniscus [222, 108].

Key points

- KU100 produced the smallest MAA in frontal and lateral horizontal positions, but the posterior precision was limited.
- The MAA increases when the reference position is lateralized.
- Significant increase of the MAA in simulated monaural condition.
- Individualized HRTF could be the best data base to use since it represents the anthropometric measures of the subject, however, measuring the HRTF of each participant can be technically demanding and time consuming.

Chapter 3

Spatial discrimination reflected by Mismatch Negativity in normal hearing and after hearing impairment.

3.1 Theoretical and methodological considerations of MisMatch Negativity in cognitive and clinical neu- roscience.

The study of event related potentials (ERP) has been widely conducted due to its high temporal resolution providing temporally high information about various stages of event processing in addition to the neural components associated with the studied behavior [223]. The family of cognitive ERPs comprises different components that reflects different stages of event processing. One component belonging to this family is the MisMatch Negativity (MMN) [224]. MMN is considered to be one of the famous ERP that shed the light on auditory sensory memory processing especially when it comes to the resolution of the auditory system in discriminating sound features [225]. MMN helps to step into the nature of sound source representation by disclosing deviance detection mechanisms [226].

The first attempts to study the MMN were not only conducted using EEG. Beside of EEG, a lot of evidence about auditory deviance detection has been recorded using magnetoencephalography (MEG) [58], positron emission tomography (PET) [227], optical imaging (OI) [228], and functional magnetic resonance imaging (fMRI) [229, 230, 231, 232].

To be elicited, the MMN is recorded in a specific paradigm, also known as the oddball paradigm. In this procedure one frequent sound, that is repetitive over time is interrupted by a rare occasional deviant sound stimulus that differs from the standard in one specific sound physical feature. During the repetition of the frequent sound, a memory trace is formed in the auditory system, once different stimulus is detected, a negative response is elicited in a latency window ranging between 100 to 250 ms [233]. This negative response is known as the MMN, and the characteristics of the MMN will reflect the ability of the auditory system to distinguish between two sounds with different physical properties.

One interesting aspect about the auditory system, is its ability to un-attentionally detect irregularities. The detection of auditory novelty can take place even when the subject is not aware of its occurrence. A study done by Van Zuijenn et al. [234] aiming to assess the ability to detect descending tone pairs among ascending tones for frequencies varying between 262 and 523 Hz, showed significant MMN for deviant pairs while more than half of the participants were unable to consciously identify the deviant pairs. The subjects underwent a training session, 2 of the participants were still unable to consciously discriminate the deviant, however, their MMN was always present.

MMN represents complex auditory processing and do not only implicate simple detection of physical stimulus novelties, but also the un-attentional processing of the information. Despite the ability of attention in specific circumstances to modify MMN characteristics, the MMN can still be elicited even when the listener is not aware of the stimuli [235, 236]. In fact, if a deviant sound is intrusive, the MMN elicitation can lead to an attentional switch towards the sound change even if the frequent stimuli was unattended. The attention switch after the generation of the intrusive deviant is usually represented by an ERP component known as the P3a that appears after the elicitation of the MMN [237, 238]. This expression of the MMN in unattended environment made of it an interesting component that has been

used in several investigations for patients with attention and communication problems [239, 240, 241, 242].

Due to its expression as a response to complex auditory information, the MMN was also beneficial in the investigations of speech sound representations of the auditory system. In fact, Winkler in 1999 suggested that stimulation related to native-languages can elicit larger MMNs when the sound changes crosses the language phonetic boundaries, rather than MMNs between physically comparable sound changes [241, 243]. In addition, sound changes related to non linguistic features are responsible of stronger MMNs in the right rather than the left hemisphere [244, 245, 227] while the MMN related to linguistic features was shown to be predominant in the left temporal lobe. These findings were confirmed using high spatial resolution methods in neuroimaging studies using phonemes, syllables as well as words [246, 247, 248, 249, 250].

In addition, even with the need of physical constancy in the oddball paradigm to get higher sensitivity to auditory changes, some studies showed that MMN elicitation does not mainly rely on this constancy. A study done by Shestakova in 2002 [251] where they used 150 exemplars of the vowel “a” articulated by different speakers, the vowel belonging to different category “e” elicited an MMN [252]. This means that the mechanisms related to the generation of the MMN are processed on a more complex level than the simple acoustic features of the sound to advanced abstracts of sound representations.

3.1.1 MMN reflecting sensory memory and attentional switching.

As already shown in the introduction of the chapter, the MMN operates at the sensory memory level, although it is affected by long term sound representation [225, 236, 253]. In 1985, Naatanen suggested that a memory trace is formed in the auditory system after each sound. In the case of violation of the present sound by a deviant, the incoming sound will violate the neural memory representation of the recently heard sounds, therefore, eliciting an MMN. In addition, it has been proposed that in the case where the Inter Stimulus Interval (ISI) is prolonged enough, the memory trace of the specific stimulus will progressively fade

away by the presentation of the following stimulus, consequently leading to the disappearance of the MMN. Mantysalo and Naatanen 1987 [254] tested this importance of sensory memory lifetime by changing ISI. Their findings were able to show significant MMN when the ISI was of 1 or 2 seconds while no MMN was noted when this interval was prolonged to 4 or 8 seconds.

Cowan et al. in 1993 [255] proved using the MMN how memory traces can last and how the trace is built up during the session. In his experiment, Cowan generated stimulus trains of nine stimuli with an ISI around 610 ms and a duration of 11 to 15 s between the trains. In the first condition the standard/stimulus frequency was constant, called constant-standard condition, and in the second condition the stimulus frequency varied between the stimulus train called roving-standard condition. A randomly occurred, higher frequency deviant stimulus at the stimulus positions 1,2,3,4,6 and 8 in the stimulus trains. In the first condition, deviants at all the positions except the first one, generated an MMN, However, in the second condition (roving-standard) the first deviant to elicit an MMN was at the 4th position. In addition, when the standard sound was similar over the different stimulus in the train, a strong memory trace appeared that enhanced the neural presentation for this specific stimulus frequency. In the second condition, the variation of the frequency between the stimulus reduced the possibility for a memory trace to build up.

One can also investigate the efficiency of the sensory memory with backward-masking paradigms. Masking stimuli in such paradigm are usually presented after sounds that participants are supposed to discriminate from one another. If the interval between the sounds and the maskers is short, subjects showed inability to discriminate, while in the case of longer sound/maskers interval, the sounds seemed to be easy to discriminate [256]. These findings demonstrated the interference of the sound memory trace by the masker. In addition, if a masker is elicited about 25s earlier after the offset of a brief tone, the tone with deviance frequencies are therefore not elicited nor discriminated from standard tones [241]. If this interval is prolonged to 150 ms, then the MMN can be elicited by the deviant sound and the deviant can be discriminated. The similarity of the masking effects on the MMN and behavioral discrimination performance suggests that the MMN in masking paradigms can be

used for probing sensory memory functions. This memory erasing effect due masking stimulus reflects the ability of the auditory system to integrate successive events to meaningful entities [257].

Some ambiguities need to be considered when using the MMN as an indicator of lifetime sensory memory especially in clinical domains [241]. First, a loss of the grand average amplitude of the MMN after an increase of the ISI, could be due to small reductions in the individual MMNs of each subject, or in other cases, a complete disappearance of the MMN for one subject that led to a change at the grand average. In addition, it remains unknown whether the reduction of the MMN is due to a gradual decay of memory or to an all/or/none phenomenon of the MMN. Second, even if the MMN is changing with the ISI, in some cases this MMN is not attributed to sensory memory even in the cases when memory is fully intact. For example when a deviant is elicited after an ISI superior to 10 s, MMN may not be elicited, since the memory trace of the standard may have disappeared during this time interval [255]. However, after an ISI of 10s if a deviant follows one single standard, the MMN is elicited, suggesting that the memory trace of this standard is still present but it is not used by the preattentive deviant detection system. The memory can be therefore reactivated after only one single standard stimulus after long silent interval [255, 258].

In the situations where no MMN is elicited after long ISI but subjects are still able to detect deviant difference, the absence of the MMN does not necessarily mean that the memory trace of a standard is completely lost, the behavioral test in this situation can in some cases tap a memory process that is not directly associated with the MMN [259]. In addition to the importance of the MMN in the reflection of the memory trace, it is important to talk about its critical role in representing attentional switching. It has been shown that MMN is also associated with triggering the orienting response, this phenomenon is characterized by different psychological responses including an increase in the heart rate and also skin conductance [260, 261, 262]. It is also known that the MMN is followed by the P3a, an ERP usually distributed in the fronto-central areas, this ERP is characterized by a positivity that appears with a latency of 300 ms after the stimulus onset. The P3a represents the attentional switch that takes place after the deviant elicitation [263, 264, 265, 146, 238].

The MMN characteristics of representing the involuntary attentional switching is proven by studies that showed an increase of the MMN and P3a amplitudes after the increase of the difference in the physical properties of the standard stimulus and the deviant stimulus [266, 238, 253].

3.1.2 MMN in clinical investigations.

A number of studies demonstrated the importance of the MMN in determining auditory capacities in subjects with special abilities (such as musicians), or in assessing hearing impairments. As already seen in the previous sections of this chapter, larger differences between standard and deviant elicited larger MMN amplitudes and shorter latencies. In the case where these physiological differences are reduced, the MMN amplitude decreases and its latency appears later [267, 268, 269].

MMN was previously used to assess attentional impairment in unilateral neglect patients. Usually, the unilateral neglect is a consequence of a hemisphere lesion in the parietal areas that leads to a complete neglect and inattention to the contralateral space [270]. Deouell et al in 2000 conducted more investigations to evaluate attention switching in hemineglect patients. Deouell recorded the MMN related to location, pitch and duration variations in the left and right hemifields. Unimpaired MMNs appeared in the right hemifield stimulation but a diminished MMN resulted in the left hemifield. These findings are found to be more robust for the location deviance and not significant for the variation of the duration of the sound [271].

MMN is also used as a clinical tool to test discrimination abilities for patients after hearing impairments [272, 273, 274]. One of the disorders that revealed a diminished MMN are related to specific language impairments for speech sound differences [275], in dyslexia for consonant [276, 277], frequency [278, 279, 280], and rhythm differences [281], and in aphasia for tone duration [282], tone-frequency [283], and speech-sound differences [284, 285, 286, 287]. In addition, large abnormal MMNs have been demonstrated in abstinent alcoholics that was suggested to reflect the withdrawal resulted by the hyper-excitability of the central

nervous system [288]. The enhanced ERPs can be explained by the dysfunctioning inhibition mechanism of GABA neurons that are supposedly the gate of cortical input into the thalamus [288].

Clinical investigations showed also an interaction of the groups of subjects with MMN and behavioral measures. A study by Baldeweg et al in 1999 showed a loss of the MMN in dyslexic individuals after frequency-deviance change [278], concluding that this group of patient presented inability to discriminate pitch compared to the control group. Hence, in the case of reading errors for regular words and non words a correlation seem to be significant between the latency of the MMN and the frequency detection performance.

In 2003 Todd et al [289] conducted a sound discrimination task, showing a selective association between sound perception impairment and a particular sub-process of the MMN. in the study they investigated tone duration perception in patients with schizophrenia, by dividing the patients in a group of normal duration discrimination another group that showed inability to discriminate variable duration. The study showed smaller MMNs at frontal areas mainly at Fz electrode site for both patients groups compared to normal control group with no difference between both group of patients, despite the behavioral evidence in sound duration discrimination abilities.

Dyslexic patients previously showed normal discrimination of large duration differences when the same sound is presented in an oddball sequence and not embedded with other stimuli, these patients elicited similar MMNs even in the cases where pseudo words and tone patterns were presented compared to normal controls.

The MMN may even be similarly elicited in two groups which, however, differ in terms of behavioral discrimination accuracy. For example, ERPs and discrimination accuracy were compared between dyslexic and control adults by using sound duration differences embedded within pseudo-words or complex sound patterns [280, 278]. However, when it comes to discriminating active sounds, dyslexic subjects seem to have poorer abilities to detect deviance compared to the control and therefore possessing smaller responses to the deviance in ERP s simultaneously recorder with their behavioral task. In addition, during the behavioral task, subjects were asked to press one of the three response keys that corresponded to the position

of the deviant detected, however, no false button press to standard pseudo-words or complex sound patterns was reported for both groups, concluding that the lower accuracy rate for dyslexic patient is resulted from his mis-identification of the deviant stimulus position. These conducted studies conclude that in many cases the processing of the MMN may be intact, however, an impairment can still be present at later information processing stages. Although the large duration differences of a sound can be discriminated at the cortical level as reflected by the MMN, the process of identifying the speech/complex stimulus part where the deviant sound detection is occurred seem to be impaired in dyslexia as reflected in the ERPs and behavioral measures in previous studies.

To sum up, while it is clear that there is a relationship between MMN and behavioral spatial discrimination (MAA), the index of the process is not direct. The process explain the sound discrimination at early cortical levels, and can be dissociated from the behavioral measures reported for different reasons. For example, the subjects motivation and attention can be a major influence especially for children [290] and patients [282, 291]. Hence, even if the MMN is intact in some cases, the auditory processing of the stimulus may be impaired after the time interval of the MMN, since the MMN is considered as an early stage auditory processing. If sound processing is impaired at later stage processing, behavioral results may be altered while MMN characteristics will remain intact [280]. The same process may also be applicable on changes preceding the MMN such as changes at the brain-stem level, therefore the response will result in an abnormal MMN.

3.1.3 MMN generators and brain plasticity.

According to the litterature, the cerebral sources implicated in the generation of the MMN varies between temporal and frontal areas. It has been reported that the major generators were located in the right and left auditory cortices. Another studies observed MMN generation in the frontal areas, that are involved in the attention switch once the recent sound (deviant) is analyzed in the temporal lobes according to Rinne et aL.in 2000 [228]. However, Girard et al. [292] suggest that the MMN appears in the frontal lobes before its generation in the temporal ones. In other studies MMN generators have been reported in the parietal

lobe [293, 294], and subcortical areas [295].

We established in the previous sections the association of the MMN with cortical discrimination accuracies. In the case of changes in the cortical accuracies after learning induced plasticity, the MMN should surely be influenced. Naatanen [225] tried to test this hypothesis in a study where he recorded the MMN during passive blocks in a session including active training conditions, supposing that in the case where subjects are able to discriminate, an MMN should be elicited. The sound patterns used in this experiment were very complex and difficult to discriminate for most subjects. They did not observe any MMN for these subjects. However, after multiple training sessions, and as predicted, subjects who learned how to discriminate were able to elicit an MMN while subjects who failed to learn did not present any MMN elicitation. Different studies have demonstrated the importance of MMN amplitude as a function of discrimination learning in many domains such as speech sounds [296, 297, 298], and sinusoidal tones [299].

For instance a study compared the ability to discriminate a Finnish phonetic contrast /e/ versus /æ/ between a group of adult Finns, Hungarians who does not speak Finnish and Hungarians who had a good command of Finnish [300]. The results showed that the contrast /e/ and /æ/ was not perceived by Hungarians that does not know Finnish, but it clearly elicited an MMN for both Finnish and Hungarians who spoke Finnish. In addition we should note that the MMNs elicited for the latter two groups were similar.

Koelsch et al [301] also studied the effect of musical expertise on the frequency discrimination. In his study, Koelsch compared frequency related MMNs between musicians playing violin specifically and non musicians. The stimulation paradigm included frequent major chords and infrequent ones where a chord was mistuned by 1 % in the middle tone. The mistuned chords evoked MMN responses in the musicians group only, in addition to more accurate automatic activation of pitch representation for violin players compared to non musicians. MMN also was used as an indicator of recovery from brain damages determining brain's plastic changes [291]. In the case of stroke for example, patients with stroke in their left hemisphere were followed up during 6 months after the stroke onset using MMN and speech comprehension tests [291]. These patients showed a progressive improvement of their speech

comprehension skills during these 6 months, in contrast the EEG recordings showed an increase in the MMN amplitude that seemed to be on normal levels during the 3 months following the stroke onset.

The MMN is a neural marker that reflects different brain functions, however, the low spatial resolution of the EEG make it difficult for us to disentangle these generators because of the large electric field that is spread over the scalp. For this reasons, in many studies MMN failed to report the laterality effects of speech elicited MMN [302, 303, 304].

However, MEG and haemodynamic methods gave great evidence about left and right temporal lobes separation. In the temporal lobes, MMN sources are tangentially oriented, which makes their detection by planar MEG gradiometer much easier [305]. Hence, planar gradiometer are sufficient to record highest signals above the source of a specific activity, therefore, the separation between MMNs for left and right temporal lobes can be more accurate and can provide high magnitude of comparison between the two lobes. This is considered to be a feasible approach in the evaluation of left/right asymmetry in head shaped models [228], [306]. Using this approach, Rinne was able to demonstrate MMN differences related to the hemispheric ratios for linguistic and non-linguistic stimuli [228].

Despite its suitable methods for separating MMNs of both hemispheres, MEG have a drawback of not detecting these generator sources with radial orientations using planar gradiometer [305]. This could be the reason behind the difficulty in detecting frontal MMN generators. A combination of MEG and high resolution EEG study has investigated temporal and frontal MMN generators [307], the findings reported the possibility of identifying MMNs after 160 ms of the stimulus change onset using EEG. Noting that its center of gravity was moving towards frontal areas over time. However, the MEG activity in this case showed an MMN in the temporal cortex only.

3.1.4 Overview on the guidelines of MMN paradigms and analysis.

Recent initiatives have been devoted to build a simple and standardized methodology for recording and analysing MMN. Optimizing the MMN paradigm is very crucial for the MMN

to become a useful tool for clinical practice [308, 274].

In a classical MMN paradigm a sequence of repeated standard sounds is presented monotonously, and occasionally interrupted by a deviant sound. The MMN guidelines suggest a range of probability around 0.05 and 0.2 for the deviant repetition. In order to achieve a convenient and sufficient signal to noise level, it is recommended to achieve sufficient stimulus series duration and a sufficient deviant sequence number of around 100 deviant stimuli for each type.

MMN is characterised by a negativity projected at fronto central regions with an amplitude of approximately 0.5 to 5 μv occurring in a latency range of 100 to 250 ms for classical MMN or frequency specific MMN. The MMN is reversed over the mastoide sites and other lateral posterior sites over the same latency range when a nose reference is used. It is known that the peak latency of the MMN appears later after the sensory N100 component. Therefore, MMN must be quantified after the latency window of the N100 component to avoid contamination of the MMN measures with differences in the N100 elicited by standard and deviant stimulus.

It is important to note that the peak latency of the MMN becomes progressively shorter with a larger peak amplitude when the difference between standard and deviant is higher. Therefore MMN can be used to evaluate spatial discrimination, by providing an objective measure of the unattentional spatial change detection.

The conditions in which the listener completely ignores the auditory stimuli are the optimal recording conditions since it eliminates other cognitive components during active attention such as N200 and P300 [309]. Different distraction techniques might be used for this purpose including visual discrimination tasks; watching a silent movie or low sound level movie, book reading etc....The frequently used method in clinical studies is mainly watching a silent subtitled movie.

Key points

- MMN reflects the ability of the brain to un-attentionally detect auditory deviations.
- MMN is clinically used to assess attentional switching abilities and short term memory.
- MMN is generated in primary auditory cortex and frontal cortex.
- Spatial MMN reflects spatial discrimination sensitivity that can be also represented behaviorally by the MAA.

3.2 Mismatch responses of NHS, UHL and BHL to deviance changes in the azimuth.

3.2.1 Aims of the study

As the previous chapter reported, spatial discrimination is closely associated with the extraction of binaural sound information from the auditory system, to help the listener in identifying target sources and speech. The spatial MMN is the reflection of the unattended spatial discrimination, since it helps to step into the nature of a sound source by disclosing the deviance detection mechanisms at preattentive stages [310]. Some studies tried to assess the reliability of the MMN as a tool to explore the resolution of acoustic space [215, 311, 312], these studies reported a close relationship between MMN sensitivity and behavioral thresholds for a large variety of acoustic stimulus features [313].

The main interest in this thesis is to search for objective neuronal markers of brain plasticity after UHL using MMN, and how these neural correlates are related to auditory spatial behavior, to be able to explain the relationship between these adaptations, and the cortical reorganisation that can take place after hearing impairment. As we observed in the previous chapter, some of these patients present high localisation accuracy despite their hearing loss. We hypothesized that the coding of the spatial information reflected by the MMN can be representative of the variation of sound localisation accuracy between patients with UHL. Therefore in this chapter, MMN amplitudes and latencies will be compared between different groups at different spatial deviations. The first objective of this investigation is to study the variation of the MMN amplitude and latency according to the spatial deviation, and to compare its variation between groups in binaural and monaural conditions. To be able to find a relationship between the neural correlates with the behavioral results already observed.

3.2.2 Experimental design.

Subjects

The MMN study was performed on the 20 NHS, 21 patients with UHL and 12 patients with BHL. The NHS were randomly assigned into two groups, the first group underwent the binaural and monaural condition *contro* where we introduced an ear plug of 39 dB of attenuation in the ear contro lateral to the standard (Mon-c). The second NHS group also underwent the binaural condition and a monaural condition *ipsi* (Mon-i) the ear plug was at the ipsilateral side of the standard.

Starting from our hypothesis that the MMN can reflect spatial acoustic perception, we decided to divide our UHL population according to the average RMS scores reported in the first chapter. Patients with UHL were assigned into three main groups: Patients with low RMS (UHL *low rms*), patients with moderate RMS (UHL *moderate rms*) and patient with high RMS (UHL *high rms*). The selection criteria will be further explained in the section (MMN variation in UHL.)

Room and speaker setup

The experimental setup was installed in a sound attenuated anechoic chamber, the walls of the chamber were additionally treated with acoustic absorbing foam to further reduce echoes. Four broad band loudspeakers were mounted at the ear level at the respective positions 50°, 60° 70° and -50°. The zero degree was designated as the center of the semicircle with a radius of 1 m centered at the center of the head. The positions of the speakers were selected following experimental designs used in previous studies. For example, Benneman [193] used a deviation of 5° from a standard at 60° in the azimuth, Deouel [215] also used a speaker deviation of 5° when they tested the MMN at central positions [215]. The MMN evaluation in these 2 studies was applied on NHS only. In our case, the target population are hearing impaired patients, therefore, the deviation from the standard that we selected was larger than the magnitudes usually used. The setup was designed with a standard position at 50°, the first deviant at 60° to asses the 10° of deviation from the standard, the second deviant

at 70° to assess the 20° magnitude of deviation from the standard, the third deviant at -50° to assess the largest magnitude of deviation in addition to the effect of crossing the midline at 100° of deviation.

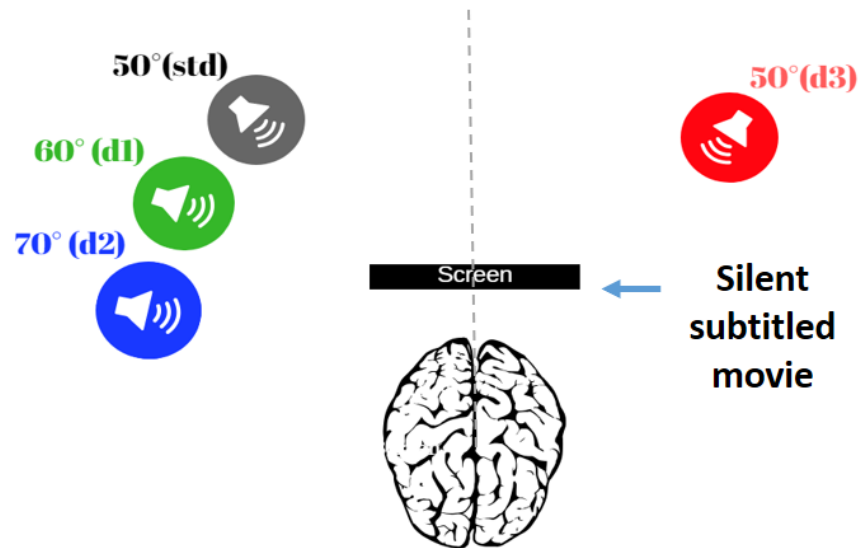


Figure 3.1: Experimental design of MMN acquisition.

Acoustic stimulations and MMN acquisition.

In this experiment we used the same acoustic stimulation already used by Benneman 2013 [193], a low frequency Gaussian white noise burst band pass filtered between 300 and 1200 Hz. The duration of the sound was set at 100 ms including a 10 ms fade in and 10 ms fade out. The ISI slightly varied between 490 and 500 ms to prevent stimulus onset prediction.

MMN was recorded using a passive oddball paradigm of 2000 stimulation. The sound was randomly emitted across the 4 loud speakers with a probability of 85% of the sound emitted from the standard position, and 15% of the stimulations equally distributed at 3 deviant speakers, resulting with a total of around 1700 standard simulations and 100 deviants for each deviant position.

During the stimuli presentation, patients were instructed to watch a silent subtitled movie followed by a questionnaire about the movie. Naatanen and Gaillard suggested that optimal

MMN recording conditions are those in which the participant ignores the auditory stimuli, such technique, plays an important role in eliminating other cognitive components elicited during active attention, such as N200 [309].

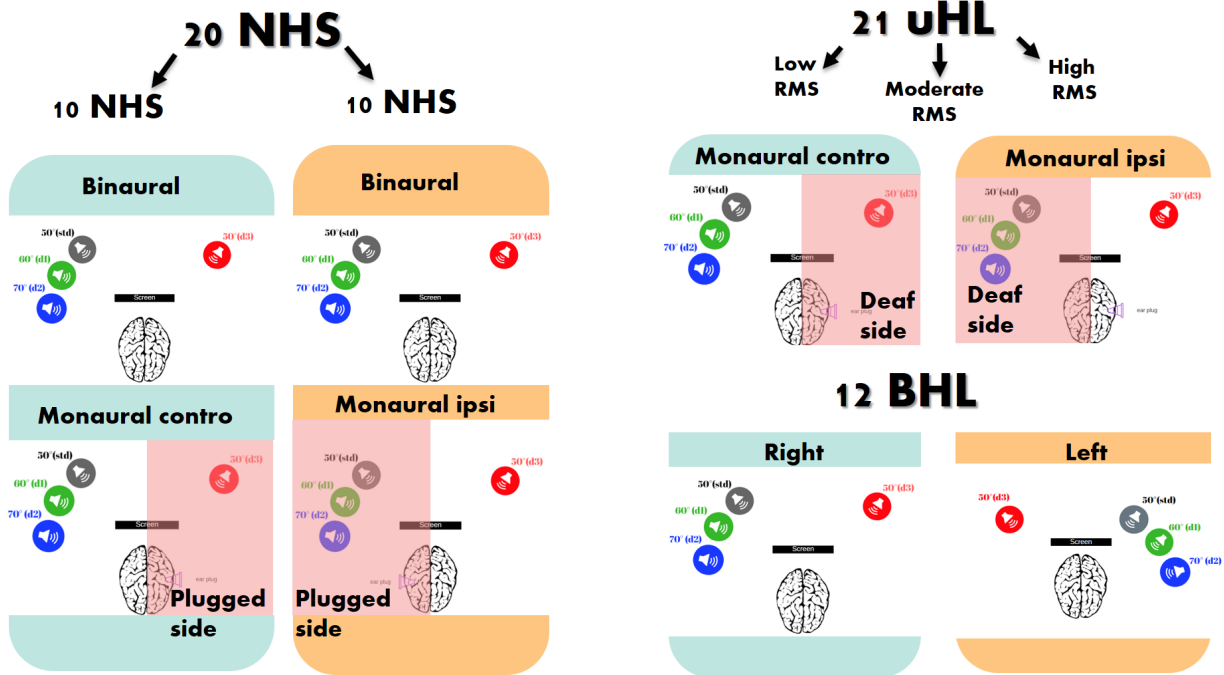


Figure 3.2: MMN setup, population and stimulation conditions.

EEG Recordings

EEG was recorded with an Active 2 system by BIOSEMI using 64 Ag/AgCl electrodes laid out according to the extended 10-20 system with 2 additional mastoid electrodes. The data was referenced online to the average of the display with the default sampling frequency of 2048 Hz. Impedance of scalp and mastoid sites was set below 40 kOhm. During the recordings subjects were instructed to avoid the excessive body and eyes movements. The data were analysed offline using Matlab and EEGLAB version 14.1.1.b [314].

3.2.3 MMN processing and analysis.

Analysis of the EEG DATA

The data were analysed offline using Matlab and EEGLAB version 14.1.1.b [314]. We also followed the EEG analysing steps followed by Benneman in 2013. Data were downsampled to 500 Hz and re-referenced to the mastoide site designated as the electrodes TP9 and TP10. The data were badnpass filtered at 1 to 20 Hz. Epoch creation was conducted using ERPLAB version 6.1.3, with a epoch duration of 600 ms including 100 ms prestimulus baseline. For artifact detection, a moving window peak to peak threshold was applied to reject amplitude changes exceeding $100 \mu v$ an all electrodes. After artifact detection and rejection all the resulting epochs were averaged. Participants were excluded from the study if they exceeded 20 percent of rejected epochs. Averaged ERP waveforms were created afterwards. Difference ERP waveforms were calculated by substracting the standard ERP waveform from the respective ERPs of the three deviants. The Grand average MMN waveform was then calculated from the average of the individual difference wave ERP at 10° , 20° and 100° degrees of deviation.

Statistical MMN testing and comparison.

Statistical significance of the MMN was investigated using two methods. **In the first method Bootstrap confidence interval analysis was employed based on the individual absolute peak. In the second method we performed the Bootstrap on the individual peak amplitude within a window of 40 ms around the grand average peak latency for each of the 3 deviation MMNs.** The reason behind the selection of two methods is to have a robust criterion in selecting significant MMN for statistical comparison, MMN amplitudes that failed to reach significance in one of the two analysis were excluded from further comparisons, the MMN was considered present **only if it was significant in both tests.** For both types of analysis the bootstrap technique was used to generate 95% confidence intervals ($\alpha=0,05$) according to zero. The tests were performed at the Fz electrode site for its high scalp distribution [315]. Statistical differences in MMN amplitudes and la-

tencies across subjects were performed on the absolute individual peak. A repeated measure design was performed using the package LMe4 in R including two factors: the condition with two levels and the magnitude of deviation with three levels (10°, 20° and 100°). The mean comparison between groups was assessed using the non parametric Wilcoxon rank sum test.

3.2.4 Results.

a- MMN of NHS in binaural condition.

Difference wave ERP was applied between the ERP of the standard and each deviant ERP. The MMN was identified as the negative deflection within a time window around 150 to 250 ms [233]. For NHS, the evoked MMN showed significant negative deflections for the 3 deviation positions at 60°, 70° and -50° with a latency between 100 and 250 ms. The table below, show the significance of the MMN at the three deviation positions. The positive sign stands for significance. The sign before the slash corresponds to a significance in the Bootstrap applied on the absolute individual peak. The sign after the slash corresponds to the significance in the Bootstrap applied in a window of 40 ms around the grand average peak.

MMN significance using Bootstrap analysis.			
	10°	20°	100°
Binaural (n=20)	+/+	+/+	+/+

Absolute peak / +-20 ms peak latency window.
 « + » MMN different from zero
 « - » MMN not different from zero

Figure 3.3: MMN significance of NHS in binaural condition.

The repeated measure design for individual MMN showed an effect of the magnitude of deviation on the MMN amplitude ($p < 0.001$). Wilcoxon rank sum test used to compare mean amplitudes (according to the absolute individual peak) showed higher MMN response at 100°

of deviation compared to 10° ($p < 0.001$) and 20° ($p < 0.001$) of deviation, but no difference was noted between 10° and 20° spatial deviance detection.

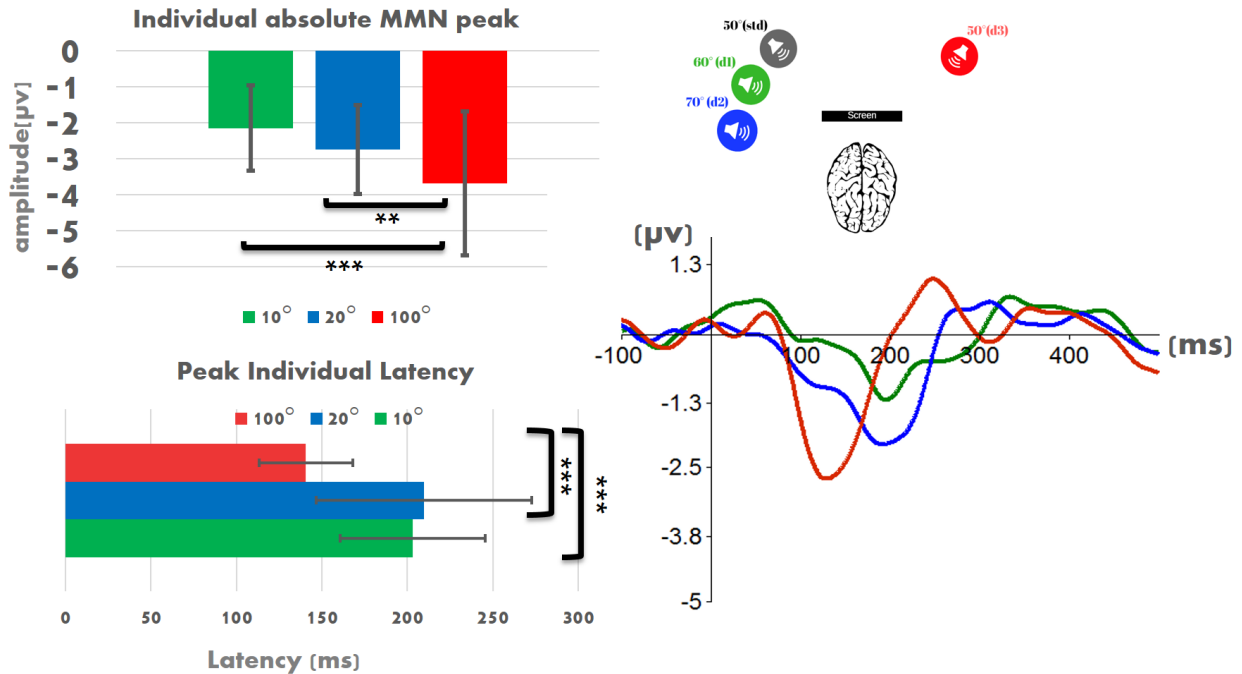


Figure 3.4: MMN amplitude and latencies for 20 NHS in binaural condition.

In addition to the variation in amplitude, NHS were able to rapidly detect spatial displacement to the opposite side (100° of deviation, peak latency= 129,4 ms), compared to the deviance detection at 10° (195,8, $p < 0,05$) and 20° (192,3 ms, $p < 0,05$).

b- MMN of NHS in monaural conditions.

The bootstrap analysis showed significant MMN at the three deviation positions when we introduced a plug in the ear contralateral to the standard (Contro-condition). However, when the plug was ipsilateral to the standard side, the MMN was significant only at 100°, therefore, results at 10° and 20° of deviation for the ipsilateral condition will be excluded from further statistical analysis.

MMN significance using Bootstrap analysis.			
	10°	20°	100°
Monaural Contro (n=10)	+/+	+/+	+/+
Monaural Ipsi (n=10)	+/-	+/-	+/+

Absolute peak / +-20 ms peak latency window.
 « + » MMN different from zero
 « - » MMN not different from zero

Figure 3.5: MMN significance of NHS in monaural conditions.

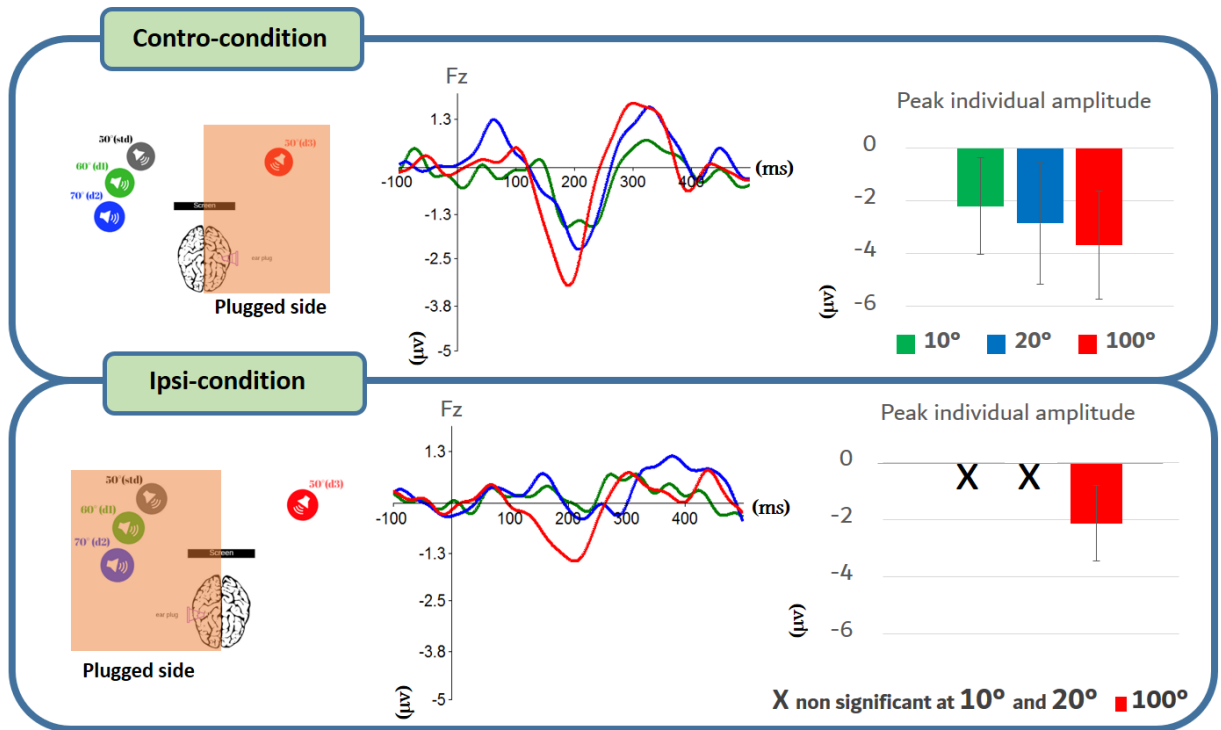


Figure 3.6: MMN results in NHS in contralateral and ipsilateral monaural conditions.

Repeated measure design showed an effect of the plugged side on the MMN amplitude variation ($p < 0,001$) in addition to an effect of the angle deviation from the standard. In the contralateral condition, MMN increased progressively with the deviation. At 100° MMN

appeared significantly later compared to the binaural condition (65 ms later than binaural response ; $p < 0,005$).

In the ipsilateral condition, MMN at 10° and 20° was not analysed. At 100° of deviation, we noticed later response compared to the binaural condition (82 ms later, $p = 0,054$), with a significant reduction in the amplitude compared to binaural condition and to monaural contralateral condition ($p < 0,005$).

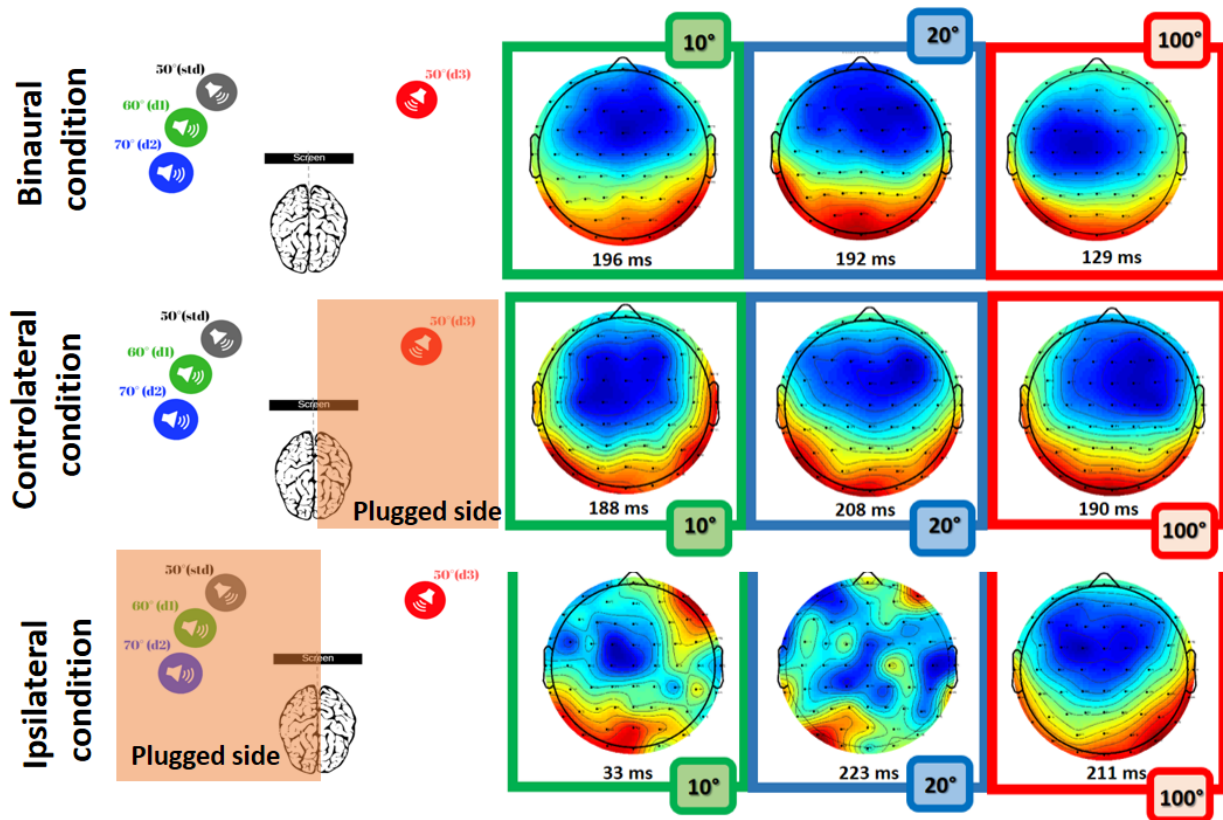


Figure 3.7: Topographic scalp distribution based on the average peak at Fz electrode.

Scalp topographies are plotted to visualize the negative voltage distribution according to the spatial position of the speakers. We plotted the scalp topographies at the moment of the average MMN peak at each position for each group.

In the binaural condition, deviations at 60° (10° of deviation) and 70° (20° of deviation) at the left side induced a negative response mainly distributed in the frontal sites, and generated to more central areas. When the deviant was at 100° of deviation, the negative

MMN distribution appeared in the contralateral hemifield.

In the monaural contralateral condition, MMN response at 10° induced a concentrated negative response in the fronto-central areas. This response is broader for the deviation at 20°. At 100° the response to the deviation showed a negative response projected in the areas contralateral to the unplugged ear.

In monaural ipsilateral condition, no significant MMNs were found at 10° and 20°. MMN at 100° of deviation showed a frontocentral negative distribution.

c- MMN in patients with UHL.

Division of the 21 patients with UHL according to RMS before EEG analysis.

In the previous chapter, we showed a high variability of sound localisation performances among the 21 UHL patients. Since the main objective of the EEG study is to examine auditory spatial discrimination and compensatory plasticity associated with hearing loss, it is important to study the MMN variation among a population with homogeneous RMS errors. Therefore patients with UHL were assigned into 3 different groups according to their average RMS scores in the sound localisation task.

In the figure 3.8, we show the division of the UHL population into the 3 groups according to the RMS, in order to verify whether the behavioral results are consistent with the upcoming EEG findings. In this figure, the individual RMS and the PTA at each ear of the patients with UHL are illustrated. In the figure 3.10 the percentage of errors towards the side of the better ear, or lateralisation, for each sub-group are also presented.

Subgroup division criteria.

As the figure below shows, the 21 patients with UHL had a high variability in performances, starting from an average RMS error of 6° up to 80°. To divide the group, we selected all the patients with RMS errors that ranged around the group median (28,05°), for whom the difference between the lowest RMS and the largest RMS was not larger than 15° (i.e. an error of one speaker)(figure 3.8). This group was considered as the intermediate group (UHL *Moderate RMS*). The subjects with an RMS smaller than the lowest RMS in the intermediate

group (RMS=24,4°, subject 7) were assigned to the UHL *low rms* group. Patients with RMS higher than the largest RMS in the intermediate group (RMS=32,2°, subject 15) were assigned to the UHL *high rms* group.

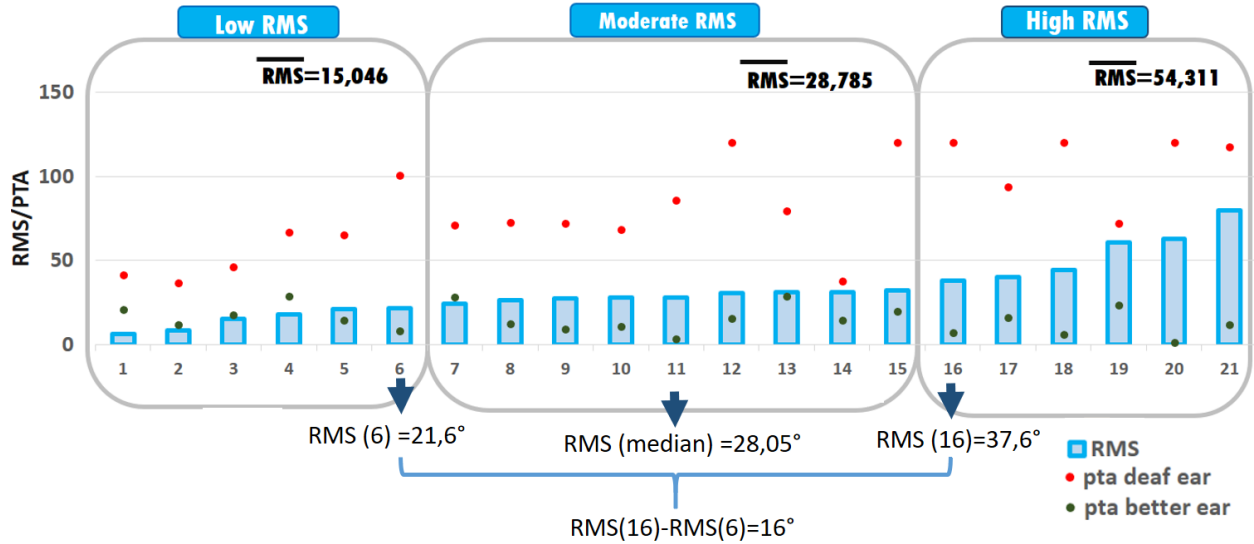


Figure 3.8: Subgroup division according to RMS.

Behavioral performances of the new UHL subdivision.

The localisation performances of UHL *low rms* and UHL *high rms* in the sound localisation task were compared with localisation scores of NHS in binaural and monaural condition in order to find a relationship between the variation of their performances in the behavioral study and the neural markers that we will discuss in this chapter. As the figure 3.9 show, NHS-bin and UHL *low rms* have equal localisation performances (global RMS = 13,4° and 15,04° respectively). In addition, while UHL *low rms* patients had a level of hearing loss that was significantly higher than NHS in monaural condition (39 dB < 59,5 dB), the patients group, despite their hearing loss, presented higher localisation accuracies.

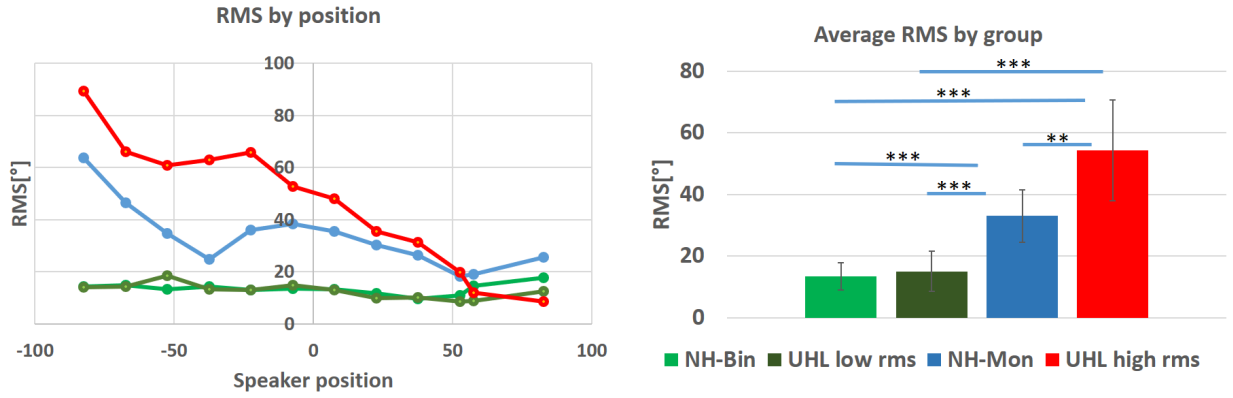


Figure 3.9: Left: Variation of the RMS for each group at each horizontal position. Right: Average RMS comparison group.

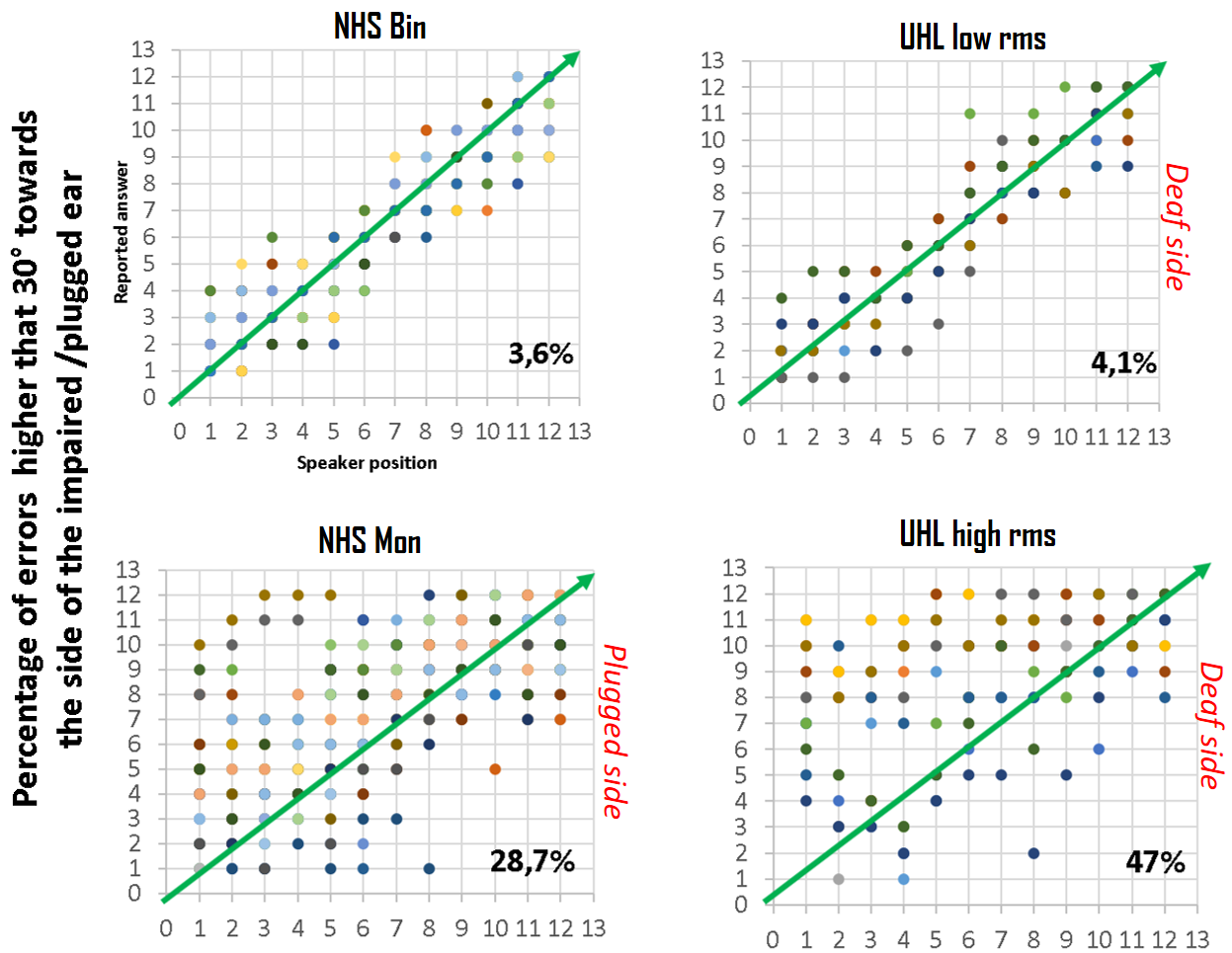


Figure 3.10: Percentage of lateralisation errors higher than 30°.

Patients with UHL *high rms* presented a deficit in the localisation task with an average error equal to 54,1°. As the figure 3.10 showed, 47% of the answers with errors larger than 30°, were projected to the side of the non deaf ear. However, patients with UHL *low rms*, showed normal localisation performances with little lateralisation (lateralisation of 4,1 %).

MMN of UHL group with low RMS.

The Bootstrap analysis around the individual MMN peak and at the window around the group average peak showed a significant MMN in patients with UHL *low rms* at the three deviations in both monaural conditions (ipsilateral and contralateral).

MMN significance using Bootstrap analysis.			
UHL Low rms (n=6)	10°	20°	100°
Contro	+/+	+/+	+/+
Ipsi	+/+	+/+	+/+

Figure 3.11: MMN significance of UHL *low rms* group in both monaural conditions

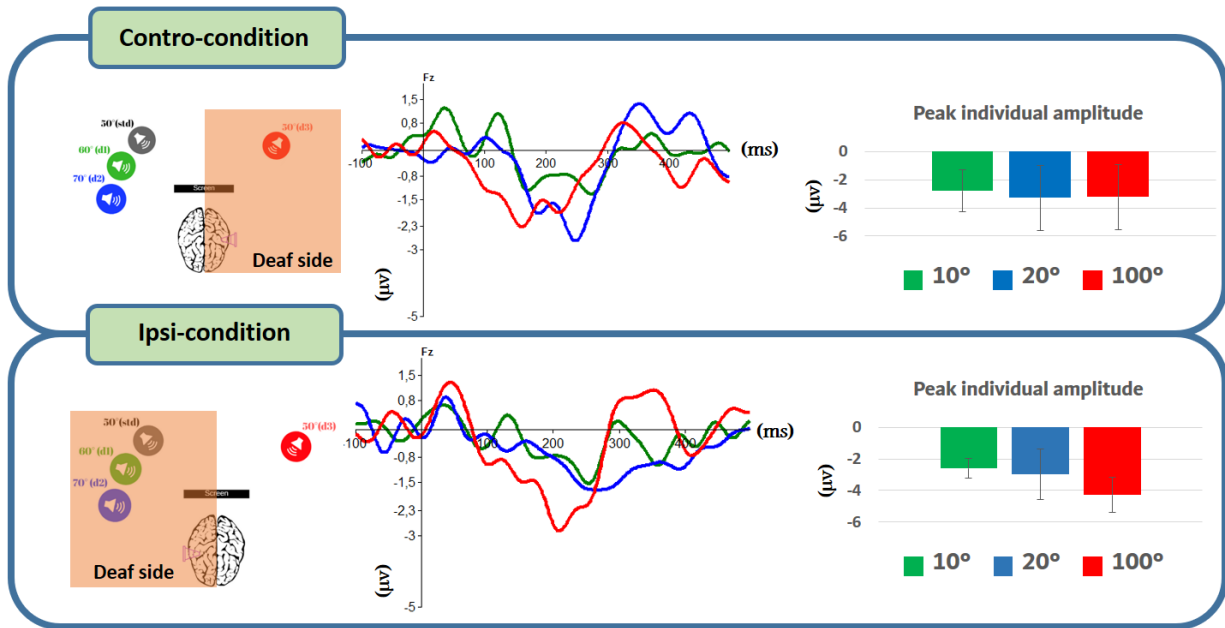


Figure 3.12: MMN variation of UHL *low rms* group.

In the contralateral condition, the deaf ear was positioned in the hemifield of the third deviant (100° of deviation), this lead to a reduction of the MMN amplitude at this position, however the MMN amplitude was not significantly different for the amplitudes at 10° and 20° of deviation. In the ipsilateral condition, the MMN appeared with a progressive increase in its amplitude according to the deviation despite the position of the standard in the hemifield of the deaf ear. Although MMNs at 100° of deviation appeared to be earlier in both conditions, the early peak was not significant compared to the peak latency of the MMN at 10° and 20° of deviation.

MMN of UHL group with high RMS.

The Bootstrap analysis of individual MMN peak in the window of the grand average did not show a significant MMN at 10° and 20° of deviation in the ipsilateral condition, and at 20° of deviation for the contralateral condition. The bootstrap on the individual absolute peak was also not significant at 10° in the contralateral condition. MMN was only present at 100° of deviation in both ipsilateral and contralateral conditions as shown in the figure below. Thus, MMN amplitude at 100° was significantly higher when the third deviant was

ipsilateral to the deaf ear.

MMN significance using Bootstrap analysis.			
UHL High rms (n=6)	10°	20°	100°
Contro	-/+	+/-	+/+
Ipsi	+/-	+/-	+/+

Figure 3.13: MMN significance of UHL *high rms* group in both monaural conditions

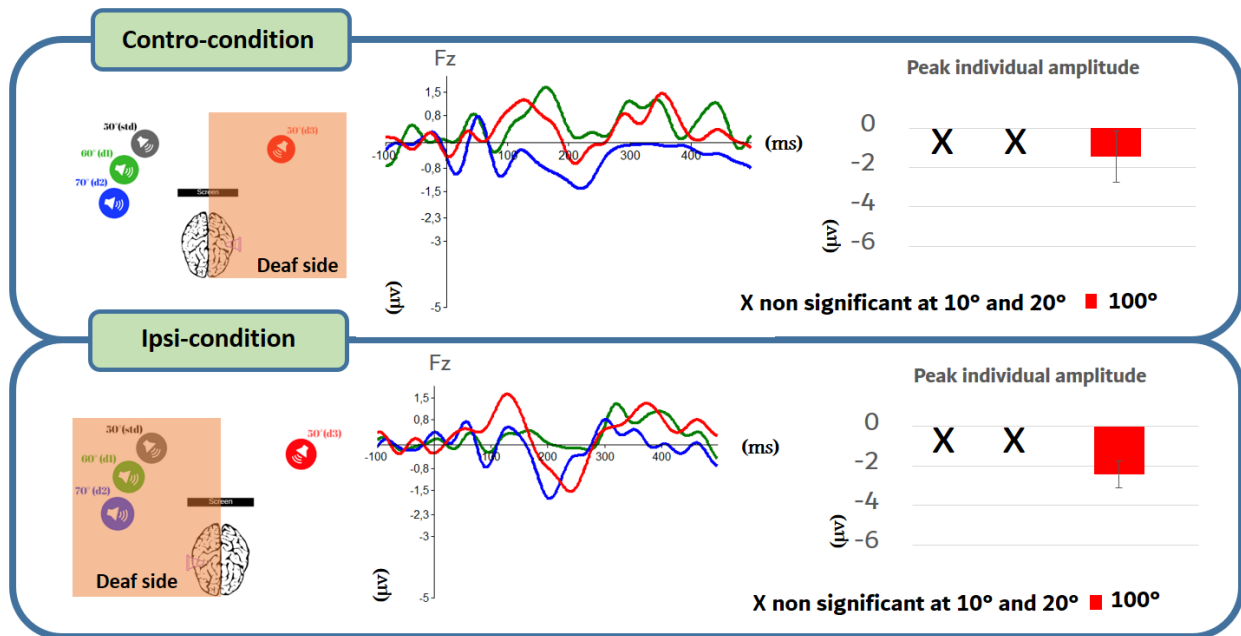


Figure 3.14: MMN variation of UHL *high rms* group in both monaural conditions

d- MMN comparison between NHS-mon VS UHL *low rms* in ipsilateral and contralateral conditions.

Our behavioral data already revealed more accurate localisation responses in UHL *low rms* group compared to NHS in monaural conditions. To check, whether this behavioral manifestation of spatial perception is consistent with the neural findings, we compared the peak

individual MMN amplitude of each group (NHS mon VS UHL *low rms*), in every monaural condition (ipsilateral and contralateral), at every spatial deviation (10°, 20° and 100° of deviation) using the non parametric Wilcoxon rank sum test.

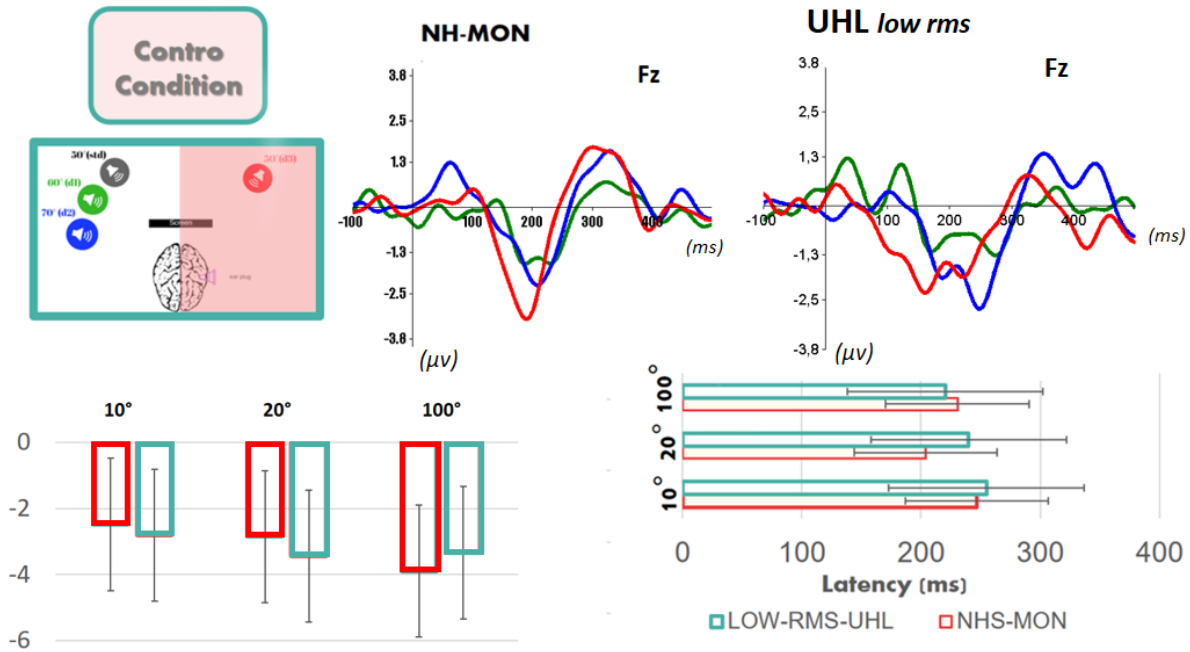


Figure 3.15: NHS vs UHL *low rms* in the Monaural contro condition.

In the contralateral condition, the hearing ear was positioned in the hemifield of the standard, and the two deviants of 10° and 20° of deviation. While the third deviant (100° of deviation) was positioned on the side of the deaf/plugged ear as shown in the figure above. We did not find any difference in the MMN in terms of amplitude or latency, between both groups at the three deviation positions.

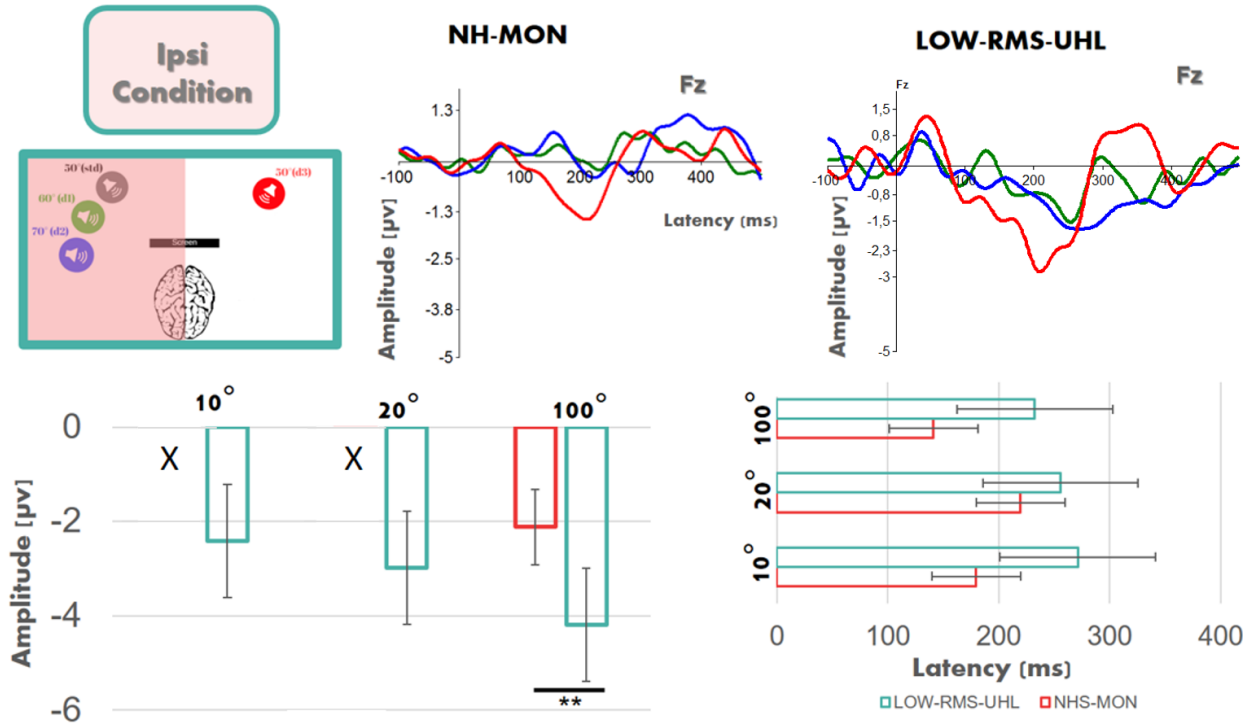


Figure 3.16: NHS vs UHL *low rms* in the Monaural ipsi condition.

In the ipsilateral condition, the deaf/plugged ear was positioned in the hemifield of the standard, and the two deviants of 10° and 20°. While the third deviant was positioned on the side of the better ear as shown in the figure above. According to the bootsrap analysis, a significant MMN at 10° and 20° appeared for UHL *low rms* but not for NHS-mon, thus, at 100° of deviation, the Wilcoxon ranksum comparison showed higher MMN amplitudes for the UHL *low rms* compared to NHS mon.

MMN analysis at 100° of deviation between NH mon and UHL low rms in ipsilateral condition.

The results in the ipsilateral condition, revealed consistent findings with the behavioral results that showed better localisation accuracy in UHL *low rms* compared to NHS mon. Especially at 100° of deviation where patients had higher neural response compared to NHS-mon. The results of the MMN at the ipsilateral condition at 100° between both group are considered as an important neural evidence of plasticity in UHL *low rms* patients, who despite their hearing loss (superior to the plug attenuation), showed higher spatial auditory abilities on both the behavioral and neural level.

Therefore, performed more detailed analysis to inspect the difference between both groups at 100° of deviation. We decided to compare the peak individual MMN amplitude at 100° of deviation in both groups (UHL *low rms* and NHS *mon*) at the following electrodes sites: (AF3, F1, FC5, FC3, AF4, F2, FC6, FC4, Cz, and Fz). These electrodes were particularly selected for two reasons: Based on the previous literature about MMN scalp distributions that suggest different electrode sites including the ones selected, and based on our scalp map results that showed negative distribution across these electrodes.

We applied the repeated measure design using the LMe4 package in R at the data with two factors, the group (NH *mon* VS UHL *low rms*) and the electrodes. The analysis revealed no effect of electrode, however, a strong effect of the group was present ($p < 0.001$). The post hoc comparison using the package (glht) showed significant differences of the peak MMN amplitudes between both groups across the 10 electrodes as shown in the figure 3.17.

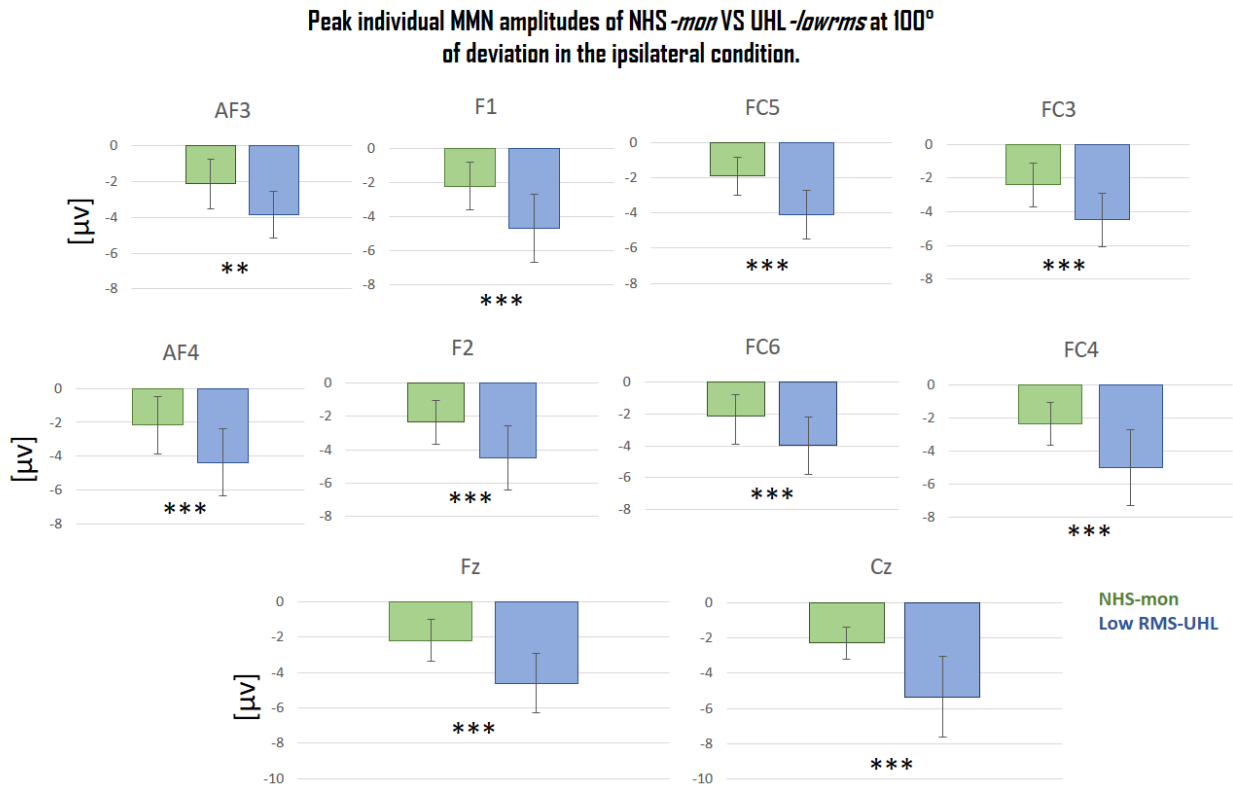


Figure 3.17: Peak individual MMN amplitude differences between NHS-*mon* and UHL *low rms* in the ipsilateral condition at 100° of deviation.

MMN analysis at 100° of deviation between NH mon and UHL high rms in ipsilateral condition.

As we observed in the beginning of the chapter, the 6 patients with UHL *high rms* had a high PTA (107,2 dB) with high average RMS error (54,3°), that was significantly larger than NHS-mon (38,7°). We compared the MMN amplitudes at 100° between both groups at the 10 electrodes previously selected. The repeated measure design applied with two factors group and electrode. We did not observe an effect of electrode neither of group on the amplitude variation of the MMN. Thus, the post hoc pairwise comparison did not show a significant difference between individual MMN amplitudes of both groups at any electrode site. These findings suggest that the spatial discrimination abilities of both groups are similar at 100° in the ipsilateral condition. It is important to also note that the MMN of UHL *high rms* failed to reach significance at 10° and 20° in both ipsilateral and contralateral monaural conditions while NHS were able to show significant MMN at 10° and 20° in the contralateral condition.

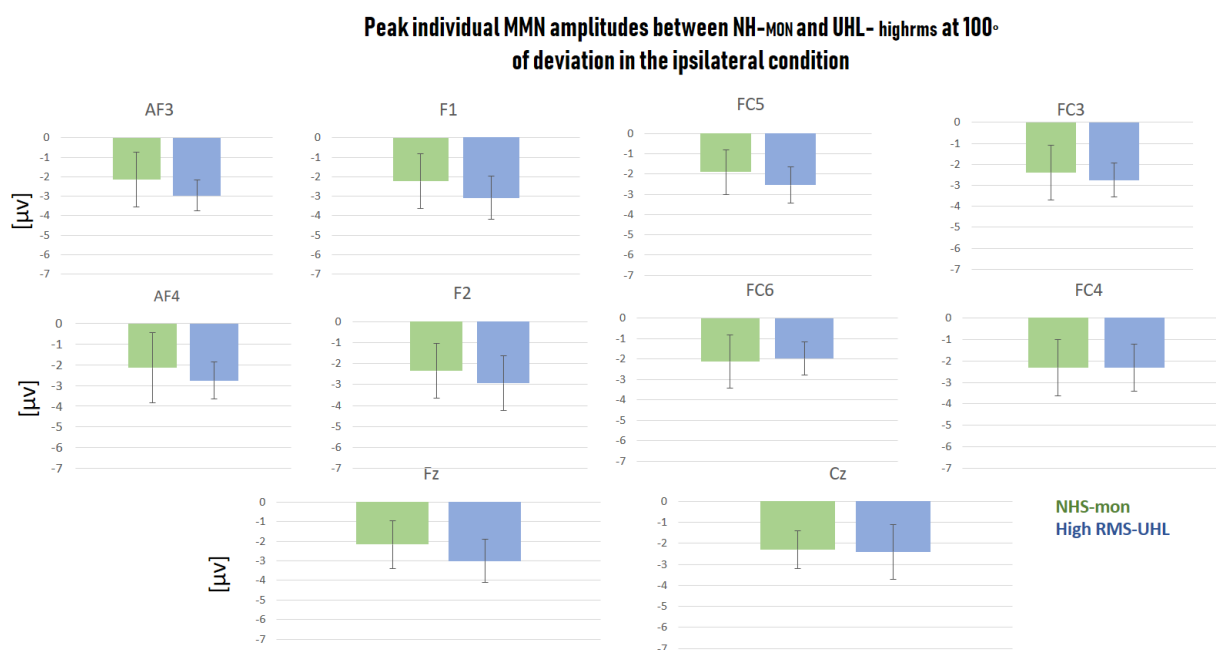


Figure 3.18: NHS mon vs UHL *high rms* in the Monaural ipsilateral condition.

e- MMN comparison between NHS VS UHL *low rms* in ipsilateral and contralateral conditions.

The comparison of MMN variation in patients with UHL and NHS seem to be important, on both behavioral and neural level. In our behavioral experiment, the sound localisation of the UHL *low rms* group showed an average RMS error of (15,04°), that was smaller than the RMS average of NHS mon (33,05°) and also equivalent to NH performances in binaural condition (13,4°). Therefore, it is important to check if the neuro-behavioral consistency that we observed between UHL *low rms* and NHS-mon is also present with NHS bin.

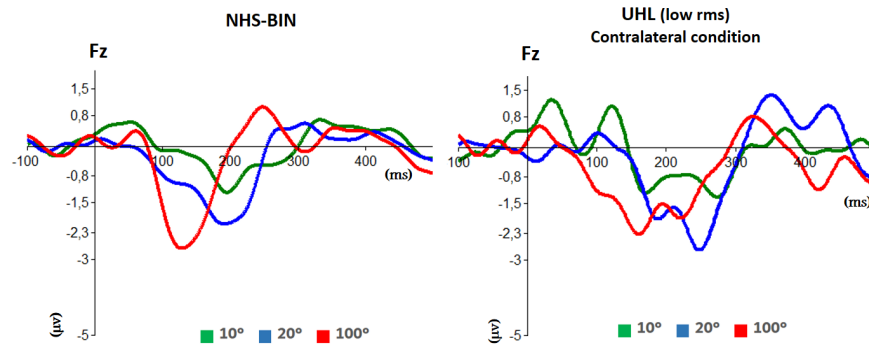


Figure 3.19: MMN waves of NHS bin vs UHL *low rms* in the contralateral condition.

We compared peak individual MMN amplitude between NHS bin and UHL *low rms* for each deviance position using the non parametric Wilcoxon rank sum test. In the UHL contralateral condition, the better ear was at the side of the standard. In this condition, patients had higher MMN amplitude at 10° of deviation compared to NHS bin. The spatial discrimination appears to be similar at 20° and 100°, as the figure below shows (figure 3.22).

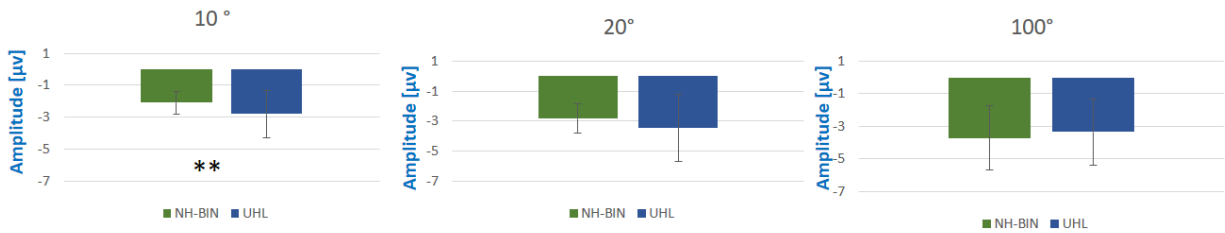


Figure 3.20: Peak individual MMN amplitude of NHS vs UHL *low rms* in the Monaural contralateral condition at the three deviation positions.

Since the deviation at 100° generated the highest MMN amplitude, higher negative response across the scalp will be observed at this position, which makes it easier for us to interpret. We compared scalp distribution between binaural NHS and the UHL *low rms* in the contralateral condition, where the third deviant was at the side of the deaf ear.

When the deaf ear is ipsilateral to the standard, the discriminative abilities between NHS and UHL *low rms* did not vary accordingly. UHL *low rms* maintained higher MMN amplitude at 10° despite the deafness ipsilateral to the stimulation. The peak individual MMN amplitudes at 20° and 100° were not significantly different between both groups.

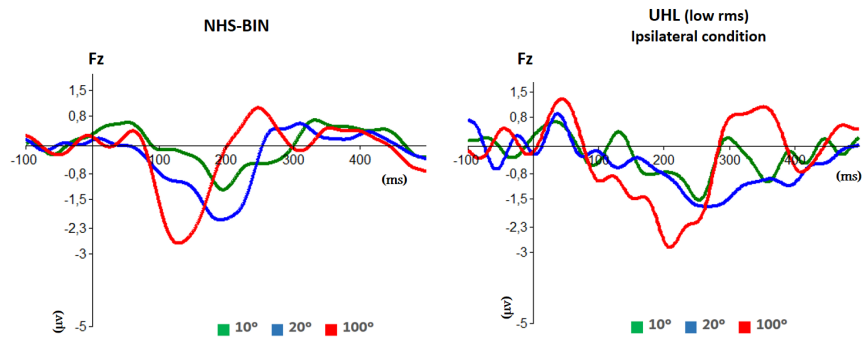


Figure 3.21: MMN waves of NHS bin vs UHL *low rms* in the contralateral condition.

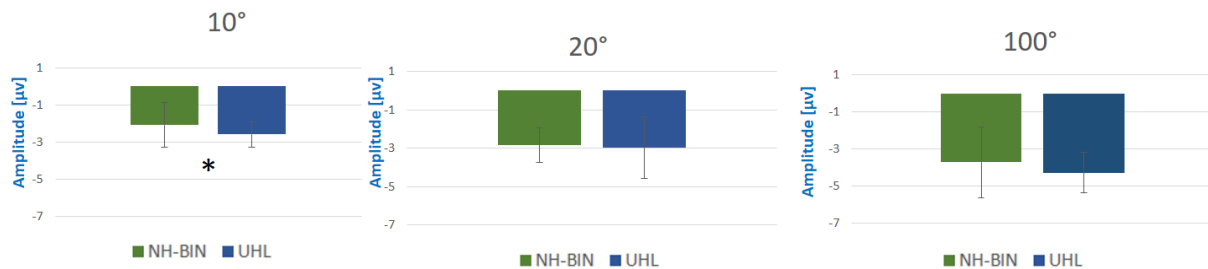


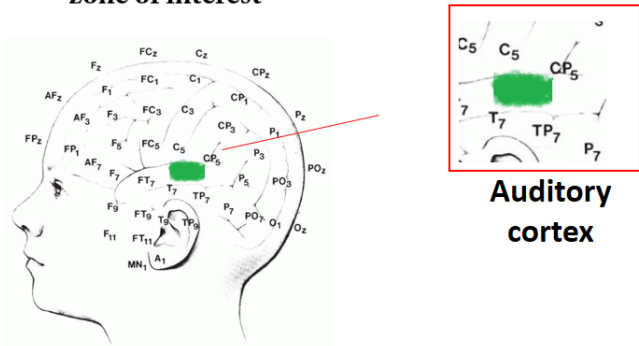
Figure 3.22: NHS vs UHL *low rms* in the Monaural ipsi condition.

f- Negative scalp distribution and ipsilateral activation.

We investigated the ipsilateral hemisphere activation to sound stimuli by looking at the amplitude of the MMN at 5 electrodes covering the primary auditory cortex ipsilateral to the deviant of 100° (C5, CP5, T7, TP7). The MMN response at 100° of deviation was averaged across the 4 electrodes in the area of interest for each of the four groups, patients with UHL low rms, patients with UHL high rms, binaural and monaural controls.

The analysis showed an effect of the group on the amplitude of the MMN in this area of interest. The Wilcoxon multiple comparison showed higher MMN amplitudes for patients with good localisation performances, compared to patients with low localisation performances and compared to monaural controls. There was no significant difference of MMN amplitudes in this area, between NHS and UHL low rms (Figure 3.23).

MMN activity in the ipsilateral temporal zone of interest



MMN amplitudes in ipsilateral temporal areas

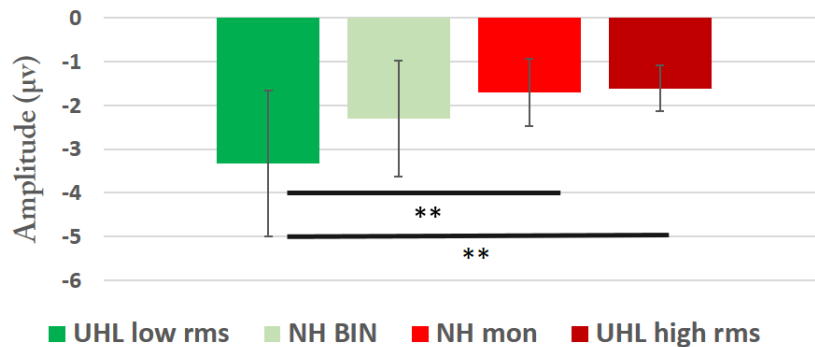


Figure 3.23: *Ipsilateral activation pattern at an area of interest covering the auditory cortex at C5, CP5, T7, TP7 in the hemisphere ipsilateral to the stimulation at 100° of deviation. Patients with better localisation performances showed highest MMN amplitudes.*

We also wanted to visualise the negative distribution of the MMN across the scalp in the 4 groups. In the figure 3.24 we visualise the scalp responses to stimulation at 100° of deviation in the ipsilateral condition, in a window of 40 ms around the MMN peak. The distribution of the MMN in the following temporal window, showed contralateral response in NHS in binaural condition with an activation of central areas also, as a response to the deviation at 100°. Patients with good localisation performances also showed centered MMN distribution. However this distribution was more frontal in patients with poor localisation performances and in monaural controls.

**Negative potential distribution 40 ms
around MMN peak at 100° of deviation.**

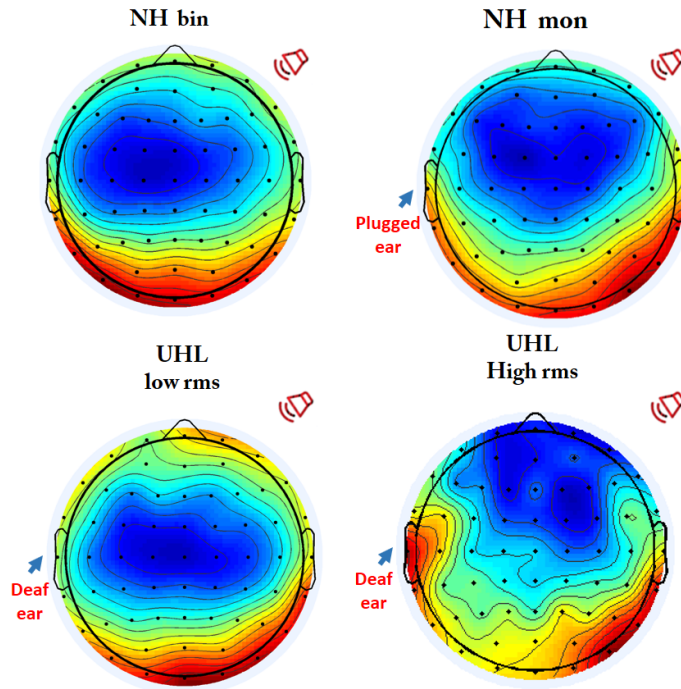


Figure 3.24: *Negative potential distribution among the 4 groups, binaural controls, monaural controls, UHL with low RMS, UHL with high RMS. The responses were visualised in the ipsilateral condition at 100° of deviation. The topographies showed higher recruitment of frontal areas in monaural controls and UHL with high RMS.*

3.2.5 Discussion of the section.

a. MMN variation as a function of magnitude of deviation.

The studies that evaluated MMN reported a linear relationship between the amplitude and latency of the MMN and the magnitude of change with higher amplitudes and shorter latencies when deviance from standard is increased. In a study of Sams in 1985 assessing auditory frequency discrimination, higher MMN amplitudes were reported when the frequency of the deviant progressively increased. In his study, Sams used a standard sound of 1000 Hz, with 4 frequency deviants (1002 Hz, 1004 Hz, 1008 Hz, 1016 Hz and 1032 Hz). The MMN slightly appeared starting from a deviation of 1008 Hz, and progressively increased to reach its max-

imal amplitude in the response to the deviant 1032 Hz. This result suggests that MMN sensitivity to frequency deviance could start from a deviation range of 8 Hz between the standard and the deviant [267].

The progressive increase of MMN with the magnitude of change was also reported assessing spatial deviance detection. Deouel in 2006 reported a progressive increase of the MMN with the deviation from the standard positioned at 5° in the frontal azimuth for NHS [215]. The deviants used by Deouel were positioned at -5°, 15°, 25° and 35°. This experimental design assessed spatial sensitivity to a deviation starting from 10° of deviance. Nevertheless, Benneman in 2015 assessed spatial sensitivity to smaller spatial deviants starting from 5° of deviation. The standard sound was positioned at 65° and the deviants were positioned at 70°, 75° and 80°. The MMN was significant in all the positions starting from the smallest deviance of 5° at 70° of position to reach its highest amplitude at 80° [193].

Until today, the smallest spatial deviance used in spatial MMN studies was of a minimum of 5°. Although studies on spatial discrimination abilities, showed an ability to discriminate sounds with a resolution of 1° in mammals, this magnitude of deviation is still not evaluated using the MMN. Nonetheless, it is known that our auditory perception is more sensitive to spatial deviance in the frontal azimuth compared to lateral space. Benneman reported auditory spatial sensitivity to 5° of deviance in lateral space, this suggests that MMN could appear in conditions with spatial deviations that are smaller than 5° if tested in the frontal azimuth.

Patients with hearing impairment may have higher thresholds of spatial deviance detection, and may need higher spatial deviation to elicit an MMN compared to NHS. The only study that evaluated spatial MMN in symmetrical and asymmetrical hearing loss was the study conducted by Cai in 2015 [204]. Cai evaluated the spatial deviance from a standard at 0° in the frontal azimuth with two large deviations of 45° and 90°. The study reported a significant MMN that increased progressively with the angle of deviation in the 3 groups (NHS, symmetrical hearing loss and asymmetrical hearing loss patients.)

The spatial MMN in hearing impaired patients is rarely assessed in the literature, the only study evaluating spatial deviance detection in these patients used a relatively large spatial

deviation of 45°. In our study, the spatial deviance detection was assessed starting 10° of deviation. Similarly to previous reports, MMN amplitudes progressively increased with the magnitude of deviation starting from 10°, to reach a high amplitude and shorter latency for 100° of deviation. The progressive increase of the MMN was present in all the groups, except in some cases where MMN was not significant (for NH *mon* in ipsilateral condition at 10° et 20° of deviation, for patients with UHL *high RMS* at 10° and 20° of deviation).

b. MMN variation as a function of group and condition.

The introduction of an acute plug in NHS induced a reduction in deviance detection of 10° and 20° of deviation when the plug was ipsilateral to the standard. This disruption in binaural integration due to ear plugging reduced neural sensitivity to spatial change in NHS, however, it seems to not impact neural spatial perception in patients with UHL *low rms* patients despite their hearing loss (PTA=60 dB).

Similarly to NHS-mon, hearing impaired group with poor localisation performances reported reduced efficiency of the neural spatial sensitivity explained by the reduction or sometimes disappearance of the MMN responses in the patients with UHL *high rms*, with later latencies compared to NHS. These findings were consistent with previous studies that investigated ERP changes in different auditory functions. For instance, Campbell and Sharma [316] showed a broad distribution of the P2 response over the cortical areas for patients suffering from moderate hearing loss when they were compared to NHS in a passive listening task using speech stimulation. It is important to note that the latency or the peak ERP is an indicator of the period needed to decode the acoustic information generated by a stimulus in the auditory system, this suggests, in the case patients with UHL *low rms*, that the auditory system is insufficient in processing the degraded inputs [317, 318], consequently leading to the activation of additional cortical regions as compensatory pathways [316].

In this study the latency of the MMN peak appeared to be later for hearing impaired patients and NHS in monaural conditions when the deviation was of 100°, this latency delay may also be accompanied with the recruitment of additional neural resources [319, 224]. In addition to the latency delay, the reduction of MMN amplitude in patients with UHL *high rms* and

NH mon at 100° and its disappearance at 10° and 20° of deviation can also be a reduction in neural recruitment in the auditory cortex [319, 224], this reduction in cortical activation supports previous findings reporting later latencies and shorter amplitudes of MMN after hearing impairments [204].

c. Relationship between neural findings (MMN) and behavioral performances (RMS).

MMN was previously used to assess neural responses in different hearing situations. For instance, MMN was used in cochlear implants to assess discrimination abilities of speech syllables. In these studies MMN findings were consistent with the performances in cochlear implanted patients [320, 321, 322]. In 2004 Singh S, used the MMN to categorise cochlear implanted patients into good and poor performers. His findings suggested that MMN can be used to assess cortical functions in terms of auditory memory and discrimination in young children with cochlear implants and can be used as tool for differentiating good from poor performers [322].

In this thesis, we used the MMN to categorise patients with unilateral hearing loss into good and poor performers based on their average RMS. The good performers (UHL *low rms*) had neural responses that were similar to the ones reported in NHS in binaural condition. This neural finding confirmed the hypothesis already adopted by Middlebrooks in 1990 [8] where they reported near normal spatial performances for some patients with UHL. Our 6 patients with UHL *low rms* presented better localisation accuracy in the free field, in addition to higher individual MMN amplitudes compared to NHS in monaural conditions, and equivalent amplitudes compared to NHS in binaural condition, even though the average hearing loss of this groups was of 60 dB.

Thus, the MMN response to 100° of deviation, does not only present reactions to spatial deviance, but it can also be considered as a marker of left right discrimination or lateralisation. The larger the MMN at 100° of deviation the more important is the spatial sensitivity to right left displacement. If the MMN amplitude was lower, left right discrimination is weaker, and the tendency to project localisation answers to the healthy side is higher (lateralisation).

This behavioral tendency is presented in the figure (3.10), where NHS and UHL *low rms* , who had similar high MMN amplitudes at 100° showed little projection of responses to the side of the deaf ear (3.6% and 4.1%), while NHS mon and UHL *high rms* showed higher answer projections towards the side of the plugged/deaf ear, that was consistent with lower MMN amplitudes at 100° compared to binaural NHS and UHL *low rms* .

Previous studies by Middlebrooks [8] did not report conclusive explanations related to the great variation of spatial performances among the patients with UHL, suggesting that in some cases patients can benefit from formal training in localisation strategies, proving an ability in these patients to learn how to spatially perceive sounds under monaural condition that explains their near normal localisation accuracy in some cases. The evidence about cortical reorganisation underlying spatial adaptation in these patients are limited and rarely investigated.

d. Cortical reorganisation after unilateral hearing loss.

Our data proved that some patients with UHL were able to adapt to monaural hearing conditions revealing normal behavioral performances that are also explained by normal MMN amplitudes. However, topographic distribution of the MMN between NHS in binaural condition and UHL *low rms* were different. While NHS showed contralateral activation in response to the deviant at 100°, patients with UHL *low rms* showed bilateral distribution of the MMN in both contralateral and ipsilateral hemispheres in addition to central areas. Therefore, different cortical MMN responses were noted in this UHL group compared to NHS, proving that this population underwent cortical reorganisations to adapt to the hearing impairment.

The studies exploring cortical reorganisation after unilateral hearing loss reported cortical changes in the auditory cortex ipsilateral to the healthy ear with more synchronous and equal activation of both hemispheres [136, 117]. Studies using magnetoencephalography (MEG) also reported stronger dipole moments in the ipsilateral hemisphere of the intact ear in subjects with late [323] and early or congenital deafness [186].

Langers in 2005 conducted a connectivity analysis to track response to auditory information

in UHL subjects. He reported symmetrical activation for auditory cortices, however, the response remained contralateral in the midbrain and in the thalamus, with no evidence for plastic reorganization on subcortical levels. Moore and King described a number of changes in the neural projection pathways in the auditory brainstem, midbrain and primary auditory cortex of non human mammals after unilateral hearing loss. However, none of these studies tried to correlate the cortical reorganisation with spatial auditory performances [324].

A study by our colleague Nicolas Vannson (submitted), aimed to assess cortical reorganisation after UHL, by correlating cortical activity with spatial localisation and auditory discrimination task. The findings suggested a stronger ipsilateral activation in the non primary auditory cortex (NPAC) in UHL patients. Nonetheless, the ipsilateral activation was negatively correlated with auditory spatial performances. With higher activation in the ipsilateral NPAC when sound localisation was poorer.

While Vannson suggested deleterious reorganisation characterized by stronger ipsilateral activation in the NPAC. Our MMN data suggest that stronger negative MMN in the ipsilateral hemisphere is in favor of the spatial adaptation. Thus, the MMN protocol reflects unattended auditory situations that does not require active listening as in Vannson study. MMN is also known to be generated in small areas specific to particular attribute that characterises the deviant [224], in addition to fronto central generators [292].

Key points

- The MMN progressively increased with the magnitude of deviation from the standard.
- NHS-mon were unable to detect spatial deviance at 10° and 20° of deviation when the plugged ear was ipsilateral to the standard, while UHL_{low rms} were able to.
- UHL_{low rms} showed similar MMN variation compared to NHS in binaural condition.
- The results observed concerning MMN variation across the groups were consistent with the localisation performances .

3.2.6 MMN variation in patients with BHL.

The advantage of the our study on symmetrical hearing loss subjects is that it helps to step into the investigation on central processing in the left and right cortical areas in order to compare activation differences. Patients with BHL underwent two conditions, one where the standard was presented at the right, the other one at the left. We carried out the bootstrap confidence interval analyses to test the significance of the MMN at each deviation positions for both left and right condition. The analysis did not reveal a significance for the MMN at 10° for both left and right responses, the MMN remained significantly negative for the rest of the positions (20° and 100°) at both conditions.

MMN significance using Bootstrap analysis.

	10°	20°	100°
BHL-R	+/-	+/+	+/+
BHL-L	+/-	+/+	+/+

Absolute peak / +20 ms peak latency window.

« + » MMN different from zero.
« - » MMN not different from zero.

Figure 3.25: Bootstrap results of the MMN significance at 10°, 20° and 100° for patients with BHL in the left and right conditions.

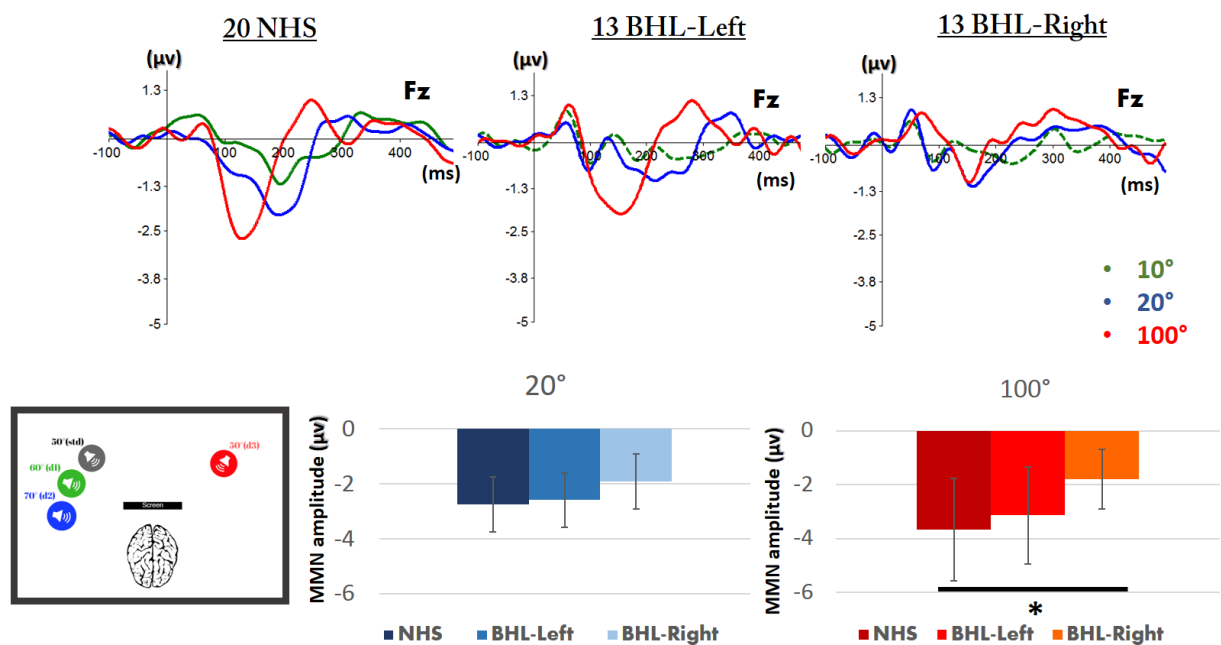


Figure 3.26: MMN amplitudes for NHS and BHL at left and right conditions.

We compared the individual peak of the MMN for patients with BHL in the right and left condition to the individual peaks of NHS at 20° and 100° of deviation, since the bootstrap analysis in the GA time window did not reveal significant negativity at 10°, individual

peak amplitudes at this position were excluded from further statistical comparisons. The Wilcoxon rank sum comparison did not reveal significance between NHS and patients with BHL in both right and left conditions when the deviant was positioned at 20° of deviation from the standard. However, the deviation towards the opposite side of the standard at 100° revealed a significance only between NHS and BHL in the condition where the standard was positioned at the right side of the subject, with the third deviant (-50°) at his left ($p < 0.05$). To further explore the significant amplitude difference at 100° of deviation for the Right condition compared to NHS that was not significant for the Left condition, we decided to conduct a comparison between right and left hemisphere activation between both right and left conditions in patients with BHL at 100° of deviation. It is important to remind that the Right stimulation is represented by a standard at the right side and the 100° of deviation that is positioned at the left, will induce a contralateral activation in the right hemisphere. Consistently, in the Left condition, the standard position is at the left, the third deviant at the right, eliciting a activation in the left hemisphere.

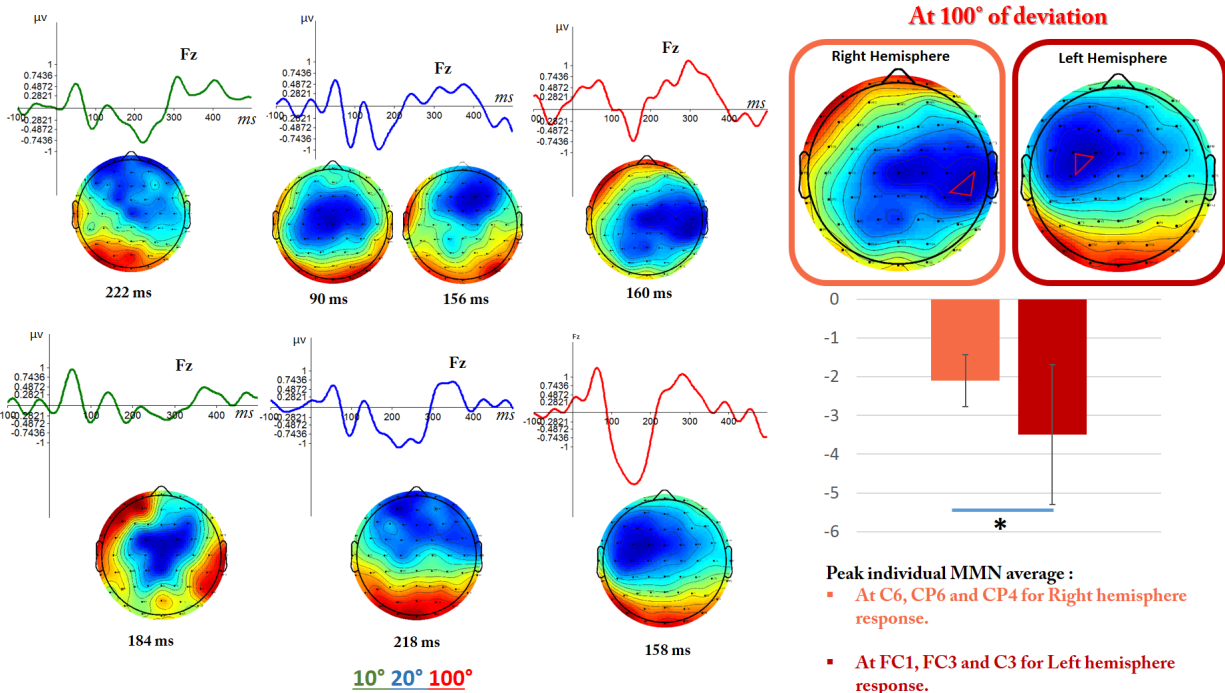


Figure 3.27: Scalp topographies representing activation patterns for 10°, 20° and 100° of deviation for patients with BHL in both Right and Left conditions. The hemisphere comparison revealed higher activation in the left hemisphere compared to the right hemisphere in response to the deviation at 100°.

Scalp topographies were presented to illustrate the voltage variation according to sound displacement and stimulation direction. At 20° a double negativity was present when the standard was positioned at the left side (peak at 90 ms and 156 ms), the earlier negative response at 90 ms was more centrally projected (Fcz, Fz) compared to the later response that was more fronto-central with more negativity at frontal electrodes (Fpz, Fp2, AF8) as shown in the figure 3.29. Thus, No significant difference was noted between the MMN responses to 20° of deviation when the speaker was at the right and at the left. However, MMN for 20° peaked later (218 ms) when the standard was presented at the left leading to later cortical activation in the right hemisphere.

The comparison using Wilcoxon test showed in the figure 3.29 that MMN response to deviation at 100° for BHL was not significantly different than MMN response for NHS when the third deviant was at the right, however, a significant reduction of the MMN peak was

noted when the 100° deviant was at the left side (Std at the right). In order to quantify this negative voltage and compare it with the Left hemisphere activation in the condition where the standard was presented at the left, we picked the three electrodes that presented highest voltages for each condition. For the right condition we picked C6, CP6 and CP4 (for right hemisphere responses). For the left condition we picked FC1, FC3, C3 (For left hemisphere responses). We didn't compare the activity in two similar brain areas, we were interested in the comparison between the areas that had a maximal activation, or higher negative responses. The individual MMN peak amplitude was selected at each electrode site and averaged for the 3 electrodes that showed largest MMN amplitude, in order to get one MMN value that represent the mean individual amplitude for the three picked electrodes. We conducted the Wilcoxon rank sum test to compare the mean amplitudes found in the left and right hemisphere. The results showed higher negative response in the left hemisphere compared to the right hemisphere that showed lower activation magnitude when the 100° of deviation was at the left.

3.2.7 Discussion of the section.

The cortical activation pattern of patients with BHL seem to differ from patients with UHL. The MMN response appeared to be reduced compared to MMN activity in normal hearing subjects while these patients reported similar behavioral performances in the free field localisation task. Many studies have put forward several models of population to code this apparent low resolution at the neural level, relatively accompanied with high behavioral performances [123, 79, 325, 326]. Recent models have suggested that the accurate performance found could be an emergent property, meaning that it is the association of responses of neurons in the auditory cortex that are tuned broadly to their ipsilateral or contralateral fields [326, 327]. However it is not the case for patients with UHL with high localisation accuracy. This is mainly related to the evidence about plasticity derived from studies on unilateral peripheral hearing loss or complete monaural deafness in human and non human mammals [136]. These studies have demonstrated that hearing loss may change the response properties of neurons at subcortical and cortical levels of the central auditory system, in addition, it has

been demonstrated that regions of their normal peripheral input often become responsive to intact adjacent frequencies in studies of frequency specific peripheral hearing loss on non human mammals [136]. These adaptational strategies adopted by patients with UHL are a consequence of the alteration of binaural cues due to the asymmetrical hearing threshold between both ears [136].

According to the behavioral results of the localisation task, symmetrical hearing loss patients seem to preserve their ITD and ILD cues that does not influence their spatial perception. However, the EEG analysis showed an inability of BHL to detect spatial deviance at 10° , but spatial discrimination between BHL and NHS were not different at 20° and 100° for the left condition. These results can have different explanations. The first is that the bilateral hearing loss of 40 dB have an influence on both spatial discrimination and spatial localisation to some extent. However, the detrimental effect of symmetrical hearing loss was probably not presented by the sound localisation task because of the simplicity of the task, that contained visual familiarisation with the locations of the speakers. Thus, the speaker separation of 15° may not be enough to reveal differential errors between NHS and patients with BHL. Another explanation, is the influence of the hearing loss on spatial discrimination but not spatial localisation, especially in our case were age range of patients with BHL is older than NHS. Thus, previous studies that tried to compare spatial localisation to spatial discrimination showed that aging have an effect on MAA thresholds but not on localisation accuracy [153], [95], thus, good localisation accuracy may not be a predictor of good spatial discriminative abilities especially in our case were control group is younger than BHL group and localisation task is less sophisticated.

Concerning hemispheric specialisation in spatial discrimination, the analysis of maximum activation of patients with BHL showed higher left hemisphere activation in response to the deviant at 100° (at the right). Hemispheric specialisation of spatial perception is not well documented as for speech and language processing. A long history of exploring hemispheric asymmetries in speech and language processing have suggested the two most often reported specializations: the general left hemisphere specialization for speech and language processing, and a right hemisphere specialization for spectral processing [328, 214, 329, 330]. In a

study by Zatorre in 2003 using PET scan to examine responses to temporal and spectral variation of sound, he confirmed the specialisation of left hemisphere for temporal processing. Hemispheres responds preferentially to different features of acoustic simulations, the left auditory cortex is thought to be more specialised in processing temporally complex and rapidly changing sounds characteristic of non-tonal speech which is the case in our stimulation paradigm, while the right hemisphere is more activated in response to tonal and spectral content [328, 331, 332, 333, 334]. In addition, brain imaging data suggested better temporal resolution for the left auditory cortex [328]. Belin [328] predicted that increasing the rate of temporal change would lead to a preferable recruitment of left cortical areas compared to right cortical ones. However, temporal and spectral processing of the sound seem to differ in the two hemispheres, the processing may be related to anatomical asymmetries in the myelination of hemispheres and spacing of cortical columns [214]. We suppose that the higher leftward activation might be related to the spectral shape of the sound used (Low frequency band noise) rather than a reaction to spatial displacement. Further inspections must be applied using different types sound stimuli in order to demystify the ambiguities about hemispheric specialisation in spatial auditory perception.

Chapter 4

Virtual Reality and sound localisation in the 3D space.

This chapter describes a multicentric study that was done with the collaboration of the Integrative, Multisensory, Perception, Action and Cognition Team (IMPACT) in the CRNL in Lyon and the university of Trento, Italy. The data acquisition in Lyon and Trento as well as the data analysis were done by the PhD student Chiara VALZHOLGER under the supervision of Francesco PAVANI.

In natural situations, the localisation on a sound consists of linking a given physical source with the position of the listener. This link is shaped by natural mechanisms that interfere next to the binaural and monaural spectral shape cues in order to reach successful results in localizing a sound. A large body of studies have been conducted to assess sound localisation in different modalities, using different methodological approaches. During the design of any experimental procedure, it is important to take into consideration the combination of various aspects that might influence spatial auditory performances. The size of the room, the duration and type of the stimulus, the contribution of head and eye movement, the state of the participant (active or static) and the spatial dimensions tested. All these scenarios are vital for a successful experimental design since they help the listener to step closer to natural spatial auditory experiences.

In auditory spatial research, designing an experimental tool to evaluate spatial perception by taking into consideration all these aspects is very challenging. Many studies face methodological limitations in controlling aspects interfering with localisation performances. Head and eye movements are necessary mechanisms that are used in the daily life to localize sounds. However, many studies tend to assess localisation with the head kept immobilized and the eyes fixated on the center of the screen. In addition, different protocols use different response reports: verbal answer, hand pointing, head pointing or localizing using more dynamic interfaces.

Clinical methodologies adopted to test patients localisation abilities are in most of the cases limited to a sound source identification task with a set of loudspeakers fixated in a specific plane that is in most of the time a horizontal plane. Although a patient with hearing loss is being evaluated with an extensive types of testings for different auditory functions, from pure tone audiometry to speech intelligibility, it is however important to mention that the testing designs provided for sound localisation are quite simple compared to the designs used for speech intelligibility testings for example.

Our previous chapters explained how plasticity is induced in unilateral hearing loss patients. A great amount of researches provided evidence about the existence of plasticity based on adaptational strategies reflected by behavioral performances, that requires regular tracking over time. This behavioral manifestation is not sufficiently assessed using only RMSE and reaction times. Further controlled parameters that could largely express compensatory strategies due to hearing loss, are head and eye movements. Therefore the assessment of spatial perception typically requires freedom of head and eye movements in addition to more realistic environments to assess the impact of audio-visual integration on spatial perception. The immersion in more realistic scenarios have a valuable impact on listeners perception. When we test localisation abilities with the head and eyes immobilized in a neutral visual environment we modulate the localisation accuracy that is strongly affected by the natural behavior of the listener in the real environment.

Additional example on the importance of realistic immersion in spatial assessment, is the multidimensional characteristic of the setup. When we test sound localisation, we tend

to restrict our protocols to one dimension, mainly the horizontal, where we only evaluate sensitivity of binaural cues, or only vertical where we inspect spectral shape cues sensitivity. In this chapter we propose a new innovative method that takes the different localisation mechanisms and modalities into consideration in one setup using virtual reality system.

Virtual reality systems provide reliable spatial tracing accuracy by immersing the subject in natural visual environment. This system also provides a high accuracy of head motion tracking and eye tracking. Researchers using VR techniques for the past 20 years have made considerable steps in approaching to real exploitable environments [335]. These experiments were able to study the perception of the subject as a listener and observer as in his everyday life [336]. Our scientific interest in VR system is mainly related to our need of a complex measuring tool to trace more sophisticated mechanisms rather than simple errors. Many studies showed that head and eye movements have a high impact on sound localisation [337].

4.1 Contribution of head and eye movement in sound localisation.

Wallach in 1938 was the first to discuss the implication of head movements in spatial auditory functions. Head movement is characterized as the momentum when the head revolves around a constant axis in order to shift the axis of the ear in one plane. If rotation of the head around an axis changes, the angle between an emitted sound and the axis of the ear also changes [337]. When we locate sound direction we tend to rotate our head horizontally so that the limen of sound localisation decreases [338, 88]. It is known that head movements are present when the spatial location of a sound is more lateral, or presented at any location away from frontal areas [339].

In 2013 Morikawa tried to study the influence of head rotation on sound localisation, using three types of stimulations: a low pass noise of 500 Hz, a high pass noise of 12 KHz and a white noise. They reported that head movements were not or slightly engaged in frontal position, in addition, the yaw angles of head rotation used to localize lateral position were

not equivalent to the angle in the azimuth, meaning that the subjects does not need to turn their heads to this extent in order to reduce source location ambiguity. Presumably, head rotation is only needed to get additional information about sound location, and it can be obtained by a slight head yaw angles to decrease difference limen.

The head rotation is mainly evoked during the stimulation, meaning that the variation of the primary binaural cues must be used as dynamic cues, creating a swinging sound image around the head when it is rotating and dramatically reducing ambiguities of sound locations. the maximum head movement was of around 60° . It appears that the interindividual variability in head movements was high, suggesting that each listener might have his own strategy of localizing sounds [340].

In another study by Mirakawa they tried to compare the variation of head movements as a function of stimulation types using three simulations: a low pass noise of 500 Hz, a high pass noise of 12 000 Hz and a white noise. They reported only slight head movements when localizing the white noise, thus, they found that the localisation of the white noise was perfectly accurate even in the head-still condition. It seems that dynamic cues are not used extensively in white noise localisation where slight head rotations seem to be sufficient. The localisation of high and low pitch noise, improved of around 20% in the active head condition, in addition to the disappearance of front back confusions, highlighting the important role of dynamic cues for localizing low and high pitch noises rather than white noise [341].

Head movements are elicited when important changing in the environmental sensory inputs occur. According to many studies assessing active head movements, the head reaction seem to be slow compared to the onset of a specific stimulus, meaning that head movements are not generated simultaneously with a stimulus. Thus, active head movements seem to be slower than passive head movements and strongly depend on the movement velocity, later perception of a stimulus, require faster head movements. Blauert suggests, in a review in 1997, that an acoustical signal elicits head movements after an average of 350 ms [64]. Thurlow and Mergener also suggested that a short stimulus duration of around 300 ms seem to have no influence on spatial accuracy or spatial auditory performance. This is probably the time required for the nucleus of the branchium of IC to send inputs through the axons to enable

reflexive head and eye movements towards the sound [2].

Next to head movement, studies tried to explore the effect of a specific stimulation on gaze shift. Usually, when a target eccentricity exceeds certain limit, gaze shift is elicited. However, its achievement requires also a combination of head and eye movements. In order to occur, a gaze shift require three important components: saccadic eye movement, head movement and compensatory eye movement. A normal gaze is elicited first by a saccadic eye movement that is initiated after 200 ms of the stimulus onset, 50 ms later, the head follows the saccadic component progressing at a slower velocity compared to the velocity of the eye saccade, the movement of the head is terminated by a final compensatory eye movement [342].

The amplitude and likelihood of head and eye movements are influenced by different factors. The eccentricity of the stimulus is one of these factors. An eccentricity exceeding 25° is enough for head movements to occur, and increase its amplitude with the increase of the eccentricity [343]. Gresty also suggests that the amplitude of head movements is influenced by the visibility or not of the stimulus [344]. He was able to show that when a stimulus was continuously visible the amplitude of head movement is reduced from 85 to 75 of total gaze displacement. Head and eye movement latencies are also influenced by the stimulus modalities, with shorter latencies when audio visual stimulations are presented simultaneously, larger latencies when only auditory stimuli is presented, and largest when only visual stimuli is presented [345].

The subjects condition or preference can also influence on gaze shift, since subjects can vary between "head movers" and "non head movers". An experiment conducted by Sander and Leger in 1991, tested the influence of restriction of visual field on head and eye movement. They used a visual target moving in a 85° horizontal range, participants were instructed to follow the stimulus either with the eyes or with the hand. When the visual field was not restricted, the amplitude of head movements was smaller in the hand pointing condition, nonetheless, when the experimenter restricted the visual field to 20° , errors with hand pointing increased [346]. An evidence from pharmacological studies showed that the velocity of head and eye movement is reduced when patients are under CNS depressants treatments and under the influence of alcohol [347]).

4.2 Multisensory nature of a spatial hearing.

Head and eye movements are important indicators of perceptual performances, their analysis provide crucial information about the behavioral strategies adopted by a subject to accomplish a perceptual task. The accurate tracking of head and eye movements is able to provide evidence that surpasses auditory and visual function information, and reflects attentional phenomena involved in the integration of surrounding stimulation. However, the contribution of multisensory integration in spatial auditory coding has been poorly investigated. Spatial auditory evaluation protocols usually restrict the localisation task to a unisensory modality with little consideration regarding visual inputs.

Nonetheless, this methodological approach does not reflect natural behavior in multisensory environment. For example, presenting or not the speakers used in an auditory experiment have a strong impact on localisation accuracy. In many studies, the experimenter tend to hide the loudspeaker behind visible barriers to prevent expectancy of spatial location. Although in this case the participant does not have a clue of the loudspeaker location, the dimensions of the room and the extremities of the setup, restrict the expected auditory-visual experimental field.

The role of vision in sound localisation has been investigated in different studies. It has been shown that the coupling of auditory and visual spatial cues is very efficient for the occurrence of adaptive cross-modal brain plasticity after hearing loss [348]. Target location is encoded in auditory and visual systems in different manners, however, in order to properly identify and detect stimulus source spatially, both modalities must provide sufficient informative auditory and visual inputs about the sound and its image. In addition to the audio-visual integration, vestibular properties of the ear will also provide inputs through head orientation and motion. However, the evidence about concordance and accuracy of these mechanisms and the spatial calibration adopted relative to these sensory modalities is a little limited [349].

The co-calibration of auditory-visual inputs is necessary to maintain cross-sensory concordance and detect spatial auditory locations at high accuracies. The cross modality calibration, have been roughly described in animals such as in bar owls, however, in humans its

exploration is quiet rudimentary. Human sound localisation has been investigated in visually compressed spatial scenes. Participants wore 0.5 lens to compress visual spatial space by half, leading to a reduction in the visual space gain. After 3 days, the reduction of spatial gain, induced similar reduction in spatial auditory localisation that was recalibrated to the spatially scaled visual space. The findings suggest that the compressed visual field led to auditory adaptive changes in sound localisation [349].

In 2000, McDonald tried to investigate the influence of auditory attention on visual motor responses. In his experiment he used signal detection measurements to check if involuntary orientation of attention to a sudden auditory stimulation, can influence the processing of subsequent visual stimulus that might appear nearby, using signal detection measurements. His experiment was able to show that a sudden auditory stimulation may improve the ability to detect a subsequent visual cue that appears at the same location, proving how the involuntary orientation of the attention to a specific sound in the space can lead to earlier processing of visual stimulations [350].

4.3 Overview on experimental designs using HTC VIVE.

Immersive VR allows us to step further in our goal of investigating spatial perception in a more controlled and principled manner. Although VR systems may still not be perfect, technology however helped in improving the system that is now extended and being used by many laboratories to investigate different stages of human perception. This progress made VR companies more interested in human research and optimized VR technology to offer a convenient framework for scientific researches. The validity and reliability of VR interventions in spatial hearing evaluation was tested in different studies using Head Mounted Displays (HMDs) that provides a built in head tracking that enables position estimating in a room allowing the users to explore real size virtual environments.

Borrego in 2018 tried to compare two VR systems to examine their validity in serious games and head related research application such as spatial auditory behavioral researches. The HTC VIVE was compared to the Oculus Rift in terms of the working range of the head

tracking and the working area, accuracy, and jitter in a room-size environment. His study showed that the HTC Vive possess twice larger working area compared to Oculus Rift with excellent accuracy and jitter at standing height. Niehorster in a study in 2017 conducted a test on the HTC VIVE to evaluate its orientation tracking capabilities and usefulness in scientific research especially in spatial auditory perception [351].

The HTC VIVE consists of a headset, two hand controllers and two infrared laser emitter units or base stations. A nominal field of view of about 110° is covered by the headset through two 1080*1200 pixel displays updated at 90 Hz. In this system, no external cameras are needed, the vive base stations have two laser emitters called light houses that sends out laser sweeps alternatingly spanning 120° in horizontal and vertical directions. The laser emitted by the Lighthouses interferes with the photo-diodes that covers the headset and the controllers. The headset position and orientation is continuously tracked and updated primarily at a high rate. The largest tracking setup was over a range of 8 m distance between both base stations. The setup involves a calibration routine that consists on calibrating the floor, the center of the room and the so called "play area" to define the coordinates of the VIVE tracking system [335].

The HTC VIVE is considered to be an accurate tool for exploring and navigating in virtual environments. The VR market is rapidly developing and it is trying to make the equipment available to a larger number of research laboratories, especially after it brought new implemented innovations such as front camera, HD displays, large field of view and a high refresh rate. All these advantages provided by this system enables it to be used on a higher level of investigation, including audio-visual perception [336].

Ahrens in 2018 aimed to test this system and its effectiveness in evaluating sound localization. He tried to combine loudspeaker-based virtual sound environments (VSE), and the HMD of HTC VIVE to study audio-visual perception in realistic environments. The auditory experimental setup, consisted on 64 loudspeakers housed in an anechoic chamber and arranged in a full sphere. The real environment was replicated in the HMD to ensure comparable visual information with and without HMD. The controller was used as a pointing device to indicate the perceived location of the stimulus, a button press on the index finger

was used to validate the answer. However, the fact that the controller was not visible during the experiment elicited a pointing bias in azimuth (average bias 1.6) and in elevation (average bias 19). He suggested that localisation error was minor when a visual information was presented in the HMD, he also adds that presenting additional visual information such as hand location, room dimensions and pointing feedback had similar influence as obtained in real environments, concluding that a VR system may allow a full immersion into audio-visual scene [352].

Ahrens also tried to explore the effect of the HMD on the transfer function in order to check whether the size of the headset could influence the localisation precision by modifying the listeners HRTFs. He compared localisation accuracy between (blindfolded) condition and (blindfolded wearing HMD). He found a slight increase of the errors of about 1.8 in elevation for example when the participants were wearing the HMD. However these errors may not be noticeable once visual information is presented in the HMD [352].

In this study, the variation of localisation accuracy according to visual representation in the HMD was easy to investigate. However, as any innovative technology in the process of development it have some limitations, mainly with the accuracy of the hand pointing to visual targets that was found to be high in azimuth, in addition to larger bias in the elevation due to the shape of the controller. In addition the effect of the size of the HMD on HRTF was negligible in the frontal locations; however it became more significant in the lateral source locations. In a general way, testing spatial auditory functions using HTC VIVE is a very innovative and promising techniques, because it takes into consideration all the aspects that a listener rely on when localizing a natural sound, and by all aspects we mean the head movement, the visual scenarios and the three dimension location of the sound (elevation, azimuth and depth).

4.4 Materials and methods.

Participants.

Thirty-six participants (age: $M = 25.08$, $SD = 2.96$, range [20-32], 13 males, 34 right-handed) were recruited to participate in the experiment at the University of Trento (Italy), at the Integrative, Multisensory, Perception, Action and Cognition Team (IMPACT) lab in Lyon and at the University of Toulouse (France). All participants signed an informed consent before starting the experiment, which was conducted according to the criteria of the Declaration of Helsinki (1964, amended in 2013) and approved by the respective ethical committees. All had normal or corrected-to-normal vision and reported no movement deficit. Hearing threshold was measured using an audiometer for all participants, testing different frequencies (250, 500, 1000, 2000, 4000 Hz), on the right and left ear separately. All participants had an average threshold below 17.8 dB HL.

Apparatus and stimuli.

Virtual reality (VR) and kinematic tracking was implemented using 3 identical HTC Vive Systems. Each of which comprised one head-mounted display (HMD, resolution: 1080 x 1200 px, Field Of View (FOV): 110°, Refresh rate : 90 Hz), 1 controller (which was used by experimenter to calibrate head position and interrupt trial data registration), 2 trackers (one which was held by participants to indicate the position of the sound and the other which was placed above the speaker to track its position in real time) (figure 4.1.A) and 2 lighthouse base stations (which served for regular scanning of the position of the controller and the tracker). Tracking precision and accuracy of the HTC Vive System is adequate for behavioural research purposes (see Verdelet et al., 2019). The HMD was equipped with an SMI eye-tracking system (250 Hz). All stimuli were controlled and delivered using a ZALMAN PC (OS: Windows 10 (10.0.0) 64bit; Graphic card: NVIDIA GeForce GTX 1060 6GB; Processor: Intel Core i7-7700K, Quad-Core 4.2 GHz/4.5 GHz Turbo - Cache 8 Mo - TDP 95W) using Steam VR software and the development platform Unity. Participants were seated on a rotating armless chair with no chin rest, in the center of the room. The

rooms had the following dimensions: Rovereto: 4x3 meters; Lyon: 3X6 meters; Tououlouse: 3x5 meters, not treated for being anechoic and quiet.

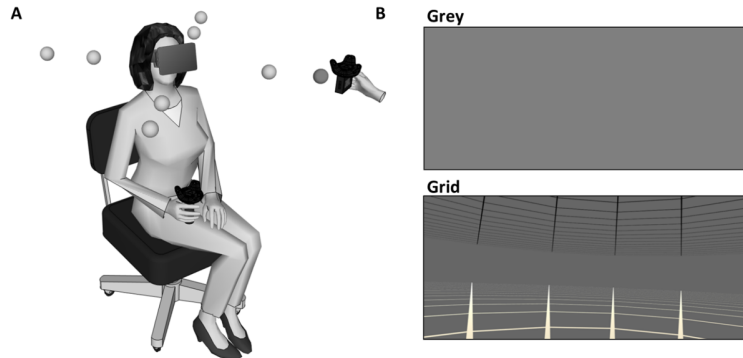


Figure 4.1: *Experimental procedure and setting. (A) Schematic representation of participant and speaker positions. Participant held in her hand the tracker, while experimenter held the speaker, which tracker attached above. (B) Representation of 2 3d visual environments: Grey and Grid.*

Auditory stimuli were delivered by a real, unseen speaker (JBL GO Black), whose position was tracked in space. The auditory stimulus was an amplitude-modulated (4 Hz) white noise bursts (about 60 dB SPL as measured by a Decibel Meter TES1350A placed at ears level). This solution allowed us to track the position of the speaker (tracker attached), the hand of participant (tracker handled) and the Head Mounted Display, via sensors on the headset and VR controllers using IR led positioned on the base stations (frequency sample 250 Hz). The software is designed to guide the experimenter to align the real loudspeaker (the sound source) with the desired 8 predetermined position in the virtual environment.

Experimental Procedure.

Before starting the experiment, participants were instructed about the task and the virtual reality equipment. Participants were asked to listen carefully to each sound (which lasted 3 seconds) and to indicate its location in space using the tracker held in their right hand (i.e., rigid body) all along the task at a pre-determinate fixed position. Participants were not allowed to move the hand neither the trunk during sound emission, they were only

authorised to move their head if needed. Once the 3 seconds stimulation is finished, they were allowed to freely move in the chair to indicate sound source. They were informed that sounds could be delivered anywhere in the 3D space around them always in a reachable position. Participants performed sound localisation under two visual conditions: a uniform grey scene (Grey) and a more structured scene with spatial references (Grid) (Figure 4.1.B). Specifically, GRID was composed by 2 horizontal figures drawn like spiderwebs of 50 m of radius, with 19 straight sides (angle around 20°) and 20 sub-figures plan separate by 2.5 m. First was placed on the floor ($Y=0$ m) and the second at 10 m of height ($Y=10$ m). So, we created a structured environment with depth clue without wall effect. The subject was sat in the center of the first grid.

The experiment began with head-center calibrations which was performed by collecting the 3D position of the two ears (using the controller). Then, an eyes calibration was performed: participants were asked to follow a moving dot with their eyes. Crucially, these head-center coordinates served as origin of the polar frame of reference that defined speaker, head and gaze positions. Both eye and head calibrations were carried out each time the HMD was removed and replaced (i.e., during pauses). The loudspeaker position in 3D space was calculated in each trial, with reference to the center of the head. In this way, despite participants sat without any chin-rest, we could carefully control the position of each sound source with respect to the ears. Eight pre-predetermined positions were used throughout the experiment, resulting from the combination of 4 different azimuths (-45° , 45° , -135° or 135°), 3 different depths (35 cm or 55 cm) and a single elevation (0° , i.e., ear-level) (Figure 4.1). In each experimental trial, the experimenter moved the loudspeaker to the desired position in 3D space, following visual instruction generated in real-time by the computer. It concerned the pre-determined azimuth and depth position for the speaker. These instructions were visible only to the experimenter, and they were delivered using the stimulus visualization monitor placed in the testing room. The monitor provided a bird-eye view of the experimental room and conveyed the pre-determined position of the sound source for that trial (as a red circle) and the actual real-time position of the speaker (as tracker picture). Using this visual instruction, the experimenter reached for computer-determined position rapidly, keeping the speaker approximately at ear-level. The computer considered the loudspeaker correctly

positioned when it entered a sphere of 5 cm diameter centered on the pre-determined sound position.

Crucially, the computer delivered the target sound was delivered only when three concurrent criteria were met: (1) the loudspeaker was in the 3D position pre-determined for the trial; (2) the participant's head was facing straight ahead; (3) the participant's eyes were directed straight ahead. Participants actively complied with criterion 2 (head pointing straight ahead) and criterion 3 (eyes gazing straight ahead) by taking advantage of visual stimuli displayed in the HMD. At the beginning of each trial two crosses were presented to the participant: a white cross in the background indicated the desired position of the head and eyes; and a thin white cross, indicating the actual head-position of the participant. Participants were instructed to move their head to align the two crosses. When the alignment was achieved the thin cross turned blue.

Likewise, participants were instructed to gaze inside the cross. They can see where they are watching because a blue small circle indicated the eyes gaze. Once these two criteria were met, and the loudspeaker was also in the pre-determined position all visual feedback (small circle and crosses) disappeared and the sound was delivered. Participants were instructed to respond only after the end of the sound, bringing the tacker to the perceived location of the sound and hold it still a moment after the desired position was reached. The experimenter terminated the registration of the track by pressing a button on the controller ending the trial. No feedback on performance was ever provided (similar procedure was used also in Gaveau et al., submitted). The experimental session was organized in 4 successive blocks, with a pause between each block in which the HMD was removed. Visual conditions (grey or grid) changed between blocks of trials. Half of the participants followed a Grid-Grey-Grey-Grid sequence, whereas the other half followed a Grey-Grid-Grid-Grey sequence. Each block comprised 40 trials (i.e., 5 trials for each of the 8 pre-determined positions), resulting in a total of 160 trials (i.e., 10 trials for each pre-determined position in each visual condition). The entire experimental protocol lasted approximately 45 minutes.

Data Analysis.

The position of all tracked elements (loudspeaker, head center and direction, hand and eyes) was inspected for each trial. Loudspeaker position was calculated as the mean of x, y, z coordinates from the beginning of the sound to the end. Head and hand positions were analyzed using custom-made software for the kinematic analysis of movements, running on MATLAB R2019b. To study head and eyes movements, we calculated the tangential velocity on the x, y, z axis (expressed in degrees of rotation) using two-points central difference derivate algorithm [353] with 5 points for the half-window. To determine the sequence of head and hand movements, the beginning and the end of all movements were automatically detected using a velocity threshold procedure ($10^\circ/\text{s}$ for head and 400 mm/s for eyes). The results of this procedure were inspected off-line and corrected manually, if necessary. This procedure served to establish the spatio-temporal profile of head and hand behaviour and extract relevant parameters for subsequent analyses (number of head movements during sounds, RT of the first head movement and first eyes movement). Importantly, it also served to reject all trials in which participants did not comply with the instructions (i.e., they made anticipatory hand movement during sound delivery) or because of artefacts or lack of data. All statistical analyses and data visualizations were performed using R, R-studio environment and JASP 0.9.1.0.

4.5 Results.

Hand pointing.

The SPHERE system gave us the opportunity to decompose localisation errors in the three dimensions of space: azimuth, elevation and depth. For each dimension, we calculated absolute and signed error as a function of target position and experimental conditions. We started by assessing the participants' ability to discriminate sound source location, irrespective of visual conditions. Sound localisation responses for each participant are shown in Figure 4.2.A and 4.2.B in bird-eye and lateral views, as a function of sound position. Participants

were able to discriminate stimulus side (overall errors in left/right discrimination = 1.1%, SD = 0.8), and made very few front/back confusions (overall errors = 1.3%, SD = 1.2).

The overall absolute error was 11.3 (6.2°) in azimuth and 13.14° (5.29°) in elevation (see also Table 1). To examine if absolute error in azimuth changed as a function of sound position we entered inter-participant absolute errors in an Analysis of Variance (ANOVA) with SIDE (left or right), ANTERO-POSTERIOR SECTOR (front or back) and DISTANCE (near or far) as within-participants factors. The analysis revealed an effect of ANTERO-POSTERIOR SECTOR, $F(1,35) = 7.85$, $p = 0.008$, $\eta^2 = 0.18$). Participants made larger errors in back space ($M = 13.3^\circ$, $SD = 8.1^\circ$) compared to front space ($M = 9.3^\circ$, $SD = 7^\circ$). The main effect of DISTANCE also reached significance, $F(1,35) = 17.60$, $p < 0.001$, $\eta^2 = 0.34$. Participants made larger errors for near ($M = 12.3^\circ$, $SD = 9.4^\circ$) compared to far targets ($M = 10.3^\circ$, $SD = 7.4^\circ$). No other main effect or interaction reached significance (all $F_s < 2.57$, all $p_s > 0.12$). A similar analysis for absolute error in elevation also revealed a main effect of DISTANCE, $F(1,35) = 19.94$, $p < 0.001$, $\eta^2 = 0.36$. Elevation errors were larger for near ($M = 14.6^\circ$, $SD = 7.8^\circ$) compared to far sounds ($M = 11.6^\circ$, $SD = 7.8^\circ$). No other main effect or interaction reached significance (all $F_s < 3.24$, all $p_s > 0.08$).

To investigate any systematic bias in azimuth or elevation we examined signed errors (speaker position minus participant's tracker position; for azimuth: positive values indicate a rightward bias; for elevation: positive values indicate an upward bias), using a similar ANOVA. The analysis on azimuth revealed a main effect of SIDE, $F(1,35) = 37.16$, $p < 0.001$, $\eta^2 = 0.52$ indicating that participants responses were more eccentric than targets (left: $M = -5.8^\circ$, $SD = 8.0^\circ$; right: $M = 5.7^\circ$, $SD = 10.4^\circ$) as shown in Figure 4.2.A. The analysis on elevation revealed an interaction between ANTERO-POSTERIOR SECTOR and DISTANCE, $F(1,35) = 6.08$, $p = 0.02$, $\eta^2 = 0.15$. This is mainly due to the positioning of the hand tracker at lower sites compared to the real speaker location in the front space, particularly for near targets ($M = -9.9^\circ$, $SD = 12.6^\circ$) compared to far ones ($M = -6.1^\circ$, $SD = 10.7^\circ$; simple main effect: $F = 29.61$, $p < 0.001$). No significant difference between near and far targets emerged instead for sounds in back space (simple main effect: $F = 1.33$, $p = 0.26$). The main effect of antero-posterior sector, $F(1,35) = 18.89$, $p < 0.001$, $\eta^2 = 0.35$, and distance, $F(1,35) =$

5.96, $p = 0.02$, $\eta^2 = 0.16$, also reached significance but subsidiary to the 2-way interaction.

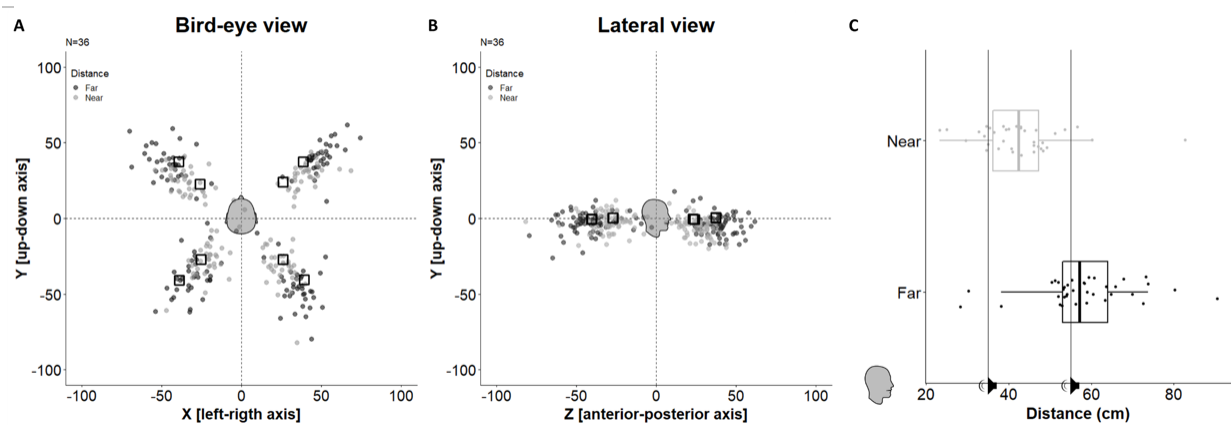


Figure 4.2: *Sound localisation performance. (A) Bird-eye view of all target positions (squares with black border) and hand-pointing responses (smaller circles) in all trials and participants. (B) Lateral view of all target positions and responses. Responses for each participant are averaged across side (left or right) and distance (near and far). Responses are color-coded as a function of target distance (far is dark grey and near is light grey). (C) Distance of participants' hand-pointing as a function of target position (Near or Far). Vertical lines represent the real position of the targets (Near: 35 cm; Far = 55 cm).*

After assessing azimuth and elevation performances, we analyzed sound localisation measures in depth. As shown in Figure 4.2.C, responses in depth were clearly segregated for near and far targets (near: $M = 42.8$ cm, $SD = 10.6$ cm; far: $M = 58.3$ cm, $SD = 12.0$ cm; $t(35) = 17.09$, $p < 0.001$). Average absolute errors in depth were entered into an ANOVA similar to the one used above. The analysis revealed an interaction between ANTERO-POSTERIOR SECTOR and DISTANCE, $F(1,35) = 16.81$, $p < 0.001$, $\eta^2 = 0.32$ and an interaction between SIDE and DISTANCE, $F(1,35) = 22.78$, $p < 0.001$, $\eta^2 = 0.23$. These interactions indicated that participants error was larger for front-near than back-near targets (simple main effect: $F = 6.43$, $p = 0.02$). Furthermore, participants error was larger for near-right position compared to near-left position (simple main effect: $F = 19.6$, $p < 0.001$).

A similar analysis on signed errors in depth (positive values indicate overestimation of target distance) revealed main effects of each variable SIDE (left or right), ANTERO-POSTERIOR

SECTOR and DISTANCE all ($F_s > 16.67$, all $p_s < 0.001$). Distance was overall overestimated ($M = 5.7$ cm, $SD = 11.1$ cm), but overestimation increased when target was in the right space ($M = 9.2$ cm, $SD = 12.3$ cm) than in the left ($M = 2.37$ cm, $SD = 12.6$ cm). A higher overestimation was observed for target in front ($M = 11.1$ cm, $SD = 11.4$ cm) compared to back ($M = 0.42$ cm, $SD = 13.5$ cm) and near ($M = 7.5$ cm, $SD = 11.8$ cm) compare to far ($M = 4.0$ cm, $SD = 13.1$ cm). Furthermore, we found interactions between SIDE and ANTERO-POSTERIOR SECTOR, between SIDE and DISTANCE ($F_s > 8.85$, all $p_s < 0.005$) and between SIDE, ANTERO-POSTERIOR SECTOR and DISTANCE ($F(1,35) = 29.34$, $p < 0.001$, $\eta^2 = 0.46$). This 3 way interaction did not reveal any difference between near and far signed errors targets when placed in the back . The over estimation for each target space dimension are represented in Figure 4.2.C.

Following Gaveau et al. (submitted), we also quantified the 3D rms error, which combines the absolute constant error and the signed error (see Rakerd and Hartmann, 1986). An ANOVA similar to the one described above on this error revealed a significant main effect of SIDE, $F(1,35) = 4.33$, $p = 0.05$, $\eta^2 = 0.11$ and significant interaction between DISTANCE and ANTERO-POSTERIOR SECTOR, $F(1,35) = 13.83$, $p < 0.001$, $\eta^2 = 0.28$ and SIDE and DISTANCE, $F(1,35) = 4.33$, $p = 0.05$. These interactions indicated that participants error was larger for front-near than back-near targets (simple main effect: $F = 7.75$, $p = 0.01$). These analyses revealed that participants' error increased for right target both when the were in the far space (simple main effect, $F = 10.17$, $p = 0.003$) and in the near space (simple main effect, $F = 11.84$, $p = 0.002$). To investigate whether the two visual scenarios affected spatial perception we entered the 3d rms error into an ANOVAs with VISUAL CONDITION (Grey, Grid) and ANTERO-POSTERIOR SECTOR as within-participants variables. The analysis revealed no effect of VISUAL CONDITION (all $F_s < 1.00$, all $p_s > 0.32$). Similar ANOVAs conducted on absolute and signed errors in azimuth, elevation and depth dimension, also did not reveal any main effect or interaction involving VISUAL CONDITION (all $F_s < 1.97$, all $p_s > 0.17$) except for signed error in elevation. For this variable, we found a main effect of ANTERO-POSTERIOR SECTOR, $F(35) = 18.89$, $p < 0.001$, $\eta^2 = 0.35$, as reported above and a significative interaction between ANTERO-POSTERIOR SECTOR and VISUAL CONDITION, $F(35) = 12.72$, $p = 0.001$, $\eta^2 = 0.27$.

When target was in the front, participants' overestimation is higher when the visual scene was grey ($M=9.2^\circ$; $DS = 10.5^\circ$) compared to grid ($M=6.8^\circ$, $DS = 10.3^\circ$), (simple main effect: $F = 12.12$, $p = 0.001$). Coherently, the underestimation in the back is higher when visual scene was grey ($M=-4.2^\circ$; $DS = 8.7^\circ$) compared to grid ($M=-2.7^\circ$, $DS = 8.6^\circ$), (simple main effect: $F = 5.84$, $p = 0.02$) (Figure 4.3.B).

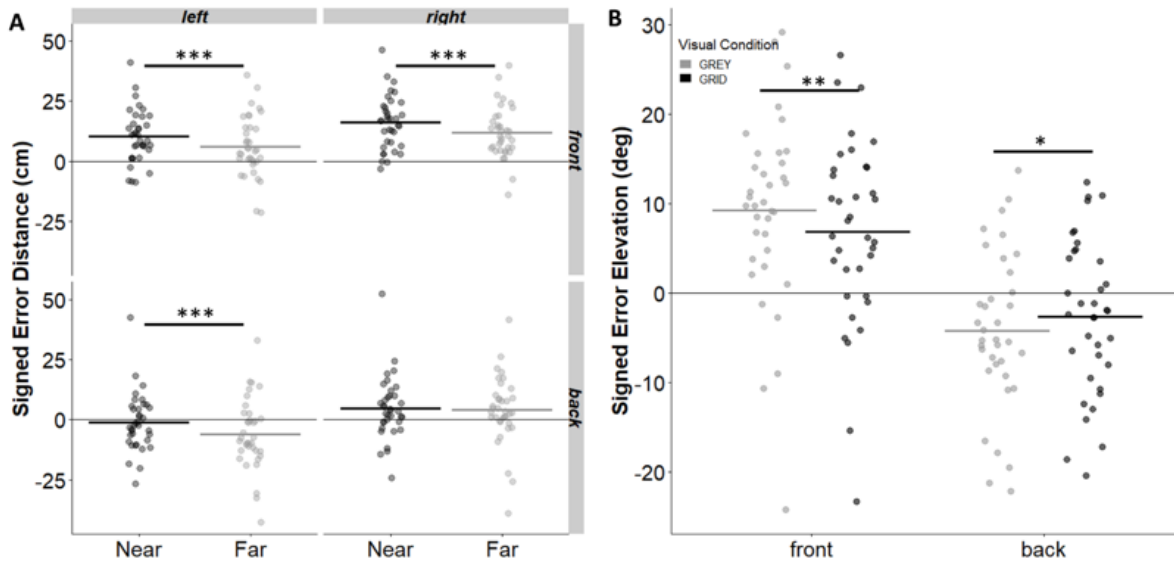


Figure 4.3: (A) *Signed Error in Distance (cm)* as a function of target distance (*Far, Near*), side (*left, right*) and antero-posterior sector (*front, back*). (B) *Signed Error in Elevation (deg)* as a function of Visual condition (*grey, grid*) and antero-posterior sector (*front, back*). In both graphs horizontal bars represent the mean of each condition, while points show participants value.

		Azimuth (deg)		Elevation (deg)		Distance (cm)		SD error (cm)
		Absolute Error	Signed Error	Absolute Error	Signed Error	Absolute Error	Signed Error	
GREY								
NEAR								
FRONT								
	<i>Left</i>	10.29 (7.80)	-5.84(9.15)	16.03(8.06)	-12.03(10.91)	12.77(9.00)	9.77(12.07)	17.43(9.14)
	<i>Right</i>	11.51(13.07)	4.87(13.46)	17.65(9.47)	-9.98(15.42)	16.57(10.16)	15.84(10.92)	21.34(9.73)
BACK								
	<i>Left</i>	15.79(13.23)	-5.73(15.50)	14.03(8.79)	5.12(12.30)	10.36(7.60)	-1.04(12.14)	17.26(9.08)
	<i>Right</i>	12.84(9.55)	6.55(11.11)	12.22(7.61)	4.67(10.46)	11.81(9.26)	4.41(13.32)	17.94(10.58)
FAR								
FRONT								
	<i>Left</i>	8.49 (6.12)	-4.54(7.51)	12.65(6.49)	-7.97(10.66)	11.91(9.27)	6.66(12.59)	18.90 (7.92)
	<i>Right</i>	7.48 (6.16)	4.18(5.25)	13.16(8.07)	-6.70(12.39)	14.00(8.31)	11.81(10.23)	20.16(8.22)
BACK								
	<i>Left</i>	13.71(12.86)	-4.68(11.38)	11.52(10.13)	3.22(7.35)	13.21(8.75)	-5.21(14.59)	20.12(9.06)
	<i>Right</i>	11.74(7.22)	5.59(10.14)	10.59(7.24)	3.84(10.33)	12.08(8.54)	4.20(13.54)	20.98(9.64)
GRID								
NEAR								
FRONT								
	<i>Left</i>	11.15(8.84)	-4.85(9.36)	15.41(8.34)	-8.65(12.57)	12.94(8.14)	10.83(10.55)	17.59(7.80)
	<i>Right</i>	9.32(6.98)	6.42(6.48)	15.72(8.90)	-8.77(14.01)	17.50(10.15)	16.31(11.74)	21.50(9.14)
BACK								
	<i>Left</i>	14.83(11.22)	-9.04(14.20)	13.78(7.85)	1.74(12.82)	10.31(7.73)	-1.23(12.36)	17.59(7.80)
	<i>Right</i>	12.35(7.58)	7.31(10.21)	12.24(7.45)	3.81(10.68)	12.64(8.14)	5.14(12.22)	18.5(9.58)
FAR								
FRONT								
	<i>Left</i>	8.92(6.35)	-4.89(8.66)	11.82(6.43)	-5.29(10.06)	11.39(8.58)	5.72(12.82)	18.17(8.71)
	<i>Right</i>	7.37(8.75)	3.69(6.00)	12.05(8.78)	-4.6(11.19)	14.34(9.08)	12.01(11.65)	19.94(8.93)
BACK								
	<i>Left</i>	13.58(9.53)	-6.34(12.13)	11.57(10.67)	2.61(12.04)	13.88(9.11)	-6.60(12.91)	21.33(10.16)
	<i>Right</i>	11.15(5.62)	7.71(7.42)	9.76(7.33)	2.53(8.79)	12.52(10.26)	3.68(15.29)	20.93(10.45)

Figure 4.4: *Absolute error and Signed error of 3 dimensions of the space as a function of target position and 3dd cumulative indices for Grid and Grey visual conditions. Standard deviation (SD) between brackets.*

Head rotation.

Kinematic tracking of the HMD allowed detailed investigation of spontaneous head movements during sound emission. Although participants were always free to move their head during sound emission, head-movements occurred in 68.3% of trials on average (SD = 38.3%; median = 89.9, range = 0-100%). Figure 4.5 shows the substantial variability of this spontaneous behavior. Head-movements occurred both for targets in front and back space (71.3% and 65.3% of trials, respectively). This difference is captured also in the average number of movements (which included also trials in which participants did not move at all). An ANOVA with ANTERO-POSTERIOR SECTOR and VISUAL CONDITION on this variable revealed that number of movements increased when sounds were delivered from the front (M = 0.73, SD = 0.41) compared to back (M = 0.69, SD = 0.41; $F(1,35) = 12.05$, p

= 0.001, $\eta^2 = 0.26$).

To analyze head movements rotation, we remove participants which did not perform any movements and considered as one movement, the rotations which were larger than 10 degrees. Here, we focused on the first head movement on the trial in which participants rotated toward the same side of the target. Thus, we considered in our analysis 25 participants (2,7,8,9,23 were not included because of lack of data; 11,14,19,21,31,34 did not move at all). On average participants rotated their head toward the target side (2.55% of trials in which the movements were not toward the side direction of source, SD = 2.03) indicating that they were able to disambiguate from which side the sound come from.

Thus, we calculated the time of the first movement (T, millisecond), which is defined as the time between the beginning of the sound stimulation and the beginning of the first head rotation movement, and the amount of head rotation (deg)¹. To test the effect of our visual manipulation as a function of target position (front or back), we entered them respectively in 2 ANOVAs with ANTERO-POSTERIOR SECTOR and VISUAL CONDITION as within variables. Participants started to rotate 978 milliseconds (SD = 155) after sound emission. ANOVA on T revealed a significative main effect of ANTERO-POSTERIOR SECTOR, $F(1,24) = 7.90$, $p = 0.02$, $\eta^2 = 0.25$. When sounds were emitted from frontal position, participants responded faster (M= 957 ms, SD = 154 ,ms) compared to when they were emitted from the back (M= 999 ms, SD = 156 ms) (Figure 4.5.A). ANOVA on head rotation after first movement revealed that participants rotated symmetrically without any lateralized bias, we did not find any significative effect (all $F_s < 1.26$, all $p_s > 0.27$). As shown in Figure 4.5.B, participants rotated the head symmetrically in both sides. For sounds at 45° to the right, the first head movement rotation was of 40.1° to the right (SD = 7.2°), whereas for sounds at 45° to the left, head rotation was 39.2° to the left (SD = 7.3°). For targets in back space, for sounds at 135° to the right , the first head rotation was of 67.9° degrees (SD = 21.0°), whereas at 135° to the left it was equal to 68.7° to the left (SD = 22.5°). Note that we did not use the term “Reaction time” because we did not ask to participants to respond as fast as they could. Nonetheless, this measure is comparable to reaction time.

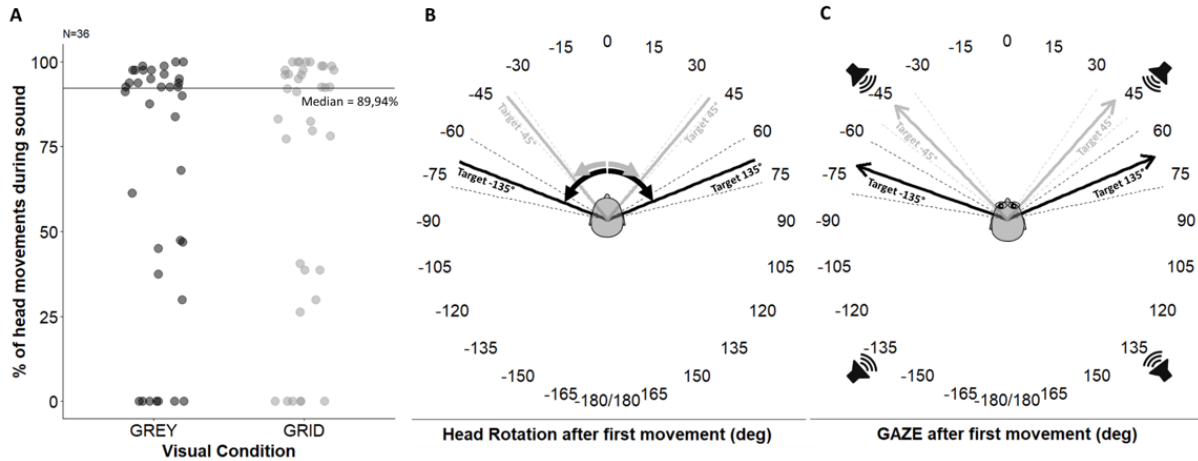


Figure 4.5: (A) Boxplot of percentage head-movements: the percentage of trials in which head movements occurred for each participant. (B) Average of the rotation around vertical axis of the first head movement only when participants turned to the side of the target (same dataset of the analysis). (C) Average of the direction of the first gaze movement only when participants turned to the side of the target (same dataset of the analysis). Dashed lines represent confidence intervals.

Gaze direction.

Our kinematic tracking system allowed detailed investigation of gaze movements (which combine eyes and head movements) during sound emission. Thus, participants were always free to move their head and eyes during sound emission. To analyze gaze movements, we remove participants which did not perform any gaze movements. Similarly to head rotation, we focused on the first gaze movement. On average participants gazed toward the same side of the target (2.88% of trials in which the movements were not toward the side direction of source, $SD = 1.72$) indicating that they were able to disambiguate from which side the sound come from, as revealed by head rotation. Thus, we focused only on trials in which participants gazed toward the same side of the target considering in our analysis 26 participants (7,8,9,11,14,19,21,23,27,31 were not included because of lack of data). We calculated T (ms) as the time between the beginning of the sound stimulation and the beginning of the first gaze movement, and the direction of the first gaze movement. To test the effect of

our visual manipulation as a function of target position (front or back), we entered them respectively in 2 ANOVAs with ANTERO-POSTERIOR SECTOR and VISUAL CONDITION as within variables. Participants started to gaze 698 milliseconds (SD = 164) after sound emission. ANOVA on T revealed a significant main effect of ANTERO-POSTERIOR SECTOR, $F(1,25) = 19.54$, $p < 0.001$, $\eta^2 = 0.44$. When sounds were emitted from frontal position, participants were faster (M = 651 ms, SD = 153 ms) compared when they were emitted from the back (M = 744 ms, SD = 174 ms) (Figure 4.6). We found also a significant main effect of VISUAL CONDITION, $F(1,25) = 12.85$, $p = 0.001$, $\eta^2 = 0.34$. When the visual scenario was grid participants were faster (M = 666 ms, SD = 146 ms) compared to when it was grey (M = 728 ms, SD = 271 ms).

We also run a post-hoc analysis (simple main effect) to deepen the interaction between VISUAL CONDITION and ANTERO-POSTERIOR SECTOR starting from the marginal statistical significance of the interaction in the ANOVA ($F(1,25) = 6.46$, $p = 0.075$, $\eta^2 = 0.12$) and to test our hypothesis that VISUAL CONDITION has a great impact specifically in the front space. Simple main effects revealed a main effect of VISUAL CONDITION when target was emitted from frontal position ($F = 19.46$, $p < 0.001$), but not for back position ($F = 3.82$, $p = 0.06$) (Figure 4.6).

ANOVA on direction of the first gaze movement (deg) revealed symmetrical gaze directions in both visual conditions for frontal target only (as observed for head first rotation). For back space targets, participants presented a bias toward the left (negative value, M = -3.4° , DS = 9.0°) only in the grid condition (interaction: $F(1,25) = 5.70$, $p = 0.03$, $\eta^2 = 0.19$, simple main effect: $F = 5.01$, $p = 0.03$). This result was not predicted, therefore it will not be discussed further. Figure 4.5.C shows the gaze direction as a function of target position (front, back left, right): for sounds delivered from 45° to the right, the first gaze was directed 42.1° (SD = 18.9°) towards the right, whereas for sounds at 45° to the left, it was directed 44.6° towards the left (SD = 20.7°). For targets in back space, for sounds at 135° to the right first gaze was directed 67.2° (SD = 27.3°) towards the right, whereas for sounds at 135° to the left it was directed 70.5° (SD = 25.2°) towards the sound direction.

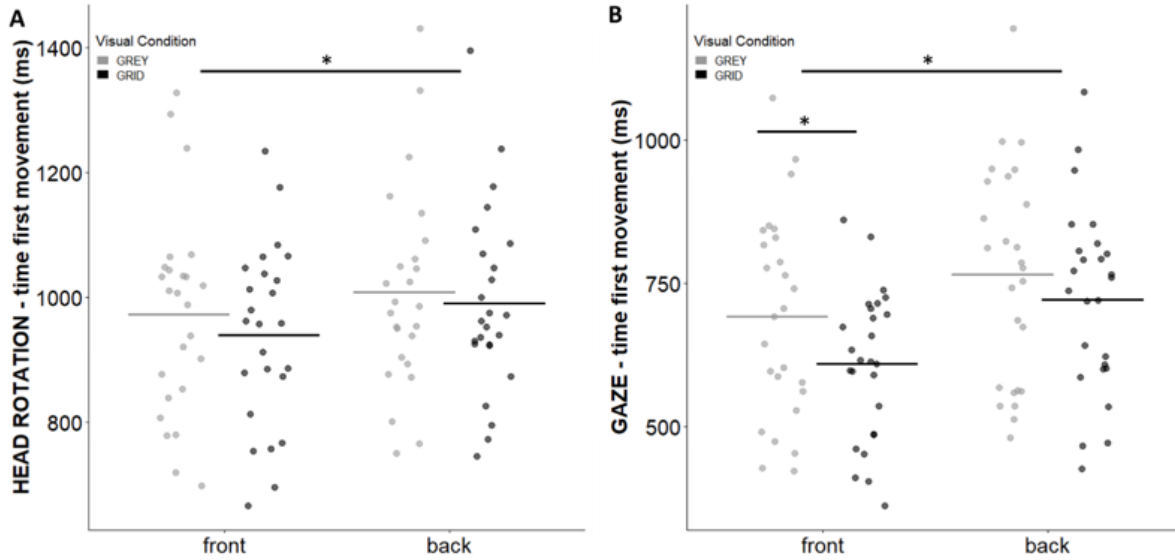


Figure 4.6: T , the time between the beginning of the sound stimulation and the beginning of the first head or eyes movement. (A) Boxplot of Head Rotation time first movement as a function of target position (Front, Back) color coded as a function of Visual Condition (Grey, Grid). (B) Boxplot of GAZE time first movement as a function of target position (Front, Back) color coded as a function of Visual Condition (Grey, Grid).

Follow-up. Head movements helped sound localisation in azimuth.

To study the relationship between performance and head-related behaviour, we correlated absolute error in azimuth, elevation and depth with the average number of head movements during each trial ($M=0.73$, $DS=0.41$, range = 0-1.19 movements) and the percentage of trial in which we detected at least one head movement during sound emission (3 sec) ($M=44.02$, $DS=37.23$, range 0-100%).

We found a significant interaction between Absolute Error Azimuth and Percent of trial with movement $R = -0.31$, $p = 0.05$ (Table 2, Figure 6). Participants who moved more (higher percent of trials), judged more accurately target position in azimuth dimension (lower error).

Furthermore, we deepen this relation by splitting the data as a function of visual condition (Grid, Grey). Interestingly, we observed that, while percent of trial with movement correlated with absolute error in azimuth when visual condition is grid ($R = -0.33$, $p = 0.05$), we did

not find any correlation for Grey ($R = -0.31$, $p = 0.07$). Similar pattern has been observed also for the correlation between absolute error in azimuth and number of head movement (Grid: $R = -0.32$, $p = 0.055$; Grey: $R = -0.28$, $p = 0.10$). Although we did not find difference comparing R of Pearson of the correlations in the two visual conditions (all $p > 0.23$), we claimed that this evidence pointed out that being immersed in a more visual structured environment had an impact on the relation between absolute error in azimuth and head-related behaviour.

		Number of head movement		Percent of trial with movement	
Absolute Error Azimuth		$R = -0.31$		$R = -0.33$	
		$p = 0.07$		$p = 0.05$	
Absolute Error Elevation		$R = -0.03$		$R = -0.018$	
		$p = 0.88$		$p = 0.92$	
Absolute Error Depth		$R = -0.22$		$R = -0.22$	
		$p = 0.20$		$p = 0.19$	

		Number of head movement		Percent of trial with movement	
		GREY	GRID	GREY	GRID
Absolute Error Azimuth	GREY	$R = -0.28$	$R = -0.29$	$R = -0.31$	$R = -0.31$
		$p = 0.10$	$p = 0.09$	$p = 0.07$	$p = 0.07$
	GRID	$R = -0.29$	$R = -0.32$	$R = -0.31$	$R = -0.33$
		$p = 0.08$	$p = 0.055$	$p = 0.07$	$p = 0.05$

Figure 4.7: Correlation between number of head movement, percent of trial with movement, absolute error in azimuth, elevation and depth. Below: Correlation between number of head movement, percent of trial with movement, absolute error in azimuth as a function of visual condition: grey or grid.

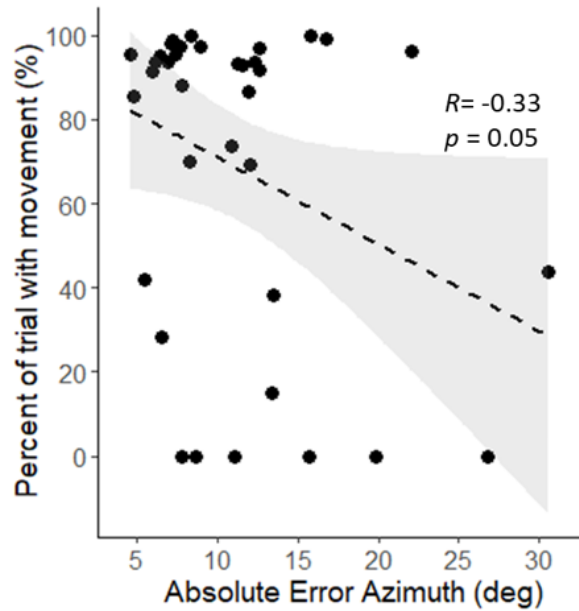


Figure 4.8: *Correlation between percent of trial with movement and absolute error in azimuth, considering all data (both visual condition).*

4.6 Discussion of the section.

In the present study, we aimed to measure sound localisation abilities in two visual condition by exploiting a novel VR system that allows replicable delivery of real sounds in 3D with respect to the head, while leaving participant free to move their head and gaze.

An innovative method for the study of 3D spatial hearing and tracking head and gaze movements. Our result confirms the validity of our system in agreement with Gaveau and colleagues (submitted). We succeed in measuring sound localisation presenting free-field sounds around participants. We measured participants performance in an ecological listening situation in which they were free to explore acoustic space while moving their head. Furthermore, we were able to split spatial components of participants performance: azimuth, elevation and depth. As we have already mentioned in the introduction, this represents a methodological progress compared previous experimental designs because it avoids using several speakers in the external space [352] or virtual auditory stimuli (i.e. Head-Related Transfer Functions

HRTFs). We presented free-field sounds without losing flexibility [354]: we could track head and gaze during sound emission. Furthermore, we controlled and changed visual scenario without affecting gaze detection. Thus, this technology fits perfectly with our experimental manipulation. We tested whether visual scenario affected both performances and behaviors (head and gaze movements) immersing participants in a total dark scenario and in a more structured one. Thus, we did not need to blind-folded participants or instructed them to close their eyes as done in previous experimental protocols [354, 352]. In addition, this gave us the opportunity to measure sound localisation without affecting oculomotor information that could influence participants performances [355].

This technology fits perfectly in our experimental manipulation aims, where we were able to modify visual scenarios from total darkness to more structured ones instead of blind folding participants or closing their eyes [352, 354]. This approach allows us to monitor behavioral spatial interactions without affecting oculomotor information that could influence participants performances [355].

With respect to the study of Gaveau, who used a similar technology of our VIVE system, here we stepped forward in the development of our VR approach: (1) measurement and analysis of head rotation; (2) measurement and analysis of the first gaze movement. The detection of these variables allows us to step into the natural behavioral strategies adopted by participants during sound emission and to study the impact of our visual manipulation directly on participants behavior, which, combined with performance errors, is crucial to study the cognitive mechanism of spatial hearing.

Normal hearing subject could localize sound in VR. Normal hearing subject in active listening posture were able to discriminate azimuth, elevation and distance (absolute average errors were 11.3 degrees, 13.1 degrees and 13.0 cm, respectively). Concerning error in azimuth, differences emerged. We found poorer performance in azimuth for back space compared to front, in agreement with previous studies with head motionless [124, 354], but in contrast with Gaveau and colleagues (submitted) without finding HMD-related effects [356, 352]. Then, we found poorer performance for near compared to far targets. We also observed a general bias to point to more eccentric positions. For elevation, inaccuracy appeared for near

sources compared to far ones and we found that perceived the frontal target as placed lower compared to their actual position. Concerning depth, we observed a general overestimation of distance, which is more pronounced for front near targets, especially for the right side.

The performance of our normal-hearing adult participants was better compared the findings of Gaveau for azimuth and elevation, while it was comparable for depth (even considering only total grey condition, which is more like the visual scenario of their experiment: total black). Nevertheless, we argued that some aspects of our paradigm may affect participants performances. First, participants were only informed that target sounds would be delivered within reaching distance but had no further information on their positions – i.e., they expected sounds to appear all around the body (as in Gaveau’s study). Second, they cannot see the tacker they were handling, so they did not receive any visual feedback about where they were placing the tracker while responding (as in Gaveau’s study). Third, participants used always the right hand to move the tracker and it may have determined some detected differences (i.e. elevation dimension; see also Supplementary materials). Fourth, participants were asked to turn (and therefore modify their proprioceptive cues [357] to place the tracker in the back after sound end to respond and thus they needed to re-calibrate the position of the target as a function of their own orientation. This may contribute to increased error in the back space.

Head and gaze: crucial components of sound localisation. As mentioned in the introduction, head-movements play a critical role in sound localisation both improving sound localisation and reducing front-back confusion [337, 341, 151, 357, 358, 188, 163]. Traditional approaches in the study of spatial hearing had limited head movements with chin-rests or preventing head and trunk movements [354, 359, 360, 361, 362]. Our approach gave us the opportunity to study sound localisation in a natural way considering spatial hearing as a real active task. During everyday life, head-orienting to sounds is a spontaneous behavior. Listeners spontaneously orient their head, eyes and trunk to the auditory source. For instance, they turn to listen to a sound from a speaker next to them or they move to approach the auditory source. Head movements are various, and they are related to the acoustic task and the way in which participants perceive sounds. For instance, head-movement strategies change in

altered hearing conditions. Hearing-impairment people have more complex head-movements [363]. Asymmetrical hearing impairment induced people to orient their head in order to enhance the level of a target sentence in their better ear to solve a speech in noise task [364]. It has documented that head-movements modify auditory cues contributing to extract spatial information of sounds [365, 366]. Sounds perception benefits from head movements: it leads to improve both sound localisation [367, 368, 188, 163, 369, 358], and speech perception [370], even in patients with hearing aids [371].

The benefit of head behavior on sound localisation is extremely related to the available auditory cues. In a previous study, we assessed the implication of head movements in an altered listening condition: monaural listening (Valzolgher et al., under rev). Normal hearing people with one ear plugged were tested in a single sound localisation task where they could listen to a sound until they identify it. When the task was repeated, participants tended to modify their head responses by increasing the number of head movements to enhance loudness in the unplugged ear. This head-motion-related spatial behavior seemed to be crucial for overcoming altered listening situations. However, our present experimental features are different, since they reflects more natural hearing situations.

Participants move head and eyes to face the sound space. As in previous studies, we emitted sound for a duration of 3 seconds ensuring that participants had enough time to use head movements if needed (Gaveau et al., submitted; [371, 210]). We documented that participants move their head to face towards speaker space. After about one second from sound emission, most of them have already performed a head rotation toward the same side of the target. Participants rotated head to point toward the sound direction and they were able to disambiguate rapidly side direction of sound. Analyzing also gaze, which considers both head and eyes directions, we observed the same behavior suggesting that participants moved to direct both effectors (head and eyes) towards the space of sound.

Participants did not perform many movements, on average they rotated one time for each trial. Thus, in this normal hearing situation, they did not need to exploit head movement to modify the auditory cues. The task is easy and most of participants naturally turn eyes and head toward the sound. Eyes started earlier to move (before the first second) follow

by head. This type of behavior is clearly related to the fact that naturally we explored the environments using both acoustic and visual inputs. Thus, as soon as we listening to a sound, we rapidly want to see where the sound come from. Our result demonstrated also that participants were able to discriminate sound direction rapidly using head and gaze, which were directed toward the sound direction for most of the trials.

Due to the simplicity of the task participants rotated the head on an average of one rotation per trial, thus, we reported earlier gaze reaction followed by head rotation which is consistent with the natural multisensory exploration of surrounding environments using both acoustic and visual cues. In most of our trials, these cues played an important role in orienting head and gaze towards source locations.

Even minimal visual references impacted on sound localisation. Starting from the concept that acoustic space perception is multisensory, we manipulated the visual experience while maintaining a binaural listening to study the effect of minimal visual references on performance and behavior. Our result confirms that even few visual references could impact on sound localisation. Specifically, we found that grid condition led to an improvement in sound localisation in term of elevation. This result is consistent with results of the study of Majdak and colleagues 2010 [170] reporting that when using manual-pointing method, participants sound localisation was enhanced by visual references compared to a dark scene. However, in our case, we did not document any effect of visual manipulation on error in the horizontal dimension.

Furthermore, grid scene impacts also on gaze behavior. Participants started gazing earlier when exposed to visual references and a similar trend was observable also for head movements. This result could be explained due to two possible reasons. On one hand, the influence of having visual references could lead to an earlier onset of a general visual exploration. Being immersed in a visual structured scene could promote exploration through eyes and head. On the other hand, in our experiment, gazing means more than moving eyes and head. The first gaze and the first head movement of participant were not casual. They were, for all the trials that we considered in our time analysis, always directed toward the side of the sound. Thus, we can assume that gaze reflected the implicit ability of the participants

to localize sounds or at least to direct their gaze towards the side of the sounds. Taking this perspective, our result revealed that a more visual structured environment, even minimal, speeded up the implicit process of sound localisation.

Using the SPHERE methodology (european patent n°17723294.6-1115), we confirmed the validity of our approach and its usability for measuring sound localisation in 3d. Furthermore, we contributed to show the importance of measuring spontaneous head and gaze movements when studying spatial hearing as complementary information to manual pointing to sounds. In addition, we emphasised the importance of considering sound localisation as a multisensory process. We found that experiencing a visual structured background, even if minimal, impacted on sound localisation both reducing errors in elevation and speeding the target direction identification through gazing.

Key points

- **The Vive system is an adequate tool for controlling and manipulating possible factors that could interfere in auditory spatial perception as a multisensory process.**
- **The Vive system provides an accurate tracking of the eyes and head movement that are involved in auditory spatial perception.**
- **In the localization task, gaze direction preceded head rotation as a reaction to auditory stimulation.**
- **Grid visual condition led to an improvement in the sound localization accuracy in elevation, in addition to earlier eye gazing movement.**

Chapter 5

General Discussion.

Hearing loss is one of the most prevalent chronic disabilities, that patients suffer from. According to the WHO, 6,1 % of the worlds population are estimated to be living with hearing loss that has a deteriorating sub-sequences on the quality of life, including loss of communication abilities, delayed language development that may lead to social isolation and frustration. A study by Vanson in 2015 concluded that patients with asymmetrical hearing loss had lower quality of life, that was correlated with their speech reception thresholds [160].

Although hearing loss have a detrimental effect on both speech recognition and sound localisation, according to previous reports, it seems that patients tend to complain mostly about speech-related deficit, rather than sound localisation, since speech intelligibility is more implicated in human social interactions compared to sound localisation. Therefore, a large number of clinical and fundamental researches were dedicated to study speech recognition rather than auditory spatial perception. According to Google scholar, 2 640 000 articles are dedicated to speech recognition, while 1 440 000 are devoted for sound localisation.

In addition, the clinical evaluation of sound localisation is mainly restricted to a simple localisation task of sounds coming from horizontal speaker arrays usually separated with a minimum angle of 10° , this clinical tool provide little amount of information about spatial auditory perception that include a variety of functions that surpasses the simple source identification task of specific type of stimuli, in a specific plane with limited visual control. On

the other hand, experimental setups dedicated to assess speech intelligibility are more sophisticated such as the Matrix test, Quick SIN (Speech in noise Test), HINT (Hearing in Noise Test) , MBAA (Marginal Benefit from Acoustic Implication) etc.. that are systematically applied on patients with hearing impairment.

In our thesis we tried to step further into the behavioral complexity of sound localisation function, by taking into account all possible factors that might be involved in auditory spatial perception. Each chapter in this research played an important role in justifying the complexity, yet the importance of advanced spatial localisation investigations in measuring, predicting and surpassing localisation deficit. The aim of this fundamental researches is to build up advanced findings about the importance of improving localisation assessments adapted in clinics, based on the previous knowledge and our present findings concerning the adaptational plasticity that occurs in patients with UHL that can improve sound localisation to reach normal hearing situations in some cases.

The clinical approach of testing behavioral auditory perception was based on a simple source identification task, that we tried to correlate with the neural-related responses reflected by the MMN, to further inspect the relationship between the neural findings using EEG and the behavioral measures using RMS. Previous studies that used MMN as a marker of reorganisation after hearing impairment, or after cochlear implantation, reported that MMN was correlated with performances. However, most of the studies that used the MMN as an assessment of auditory performance were applied to assess speech related auditory functions and not on spatial auditory functions [321, 320]. The MMN investigations assessing spatial resolution were limited and mostly applied in normal hearing conditions [193, 215, 63], therefore it is important to identify the relationship between spatial MMN and behavioral sound localisation performances in patients with impaired binaural functions.

However, before discussing the nature of this relationship, it is important to clarify some limitations, that we faced during our project. As the literature already described it, the spatial MMN is an event related potential component that reflects un-attentional spatial shift detection, that reflects passive and involuntary listening through a repetitive oddball paradigm [246]. However, the behavioral test required active listening that involves source

identification task rather than spatial discrimination, which underlies different auditory functions as we clarified in the first chapter. The debate about the relationship between spatial accuracy and spatial discrimination continues to unfold, for instance many studies suggest a direct relationship between both functions, claiming that the ability to perceive spatial auditory displacement vary according to the localisation precision [95].

Recanzone tried to directly relate both psycho-physical methods by comparing them through relative localisation task (MAA) and absolute localisation task using different types of stimulation [372]. He found out that relative localisation threshold (MAA) was not a successful predictor of absolute localisation threshold. Freigang found a weak correlation between the measures of MAA and RMSE only in younger listeners at a reference position of 9° . Freigang suggests stronger influence of aging on spatial discrimination rather than on absolute localisation [63]. Thus, it seems that the auditory source width (ASW) does not influence localisation accuracy that mainly rely on the mean position of the source. However the spatial discrimination is a function that perceives the width of different sounds to be able to detect a difference, therefore, MAA might increase in stimulations with large (ASW). The results of different studies that tried to compare localisation to discrimination, lead to the conclusion that a poor spatial discrimination can play a role as an indicator of poorer localisation accuracy, however, the localisation performance measured using RMS cannot be a predictor of spatial discrimination. It is however important to take into consideration the experimental task assigned to test each function. Where most of the MAA experimental setups can reach a precision of 2° in addition to the repetitive staircase procedure that guarantees higher answer certainty compared to absolute localisation where in most of the cases the source identification answer is reported after a single non repetitive stimulation.

Despite the long debate about the neural dynamics underlying both spatial discrimination and spatial accuracy, clinical interventions assess spatial perception as absolute source identification task or RMSE only. In the second chapter of the thesis we validated the utility and feasibility of using HRTF in headphones to measure the MAA. We were also able to show that the average MAA in normal conditions is similar to what was already reported in the litterature (MAA= $5,6^\circ$ using KU100 in frontal space). Measuring MAA in headphones

using simulated HRTF such as KU100, can provide additional data about the progress of spatial perception adaptation after UHL. The follow up of the adaptation of a patients spatial discrimination is essential, especially after our findings in spatial MMN that reflect neural signatures of spatial discrimination abilities rather than spatial accuracy.

In the third chapter, we tried to find the relationship between the behavioral localisation and the neural marker represented by the amplitude and latency of the MMN, the project aimed to explain the adaptational spatial perceptive behavior of patients with UHL, using a spatial discriminative neural response. To check whether the MMN is representative of the adaptational plasticity, observed through behavioral response to a simple localisation task. We pursued the variation of the average RMS across the 21 patients with UHL and we divided the group according to the individual RMS score, regardless of their hearing asymmetry . Patients with UHL who had high performance, revealed normal behavior in detecting spatial displacement at the three deviations. The 6 patients with UHL had a hearing loss that varied between 36,5 and 100,5 dB in the deaf ear. According to previous reports, adaptational plasticity occurs in the first two years following hearing loss [136], [117]. Our group of performant hearing loss patients had a duration of hearing loss that was superior to the phase of functional reorganisation (occurrence of HI between 2004 and 2018).

In mammals, the experimentally induced hearing loss was followed in many cases by a functional reorganisation that is explained by two significant changes in the activity of the central auditory system: first by the reorganisation of the frequency map in the auditory cortex, second, the alteration of binaural interactions at different levels of the ascending and descending auditory pathways, these changes occur in both the developing and the mature auditory system [143]. Usually reorganisation occurs, in the tonotopic maps ipsilateral to the intact ears, as reported in cats reared with unilateral cochlear ablation. In addition, an expanded representation of the frequencies was found to be adjacent to the range of the damage after cochlear lesion in guinea pigs [121].

All the previous findings, including ours, arrived to the conclusion that cortical plasticity occurs when adapting to new stimulating conditions, however, the evidence about the mech-

anisms underlying this plasticity remain ambiguous. Our study was able to prove that the plastic reorganisation is also expressed by the MMN, the findings about the similarity of response to spatial changes between NHS and UHL *low rms* suggest the occurrence of possible compensatory changes that were also reflected on the behavioral level. Although spatial resolution of EEG is not well expressed, negative distribution of the MMN showed the classical manifestation of contralateral activation in response to stimulus in NHS. Negative MMN distribution across the scalp seems to shift in the case of UHL *low rms*, to more central areas. Different studies tried to address the hemispheric asymmetry using scalp field distribution in UHL cases. For instance, Cambell and Sharma examined the scalp distribution of N1-P2 responses to non sens speech syllables in mild to moderate hearing loss, they reported that cortical plasticity led to a reduction in the activation of temporal cortex and more activation in frontal areas [316]. However, in spatial MMN, the pre-attentive cortical mechanisms seem to have less sensitivity to spatial changes compared to change in speech syllables. Therefore, in order to further understand the neural implications of the spatial MMN, it is important to elaborate the debate in the litterature around the nature of the cortical phenomenons represented by the MMN. Although most of the literature about the MMN agree around its utility in reflecting preattentive cortical reactions, it seems, nonetheless, that some studies criticise the neural adaptation to auditory stimuli for not being fully accounted for the MMN. Some suggest that, the N1 activity seem to be the evoked potential that rises the MMN, meaning that the MMN is not necessarily generated by other auditory cortical processes [373]. Thus, a study by Bottcher-Gandor and Ullsperger in 1992 showed that the MMN can be present even after 10 s of standard onset, which is consistent with the time of recovery from the adaptation for LAEP including N1, in another way, MMN can be characterized as the differential adaptation emerged by N1, meaning that the mechanisms of change detection are based on the neural adaptation to specific stimulation that leads to the obligatory N1, this notion is also known as the afferent model [373].

Nevertheless, Naatanen and his colleagues had a different opinion regarding MMN generators, suggesting that the MMN possess its separate memory trace in encoding the regularities in the environment. In his memory trace model, Naatanen insists on the importance of the

deviation stimulus from a repetitive acoustic context. Claiming that an afferent N1 can contribute to deviance related negativity if the the phase of deviant related response is as early as 100 ms [87, 233, 374]. It is also known that MMN generators are not confined in auditory temporal areas, but they can also exceed to central and frontal areas, meaning that functional reorganisation that takes place in HI conditions might also involve additional reliance on more sophisticated cognitive functions rather than only auditory functions. The increment of the MMN amplitude in patients with UHL *low rms* compared to NHS in monaural condition, is an important evidence of the occurrence of brain plasticity, and the association of the MMN with these plastic changes. However, it is not enough to prove that MMN is a neural correlate that underlie spatial auditory plasticity, its is important to improve localisation ability, and therefore express the improvement and adaptation using this MMN. The MMN was applied in previous studies to determine the effect of language learning and musical expertise [375, 376, 301, 377, 378], it has also been used in exploiting plastic changes after the recovery from brain damage as a result of brain intervention [223]. This thesis was able to combine different evidence regarding the neural correlates that underlie adaptational plasticity occurring in patients with UHL *low rms* using the MMN. The experimental procedure that we used was able to exploit the ability of patients to spatially discriminate stimulation, but the thesis can also be described as an exploitation of the MMN itself. While we were able to explore patients ability to discriminate spatial separations of 10°, we were also able to exploit the characteristics of the MMN and its ability to reflect not only spatial behavior, but also plastic changes.

These results draw back the main objective of this research and most of the hearing research, that intend to improve clinical intervention for better hearing quality, that leads to better life quality and satisfaction. This thesis provides fundamental findings about some neural correlates underlying spatial discrimination, but also suggests ne clinical notices that should be taken into consideration. The first, is the need to put further effort in examining the spatial deficit of patients, even though speech recognition seem to be prioritizing for the patient compared to sound localisation, spatial perception is however, an essential defense function that provides security and better space orientation. Deeper investigation and follow

up of the spatial perception, with both spatial discrimination (MAA) and spatial accuracy (RMSE) assessments should be deeply elaborated in order to target each function in more sophisticated training. The second is the importance of spatial training in hearing impaired conditions. Although many patients had high localisation errors with poor discrimination abilities in the UHL *high rms* group, however, our current data is enough to prove that sound localisation is an auditory function that can be learned and improved through training. The acute deterioration of the spatial localisation in NHS after the introduction of the plug, and its improvement in patients with unilateral hearing loss that largely surpasses the plug attenuation, confirm the efficiency of training in hearing loss cases. Thus, spatial audiovisual training have already showed behavioral improvement when it was applied on NHS with ear plug. In 2011, our colleague Kuzma Strelnikov designed a training technique for NHS in monaural condition. After training, the audiovisual integration helped increasing the spatial perception of the subjects in a very significant manner, especially when the sound was associated with a visual spatial cue rather than simple feedback [379].

In addition to the importance of rehabilitative spatial training, it is important to take into consideration the methodological pressure of building training setups and implementing them in clinics. In the chapter 4 of the thesis, we suggest the innovative localisation measurement using HTC VIVE, because of its efficiency at three levels, first, this system is able to assess localisation at any dimension of the space, second, it provides continuous tracking of the head eyes and hand, and therefore controlling the different dynamic reaction that are involved in the task, third, HTC VIVE is a virtual reality system that is easy to implement and manipulate, and provides a vivid immersion in more realistic scenes that may be more usefull for assessing and training in real-life-spatial auditory behavior.

To conclude, patients with UHL possess the ability to surpass localisation deficit with near normal discrimination abilities that could start from a resolution of 10° . This notion however needs to be validated by a follow up procedure of spatial discrimination testings in clinics that can be possible using simulated HRTF rather than more complex technical setups. This approach will provide additional evidence about the importance of multisensory training to improve and target specific spatial deficit in patients with HI. Thus a multisensory train-

ing can be easy to implement in hospitals with less materialistic complexities and real-life immersive situations such as the case with HTC VIVE VR system.

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