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COORDINATORE Prof. Maria Pia Amato

Repetitive Transcranial Magnetic Stimulation in patients with hearing loss

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Dottorando
Dott. Neri Francesco
Neri Francesco
(firma)

Tutore
Prof. Rossi Simone
(firma)

Coordinatore
Prof. Maria Pia Amato
(firma)

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SUMMARY

In the noisy environment of the normal daily life, the comprehension of sound and speech requires a good functioning of the auditory system. Hearing loss (HL) is the permanent partial/total inability to perceive sounds and it is usually accompanied by whole ears-brain pathways modification and a marked reduced ability to perceive stimuli, especially with a background noise. Removable hearing aids (RHA) and cochlear implants (CI) compensate the disability, but deficits in the receptive language abilities are still reported by patients, especially in an environment with a background noise. This impairment can lead to a decrease in daily activities and to social withdrawal. Here, we used Repetitive Transcranial Magnetic Stimulation (rTMS), a non-invasive brain stimulation (NIBS) technique used to promote cortical network plasticity, to improve speech perception in the post CI period. To this aim, we capitalized from the following evidences: i) rTMS has been already used in patients with sudden sensorineural HL for helping the recovery of hearing function and tinnitus; ii) we present here a study in which we have used rTMS of the auditory cortex to improve speech perception in background noise in 24 patients with removable hearing aids and chronic hearing loss; iii) we have verified the feasibility of rTMS in patients with CI that, according to currently available safety guidelines, cannot undergo rTMS treatment due to possible damage to implants caused by the TMS pulses. New generation CI - that resist to a static magnetic field, such as those of a magnetic resonance - might resist to pulses that vary rapidly, such as those of TMS. In a preliminary experiment, magnetocompatible CI were tested by repeated applications of rTMS protocols. Then, 9 CI patients underwent an active or a sham 5 days rTMS treatment delivered over the left auditory association cortex. In CI patients, rTMS was also followed by one hour of speech therapy (ST). Before (T0), after (T1), one week after (T2) and 6 months after (T3) the end of the treatment, Italian Matrix Sentence Test, Paced-Auditory-Serial-Addition-Test (PASAT) and speech tests were administered, with and without a background noise, in order to assess the patients' speech-reception-threshold (SRT), verbal working memory and speech perception skills respectively.

No damage was caused to the tested CI in the preliminary experiment. A significant long-lasting reduction of SRT was detected in RHA patients of the active group compared to the sham one. Moreover, a pattern of improvement in the SRT, in the working memory and in the speech perception was also detected in CI patients of the active group compared to the placebo treatment group. Results suggest that active rTMS might favour brain neuromodulatory changes in RHA and in CI patients, which are pivotal to the sounds and the speech intelligibility in the noisy environment daily-life.

CHAPTER 1 - NON-INVASIVE BRAIN STIMULATION

1.1 - Non-invasive brain stimulation: history and principles

Non-invasive brain stimulation (NIBS) techniques are capable to generate cortical electric fields without damaging the integrity of the tissues that cover the central nervous system (CNS). By injecting currents into the cortical superficial layers, NIBS methods change the communication between underlying neurons and modify the cognitive and behavioral functions of patients and healthy subjects. Transcranial electrical stimulation (tES) and transcranial magnetic stimulation (TMS) are the main NIBS techniques that are used both experimentally and clinically (Antal et al., 2017; Rossi et al., 2009, 2021).

NIBS are safe and reliable techniques, but the first curious experiments of non-invasive stimulation dates back to the ancient world. Scribonio Largo, Plinio il Vecchio and Claudio Galeno described how the application of a torpedo on the skin of the head was able to generate a transient stupor with temporary reduction of headache - and dullness, numbness and narcosis. Later on, the Arabian doctor Ibn-Sidah suggested the application of the electric catfish on the frontal bones of the skull for the treatment of epilepsy (Kellaway, 1946). These studies can rightly be considered the predecessors of modern electrophysiology, which began to be considered a science only centuries later. With the advent of modern technologies and the systematic studies carried out by Walsh in 1773 (Edwards, 2022) and by the Italian scientists Luigi Galvani and Alessandro Volta (Galvani et al., 1797; Volta, 1918), a clear connection between the tissue of the CNS and the electricity was found.

Galvanic currents - consisting of direct current waves - were used to treat mental disorders. Although procedures and observations are often unclear and not very reproducible, the general belief that by reversing the polarity of stimulations, opposite effects were obtained, was consolidated. In 1969, the first study of the predecessors of transcranial direct current stimulation (tDCS) was published (Redfearn et al., 1964).

Merton and Morton designed the first procedure to electrically stimulate the motor cortex using stick-on silver-cup electrodes that were applied on the scalp of healthy humans. The technique caused the excitation of the corticospinal bundle and induced a motor response of the contralateral hand without undue discomfort (Merton & Morton, 1980). For the first time, it was finally possible to observe and to study the cortical excitability and the mechanism of propagation of an electrical pulse in the CNS in healthy subjects. Later, the physiological basis of neuromodulation after a short applications of tDCS were investigated (Priori et al., 1998);

and it was confirmed that tDCS was capable to produce long-lasting changes of cortical excitability (Nitsche & Paulus, 2000).

In parallel to tDCS, TMS technique was introduced by Barker and colleagues, which developed a circular coil capable of generating a 2 Tesla field. In the experiment, authors stimulated the motor cortex causing movement in the subject's contralateral hand (Barker et al., 1985). However, the original tools need a long time to complete recharging and repetitive use causes an increase in the coil temperature (Noohi & Amirsalari, 2016). Today, the TMS is an essential research tool in the neurophysiological field, and it is increasingly exploited in the clinical setting for therapeutic purposes.

1.2 - TMS

1.2.1 - Principles of the TMS

The TMS allows the neuromodulation of CNS tissues (Cavaleri et al., 2017; Rossi et al., 2009, 2021). The use this technique is based on Faraday's principle of electromagnetic induction according to which a potential difference of intensity is generated equal to the variation over time of the flux of a magnetic field that crosses the circuit (Faraday, 1932). TMS allows the stimulation of CNS tissue at the cortical, the peripheral and the root level of the cranial and spinal nerves (Kobayashi & Pascual-Leone, 2003). The stimulator device consists of a copper coil connected to a high voltage electrical generator that regulates the flow of current through the coil with a duration of few hundred microseconds for each magnetic pulse. According to Faraday's principle, a coil traversed by a rapid pulse of alternating current creates an oscillating, oriented magnetic field perpendicular to it (Figure 1). Thus, the pulse passes through the scalp and the skull without significant attenuation, inducing an electric field in the nearest structure with properties similar to a coil, i.e. the brain (Cowey, 2005).

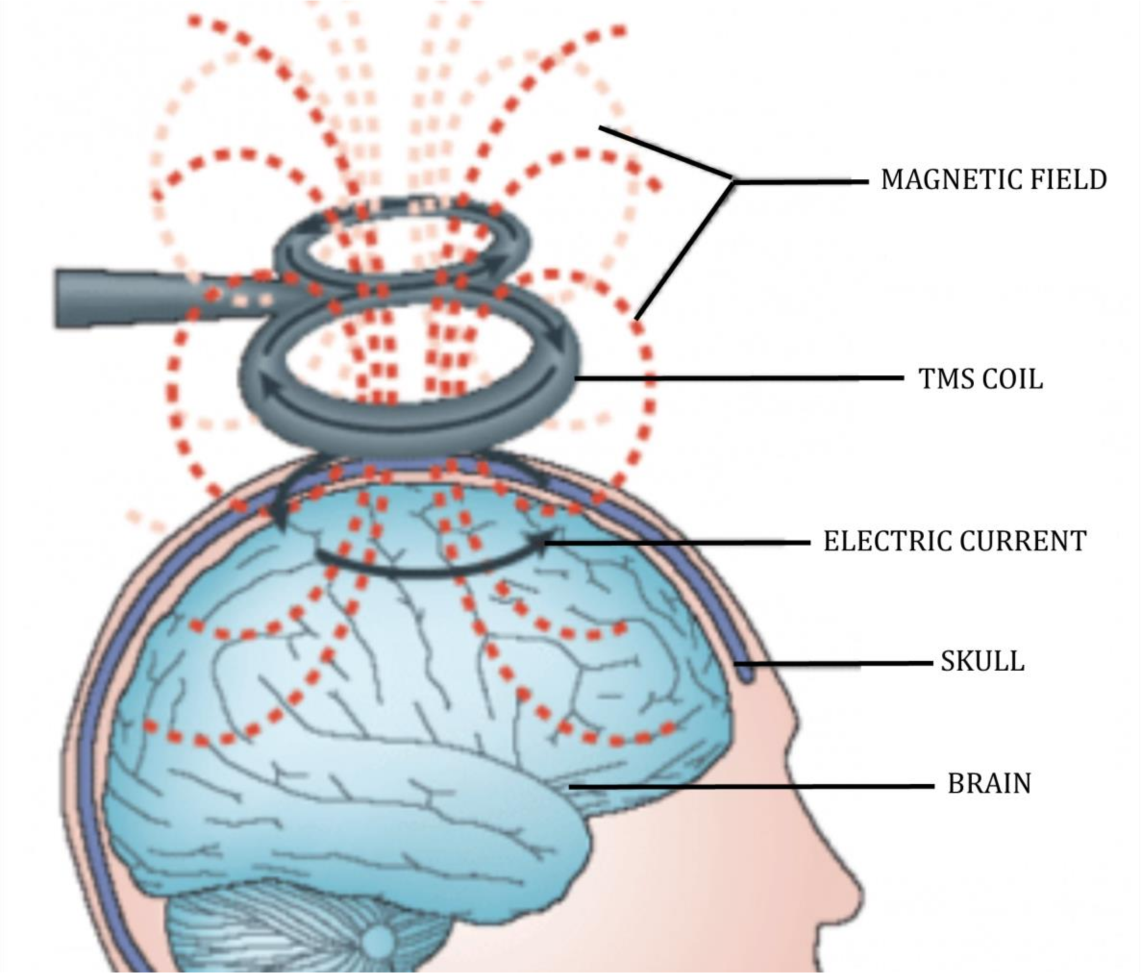

Figure 1. TMS principle. The magnetic impulse delivered by the coil passes the scalp and the bone without being attenuated and exerts its action on the underlying neurons.

The result of the stimulation is determined by the strength of the magnetic field - usually between 1-3 Tesla - and by the physical proprieties of the pulse, that can be monophasic or biphasic (Chakalov et al., 2022). At the cortical level, TMS modulates specific motor, sensory or cognitive functions, based on the location of the coil on the scalp (Anand & Hotson, 2002).

Although the direct effects of TMS pulses are mainly observed in the cortex - since the stimulus power decays with the squared increase of the distance (Barker, 1991) - recent studies demonstrated that TMS pulses has the capability to modify the intracortical excitability and indirectly activate other cortical sites far away from the stimulated area, or subcortical and spinal structures, through extant specific connections present (Klomjai et al., 2015).

1.2.2 - Coils

The difference of the coil design must be considered, because important elements such as the type of material, the geometry and specific characteristics of the magnetic pulse are associated with the purpose of the stimulation (Figure 2). There are two types of core materials: air cores are magnetically inert substrates, and solid cores are magnetically active materials. Consequently, solid cores allow electrical energy to be transferred to a magnetic field more efficiently and reduce energy loss through heat, allowing them to operate with a greater volume of therapy protocols without overheating. Varying the geometric shape of the coil itself can cause changes in focus, shape and depth of penetration. The differences in the coil material and its feed also affect the amplitude and the duration of the magnetic pulse (Lu & Ueno, 2017).

Figure 2. Coil of different shapes. Circular coils (1 - 2), 180° Figure-of-8 coil (3), 90° Figure-of-8 coil (4), 120° Figure-of-8 coil (5), Double cone coil (6), Air-cooled figure-of-8 coil (7 – 8). [Ates-EBNeuro Ltd].

The two types of coils that are normally used are the figure-of-8 (or butterfly), mostly used in research and neuromodulatory treatments, and the circular, with a diameter of 8-15 cm, usually used for diagnostic purposes. The first guarantees greater spatial resolution of the pulse delivered. The conformation of the coil opposes less resistance to the passage of current and consequently releases less heat (Weyh et al., 2005; Bersani et al., 2013). The second generates a field large enough to guarantee even one bi-hemispheric stimulation, particularly useful in the study of central motor conduction times (Kobayashi & Pascual-Leone, 2003). Although rarely used, there are other types of larger coils and intended for deeper stimulation. The double-cone, which is better adapted to the shape of the head, consists of two large coils joined to form a an obtuse angle of 95 °, and it is capable to induce pulses that are capable to reach deep brain sites (Lontis et al., 2006), such as representation of the lower extremities in the motor cortex (located in the left interhemispheric scissure) and the cerebellum. The H-coil (Roth et al., 2002), the C-core coil and the circular crown-coil (Deng et al., 2014) represent a good compromise in order to produce a focal stimulation to deep brain sites (Rossini et al., 2015). There is no evidence of a significant difference in terms of an higher safety between coil types (Rossi et al., 2021), although those that induce stimuli of greater power may be more annoying (Rossi et al., 2009).

1.2.3 - TMS protocols

Magnetic pulses can be applied through different protocols. Single-pulse TMS (spTMS), apply single stimuli spaced by a variable and randomized interstimulus interval (ISI) of several seconds. It is commonly used to stimulate motor cortex in order to cause a depolarization of the motor neurons, of the descending motor pathway and finally to induce a motor response in contralateral muscles (Day et al., 1989). The motor evoked potential (MEP) - that is the electrical signal of the muscle response - is recordable using an electromyography and it is characterized by a threshold amplitude, a latency and a duration (Bestmann & Krakauer, 2015). spTMS protocol is widely used in clinical investigation and in cognitive neuroscience (Farzan, 2014). Paired-pulse TMS (ppTMS) is a type of protocol that is used to assess cortical excitability through the use of two stimuli separated by few ms: a conditioning subthreshold stimulus (CS) and a test stimulus (TS) (Torii et al., 2019). When CS and TS are separated by 2-3 ms, intracortical inhibition can be assessed; when CS and TS are separated by 10-12 ms, intracortical facilitation can be assessed. Finally, with the repetitive TMS (rTMS), trains of stimuli are delivered at specific frequency and intensity. This protocol has been used in this work and it will be described in detail in the next paragraph.

1.2.4 - rTMS

The rTMS consists in the application of trains of pulses at a determined intensity, frequency and for a certain period. The parameters influence the effect on the stimulation site and its connectivity with the rest of the brain. The use of high frequencies, generally above ≥ 5 Hz, has a excitatory effect, while low frequencies, between 0.2 and 1 Hz, inhibit cortical activity (Cusin & Dougherty, 2012).

A subtype of rTMS is the theta burst stimulation (TBS), delivering stimulation patterns that are similar to those of the natural oscillation of the brain: an high stimulation frequency released approximately every 200 ms and a shorter duration of the protocol (Huang et al., 2005). The most frequently used involves three short trains of rTMS at a frequency of 50Hz. In literature, an increase of activity in case of intermittent TBS (iTBS) and a suppression, with continuous TBS (cTBS) is usually reported (Schulz et al., 2014).

However, the delivering of multiple trains of rTMS can transiently modulate all cortical functions (Walsh & Cowey, 2000) and in general all rTMS protocols induce a more consistent and long-lasting effect on the brain circuits (Anand & Hotson, 2002; Rossi et al., 2009). Therefore, the neuroplastic capacity of rTMS will be subdivided based on how neuroplastic changes are revealed. The temporary alteration of cortical function is named as "virtual lesion" (Pascual-Leone et al., 2000), it depends on the transient synchronization of a large number of underlying population of neurons hit by magnetic stimulus, which results in a generalized postsynaptic inhibition that blocks neuronal activity for the next 50-200 ms, based on the intensity and duration of the stimulus, (Rossini & Rossi, 2007).

The long-term after-effect of TMS has been described as being biologically similar to processes such as long-term potentiation and depression (LTP/LTD; (Hallett, 2007)). This mechanism involves changes in synaptic plasticity (i.e. the ability of synapses to strengthen themselves or depower in response to their greater o less activation over time) (Fitzgerald et al., 2006). LTP and LTD are widely studied phenomena since they would represent the correlates of memory and learning (Lüscher & Malenka, 2012). A study investigating changes entorhinal-hippocampal brain slice of a mouse provides the most direct evidence for this hypothesis. rTMS can induce LTP of synaptic transmission mediated by N-methyl-D-aspartate receptors (NMDARs). In a study, the CA1 pyramidal neurons were stimulated with a 10-Hz rTMS protocol (2–4 h after stimulation) for an enlargement of dendritic spines and a strengthening of excitatory inputs (Vlachos et al., 2012). In addition to increasing glutamatergic synaptic strength for a prolonged period of time, 10 Hz stimulation was found to increase GluA1 levels and enlarge dendritic spine size (Lenz et al., 2016). Because direct evidence is difficult to obtain on human subjects, pharmacological studies can provide important insight into the underlying mechanisms involved in rTMS-induced neuroplasticity by employing drugs that stimulate neuroplasticity receptors.

An experimental study by Huang et al. demonstrated that selective NMDA receptor antagonists interfered with the suppressive effects of cTBS and the facilitatory effects of iTBS (Huang et al., 2007). PAS-induced after-effects and 1 Hz rTMS were also found to be affected by NMDA receptor antagonists (Stefan et al., 2002; Wolters et al., 2003; Fitzgerald et al., 2005). Conversely, the use of d-cycloserine, a partial NMDA agonist, has been shown to further potentiate motor excitability after 10 Hz rTMS (Brown et al., 2020). Additionally, it modifies TBS-induced plasticity, although it appears here to reverse the facilitation-to-inhibition effects of iTBS. This could be explained by simultaneous inhibitory and excitatory effects with differing time courses. In addition, calcium channel antagonists have been shown to modulate PAS- and TBS-induced plasticity (Teo et al., 2007; Selby et al., 2019). As a result of these findings, it appears that rTMS after-effects are mediated by glutamatergic NMDA receptors, suggesting that LTP/LTD mechanisms are involved (Wankerl et al., 2010; Weise et al., 2017).

By using a low frequency rTMS paradigm in conjunction with a temporary ischaemic block of the hand, Ziemann and colleagues were able to induce plasticity in the contralateral motor cortex with GABAA inhibition reduced (Ziemann et al., 1998). The results of this study are comparable to what has been found in in vitro studies, and this provides further evidence that the effects of rTMS are the result of LTP-LTD-like mechanisms. Despite the fact that these studies indicate that TMS potentiation and inhibition are mediated by NMDA receptors, the evidence suggests that other processes, such as neurotrophic, neuroinflammatory, neuroendocrine, or even neuroglial networks, may also contribute to the observed after-effects (Cirillo et al., 2017). The studies of brain-derived neurotrophic factor (BDNF) provide an example of this type of evidence. In the normal population, a single nucleotide polymorphism (SNP) on the BDNF gene known as Val66Met is associated with hippocampal volume, episodic memory, and a decrease in the plasticity of the motor cortex in response to experience (Kleim et al., 2006). According to Cheeran and colleagues, Val66Met carriers show different responses to cTBS, iTBS, and paired associative stimulation protocols than Val66Val carriers, suggesting that BDNF may have a role to play in inducing rTMS aftereffects. For example, Val66Met polymorphism modulates the impact of rTMS in a memory protocol both at the cognitive as well as at the associated brain networks expression levels (Abellaneda-Pérez et al., 2022). Accordingly, rTMS is believed to affect neuroplasticity in a positive manner (Cheeran et al., 2008).

As shown in the literature reviewed above, rTMS can evoke after-effects in the brain that last beyond the duration of stimulation, which in turn may indicate neuroplasticity. As a consequence of their interaction with voluntary muscle activity and behavioral learning, the exact nature of the after-effects is further complicated (Ziemann, 2004) and is influenced by the history of synaptic activity in the stimulated area, in a manner that complies with a concept known as "metaplasticity" (Abraham, 2008). In terms of synaptic plasticity, metaplasticity is an advanced form of synaptic plasticity that occurs when neuronal activity primes the subsequent initiation of LTP and LTD (Karabanov et al., 2015). There is a theoretical model of homeostatic metaplasticity called the Bienenstock- Cooper-Munro theory (Bienestock et al., 1982). The theory suggests that the threshold for triggering LTP and LTD is adapted according to previous time-averaged levels of post-synaptic activity. It is important to note that the rTMS plasticity paradigm appears to be in accordance with the rules of metaplasticity, as demonstrated in studies using priming stimulation (Bienenstock et al., 1982; Müller et al., 2007; Abraham, 2008;

Karabanov A et al., 2015). It may be noted that antagonistic rTMS protocols are more effective if there has been a prior history of increased activity (i.e., induced by another TMS protocol), while facilitatory rTMS protocols are more effective if there has been a prior history of reduced activity (Karabanov A et al., 2015; Murakami et al., 2012; Ni G et al., 2014; Todd et al., 2009). Additionally, motor learning appears to influence rTMS after-effects on a homeostatic level (Hamada M et al., 2008; Stefan et al., 2006).

However, it would be simplistic to invoke this mechanism to explain the effects of rTMS and further research is therefore needed (Hoogendam et al., 2010). Numerous studies indicate than in patients with depression, many brain circuits are altered but also that the degree of the connectivity change of brain networks is predictive of the severity of depression (Salomons et al., 2014). rTMS on the focal nodes might produce a reorganization of functional connectivity of the brain networks, thanks to intrinsic plasticity of the brain (Kito et al., 2008).

Controlling the parameters of stimulation is pivotal, because they might influence the observed effects (Siebner & Rothwell, 2003). For instance, trains of 10 pulses at 150% of the RMT, with a frequency of 20 Hz cause an increase of the MEP amplitude lasting about 3 minutes (Pascual-Leone et al., 1994); or trains of 30 pulses at 120% of the resting motor threshold (RMT) with a frequency of 15 Hz cause a minor increase of the MEP amplitude lasting no more than 90 seconds (Wu et al., 2000). For security reasons, while inhibitory protocols consist of continuous applications of low frequency rTMS, excitatory stimulations require an intertrain interval which vary according to the frequency itself (Rossi et al., 2009). Beyond safety, such breaks are believed to also bring a contribution to the effect of rTMS (Cash et al., 2017).

Duration of the rTMS effects at the end of the stimulation grows with the increase in the number of applied stimuli (Maeda et al., 2000; Touge et al., 2001; Gangitano et al., 2002). 15 minutes of TMS trains with a frequency of 0.9 Hz, applied at 115% of the RMT, on the primary motor cortex, reduce corticospinal excitability for 15 minutes after the end of stimulation (Chen et al., 1997; Muellbacher et al., 2002). The lasting effects of rTMS would also seem to be cumulative type and the application of consecutive days of rTMS is more effective than one single (Bäumer et al., 2009). However, current evidences require a revaluation of the excitation/inhibition dichotomy that were usually used on the basis of frequency alone, concluding instead that any protocol may have mixed effects (Houdayer et al., 2008).

It has also been shown that the influence of rTMS is not limited to the area below the coil, directly influenced by the magnetic field, but it is also extended to connected brain areas (Siebner & Rothwell, 2003). Another factor that appears to influence the possibility to activate distant areas is the geometric orientation of the neural fibers or of the coil (Fox et al., 1997; Di Lazzaro et al., 2011; Lefaucheur, 2012).

Although most studies focus on the direct effects due the stimulation of the motor cortex, it is demonstrated the possibility to observe excitatory and inhibitory effects by targeting others brain areas, as the occipital cortex (Siebner & Rothwell, 2003; Rafique & Steeves, 2022) or the somatosensory areas (Holmes et al., 2019).

MEPs changes are commonly used to measure the modification in cortical excitability before and after the application of an rTMS protocol, but it is possible to observe neuromodulatory effects in areas of the brain that do not elicit a direct physiological response by means of TMS-evoked potentials (TEPs) and neuroimaging techniques. Changes of TEPs latency and amplitude are measurable with EEG and they are used to infer reliable and sensitive modulatory effects of rTMS on the cortical excitability (Casarotto et al., 2010). Inhibitory protocols have been shown to reduce cortical excitability, while traditional excitatory protocols have been shown to increase cortical excitability (Vernet et al., 2013; Veniero et al., 2010). In contrast to the MEP paradigm, which is largely restricted to the M1 cortex, the conjoint use of TMS-EEG allows the study of the rTMS after-effects on all cortical area. It has been demonstrated, for instance, that TEPs are well defined when rTMS is applied to the dorsolateral prefrontal cortex (DLPFC) and that the DLPFC displays plasticity-like after-effects when rTMS is applied there (Kerwin et al., 2018). As a result of the application of TMS to other areas of the brain other than the primary motor cortex, it has been possible to gather important insights about the effects of a protocol intensity and duration (Tremblay et al., 2019). The combination of TMS with EEG does have some advantages, but a well-known limitation may be the risk to observe various evoked artifacts in the EEG signal as a result of TMS injection, such as TMS-induced muscle, decay, auditory, and blink startle artifacts (Lioumis et al., 2018).

In addition to TEPs, rTMS is also known to produce changes in other EEG measures, such as in brain oscillatory activity (Chung et al., 2015; Casula et al., 2016; Qiu et al., 2020). The exact timing of rTMS pulses can be determined by using feedback provided by the EEG by coupling the TMS parameters to real-time EEG oscillations; these approaches are known as closed-loop stimulation, and they aim to enhance the neuroplastic capacity of rTMS (Zrenner et al., 2016; Tervo et al., 2022).

Neuroimaging studies demonstrated that rTMS induces changes not only in the area directly under the coil, but also in regions in the brain that are further away as for example in subcortical regions, (Strafella et al., 2001). A dose of 0.3 mg/kg of d-amphetamine, a substance known to increase synaptic dopamine signaling, has been shown to produce similar levels of dopamine (DA) release in response to a single rTMS session (Pogarell et al., 2007). As well as dopaminergic transmission, serotonergic transmission and cholinergic transmission appear to play a role in promoting the after effects of rTMS (Cirillo et al., 2017).

Further evidence for neuroplastic changes after rTMS and acute reorganization of activity to connected areas were provided by positron emission tomography (PET) studies, which have shown that rTMS of the left M1 affects the brain activity of the brain motor network after the end of the stimulation (Lee et al., 2003). In addition, metabolic changes were also evoked in brain regions that were interconnected to the stimulation site (Rounis et al., 2005). As a result of inhibitory rTMS, movement-related activity in the non-stimulated hemisphere of the premotor cortex increased as a compensatory reaction to the inhibitory effect of 1 Hz rTMS (Lee et al., 2003). This reorganization is probably similar to the effect in patients after a stroke recovery (Ridding & Rothwell, 2007).

By using fMRI, it is also possible to observe a rapid reorganization of functional brain networks induced by rTMS. A short-term reorganization of the right premotor cortex was observed following 1 Hz rTMS to the left dorsal premotor cortex (O'Shea et al., 2007). In another fMRI study, it has been found that both supra- and subthreshold rTMS over left M1/S1 affect blood oxygenation level-dependent (BOLD) signal outside the stimulated area (i.e., the contralateral M1/S1), whereas only supra-threshold rTMS increases BOLD signals in the stimulated area (Bestmann et al., 2003). With a systematic review of 33 fMRI resting-state functional connectivity (RSFC) studies conducted pre- and post-rTMS, reliable changes in RSFC have been demonstrated after rTMS (Beynel et al., 2020). It is interesting to note that the direction of the change was often not in accordance with what has been traditionally observed in the stimulated brain area: the direction of changes following conventional inhibitory and excitatory rTMS protocols was mixed And the changes were not limited to the activated functional network, but were also observed in other brain networks (Beynel et al., 2020).

Hence, effects of rTMS tend to spread across brain networks. This concept can be of particular importance, as research is currently focusing on targeting indirect and distant brain areas through their connections with more accessible cortical areas. By stimulating a subject-specific, parietal region that displayed high functional connectivity with the hippocampus, Wang and colleagues enhanced the connection between cortical-hippocampal networks (Wang et al., 2014). It is particularly noteworthy that they were able to demonstrate that functional connectivity in these networks correlated positively with higher associative memory after multiple sessions of rTMS, and considering that the effect persisted for 24 hours following stimulation, these changes were likely the result of neuroplasticity (Wang et al., 2014). In another study, the left dorsolateral prefrontal cortex activity was enhanced by daily stimulation sessions of iTBS over individual parietal targets that were functionally connected to the hippocampus for major depression treatment. It was found that the hippocampus and the left dorsolateral prefrontal cortex were more connected with the stimulation site, lasting for days after the end of the stimulation (Mielacher et al., 2020).

TMS-induced neuroplasticity is also evident by structural changes beneath the site of stimulation, as well as in distal brain regions (May et al., 2007). According to a rTMS study conducted in patients with major depression disease, gray matter density and brain volume increased in the left anterior cingulate cortex as a function which was also revealed by measuring the thickness of the cortical layers in the same region (Lan et al., 2016). Different brain regions were found to have increased volumes after treatment in another study, but these changes did not correlate with the response to treatment (left anterior cingulate cortex, left insula, left superior temporal gyrus, and right angular gyrus) nor to an increase in hippocampus volume (Boes et al., 2018). Despite the absence of a correlation between the treatment response and the plastic changes after prolonged rTMS therapy, a corresponding study emphasized another important aspect: Noda and colleagues reported enhanced theta-gamma coupling at the C3 EEG-electrode that correlated with hippocampal volumetric change, suggesting a potential relation by the rTMS-induced plasticity (Noda et al., 2018). It is necessary to note that the physical basis of these morphological imaging methods remains unclear and appears to reflect tissue characteristics as well as the abundance and distribution of specific cell types (including neurons, glia, vasculature, as well as subcellular components such as dendrites and spines) (Asan et al., 2021).

It appears that after-effects also influence behavior and cognition, including cognitive enhancement both in healthy individuals (Patel et al., 2020) as well as in individuals suffering from psychiatric/neurological disorders (Lefaucheur et al., 2017). rTMS may be successful as a therapeutic intervention because of lasting after-effects in several pathological conditions, which might significantly improve when rTMS sessions are applied daily over a period of days or weeks (Lefaucheur, 2012).

Major depressive disorder (MDD) is the most common psychiatric disorder where rTMS protocol are applied, in cases of inefficacy of antidepressants (Kiebs et al., 2019; Mutz et al., 2019). For the treatment of major depression disease, a high-frequency stimulation rTMS protocol is commonly applied to the left dorsolateral prefrontal cortex. Furthermore, a high-dose (90,000 pulses administered over 50 sessions in five days (10 sessions per day)) intermittent TBS protocol with functional-connectivity-guided targeting, has demonstrated rapid-acting antidepressant effects, even in patients with highly resistant depression (Cole et al., 2022). In the healthy subjects, its application to the left prefrontal cortex can increase the perception of sadness and reduce that of happiness, on the right the opposite mechanism is observed (Pascual-Leone et al., 1999). The mechanism is not clear with which TMS can influence mood, there are three theories to date accredited: activation of the striatal release of dopamine (Strafella et al., 2001); the modulation of neurotransmitter release (Keck et al., 2000); the increase of blood flow in the stimulated areas (Speer et al., 2000).

rTMS is also used to explore different functions of the human brain, such as language. For example, stimuli applied to the temporal cortex are able to induce anomie, but also to speed up the process of naming of images (Wassermann et al., 2008). The temporal lobe has also been shown to play a critical role in picture naming and word comprehension by Pobric, Jefferies, and Ralph (Pobric et al., 2010). Several studies have demonstrated the facilitation of left-hemispheric language areas when rTMS was applied immediately before picture naming, either as single pulses or repetitive high-frequency online rTMS (Mottaghy et al., 1999, Mottaghy et al., 2006, Sparing et al., 2001, Topper et al., 1998, Wassermann et al., 1999). Recent research by Schuhmann, Schiller, Goebel, and Sack (2012) demonstrates that frontal and temporal areas play a different essential role in picture naming as a function of their critical time windows using a chronometric triple-pulse TMS approach. It was observed that response latencies were higher when TMS was applied at 225 milliseconds after picture onset to the left middle temporal gyrus, while Broca's area became functionally relevant at 300 milliseconds and Wernicke's area at 400 milliseconds following picture onset. By examining the temporal signature of word generation, these data provide new insight into the temporal characteristics of speech production and complement studies utilizing electroencephalography and magnetoencephalography (Indefrey & Levelt, 2004).

fMRI procedure was performed prior the application of low frequency rTMS to the left posterior superior temporal gyrus (pSTG) to investigate its role in semantic and phonological processing. In the following step, the authors applied stereotactically guided 1 Hz rTMS to the left pSTG or posterior IFG while subjects performed a language fragment detection task. As a result of rTMS over the pSTG but not IFG, the authors reported greater facilitation of response speed for native languages. This suggests a lexical processing function for this area. Despite the "standard" virtual lesion rTMS protocols, these results demonstrate paradoxical facilitation effects (Andoh et al., 2006).

In a priming approach, the same group examined whether rTMS at different frequencies applied to left pSTG during auditory word detection could modulate the effects of low frequency rTMS applied to the same area (Andoh et al., 2008). Two virtual lesion protocols were used in that study to prepare participants for the task, consisting of either 600 pulses of 1Hz rTMS or 600 pulses of continuous theta-burst stimulation (cTBS) at 50Hz. A word-detection task was then conducted with 300 pulses of 1 Hz rTMS, either real or sham. Priming with 1 Hz rTMS enabled native words to be detected, while priming with cTBS enabled foreign words to be identified. Accordingly, it was suggested that the priming frequency of the TMS protocol plays a crucial role in word detection in the auditory stream.

In the next chapter the function of the peripheral and central auditory system will be illustrated and furthermore the perceptive processing of speech at the CNS level will be described in detail.

CHAPTER 2 – HEARING

2.1 - The auditory system

Hearing is the human sense by which sounds, and noise are perceived as stimuli, and it is divided into two major components: the peripheral and central auditory systems (Figure 3). The peripheral system includes the outer ear, the middle ear, the cochlea (contained in the inner ear, alongside the semicircular canals), and the auditory nerve (AN). The central auditory system includes the cochlear nucleus (CN), the superior olivary complex (SOC), the lateral lemniscus (LL) (both nuclei and pathways), the inferior colliculus (IC), the medial geniculate body (MGB), the auditory cortex (AC).

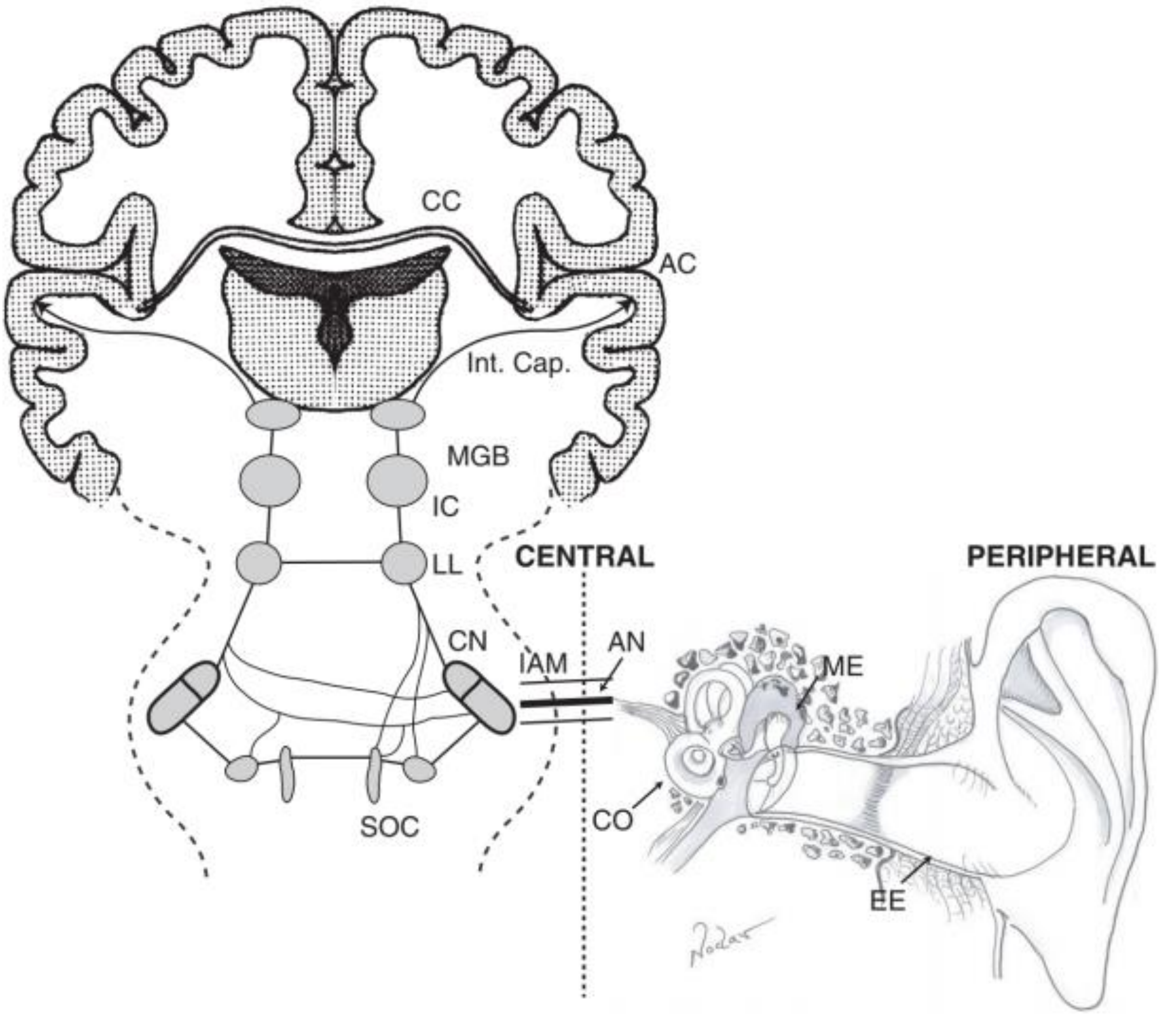

Figure 3. **Peripheral and central auditory systems**. Key EE= external ear and canal, ME= middle ear, CO= cochlea, AN= auditory nerve, IAM= internal auditory meatus, CN= cochlear nucleus, SOC= superior olivary complex, LL= lateral lemniscus, IC= inferior colliculus, MGB= medial geniculate body, Int. cap.= internal capsule, AC= auditory cortex, CC= corpus callosum.

Generally speaking, there are two forms of acoustic stimuli processing: sequential and parallel. Sequential processing involves the ascending and hierarchical transferring of information from one node of the auditory network to the next one, and it takes place at every level of the auditory system, from peripheral to central. Parallel processing, on the other hand, entails simultaneous functions occurring at the same time along different channels, and it takes place, for the most part, in the CNS; an example of parallel processing is found in the pathway starting from the auditory nerve, whose branches distribute information to the various cell groups in the cochlear nucleus. Each cell group then transforms the incoming spike trains uniquely, and then distributes that information along a series of parallel pathways to many auditory nuclei in the medulla and pons (Musiek & Baran, 2018; Pollak et al., 2003).

2.2 - The peripheral auditory system

2.2.1 - The outer ear

The outer ear consists of the pinna and the external auditory meatus (or ear canal).

The pinna is made up of ligaments and cartilage, it is covered by skin and with its peculiar structure of folds and ridges it serves the purpose of channelling the sound energy towards the middle ear. Furthermore, this unique morphology is determinant to a maximal response to sounds set around a 5000 Hz frequency band, and it is believed to hold a significant role in the localization of sounds (Yost & Schlauch, 2001).

The external acoustic meatus is a 2,5 cm long canal, with roughly the shape of an S, made of fibro-cartilage structure in the 1/3 of its lateral side and of bone in the remaining 2/3 of its medial side. It extends from the concha of the pinna to the middle ear, ending in the tympanic membrane. The inner wall of the meatus is lined with skin bearing hairs and cerumen (secreted by sebaceous cells and ceruminous glands).

The external acoustic meatus directs the sound signal arriving from the pinna towards the eardrum and it generates a resonance determined by the dimensions of the canal; this signal enhancement is around 10-15 dB and typically happens at a frequency from 3000 to 4000 Hz. The ear canal resonance is essential to the natural perception of sounds and, when it is compromised by damage or loss of the ear canal physiological response (usually in patients with ears occluded by earmolds or with hearing aids), it is responsible for the perception of an “unnatural” and “tinny” sound.

2.2.2 - The middle ear

The middle ear is an air-filled volume situated in the temporal bone, and its constituents are the tympanic cavity, the tympanic membrane, the ossicular chain, the Eustachian tube and the mastoid air cells.

The tympanic cavity is a biconcave bone chamber located in the petrous part of the temporal bone, between the middle and inner ear. It contains the ossicular chain, communicates with the pharynx through the Eustachian tube, and with the mastoid air cells through the aditus and the antrum. The tympanic membrane forms the lateral wall of this structure, while its medial side is defined by the promontory, formed by the outward projection of the cochlea. Here, the middle ear communicates with the cochlea through two cavities, the oval and round windows. Jacobson's nerve (a branch of the glossopharyngeal nerve) passes upon the promontory's surface, providing sensation to the middle ear, the Eustachian tube, the parotid gland, and mastoid air cells.

The tympanic membrane, or eardrum, separates the ear canal from the middle ear; it is a cone-shaped structure kept in place by the insertion of its fibrous border (the annulus) into a ridge of the bony wall of the ear canal. The membrane consists of the pars tensa and the pars flaccida. The pars tensa is made up of three layers: the external one is continuous with the lining of the external acoustic meatus, the internal one is continuous with the lining of the middle ear, and the middle layer represents the fibrous structure that gives the eardrum its typical conical shape and stability. The pars flaccida is smaller and located on the superior side of the membrane, it lacks the fibrous layer and loose connective tissue takes its place.

The outermost bone of the ossicular chain is the malleus and is attached to the tympanic membrane by the manubrium (its long appendix); in such manner, the movements of the eardrum are conveyed to the malleus, and subsequently to the other two bones of the ossicular chain, the incus and the stapes (the three of them form functional unit). The footplate of the stapes is flexibly connected to the oval window, thus transmitting the tympanic vibrations to the cochlea.

The function of the middle ear is to convert airborne vibrations into pressure waves in the fluid that fills the cochlea and to match impedance between this fluid and the air.

This purpose is mediated by three mechanisms:

- there is a significant difference between the bigger surface of the eardrum and the smaller one of the stapes' footplates, thus creating an increase of the force applied on the oval window.
- the ossicular chain represents, as a whole, a lever mechanism, and as such it further increases the force imparted on the cochlea.

- the eardrum conical structure buckles flexibly under vibration, while creating a minor displacement of the ossicular chain, whose joints are relatively firm.

By increasing the vibrations' energy imparted to the cochlea, the middle ear can bypass the impedance mismatch caused by the transfer of energy from an air medium, with low impedance, to a fluid one, with high impedance. Muscle tendons of the stapedius and the tensor tympani are responsible for the acoustic reflex: in response to loud sounds the two muscles contract, thus stiffening the ossicular chain and obstructing the vibratory transmission from the eardrum to the oval window (Dallos, 2008; Musiek & Baran, 2018).

The Eustachian tube (otherwise called the auditory tube) is a 34-45 mm long conduit that creates an important communication between the tympanic cavity and the rhinopharynx. The tube consists of a bony part, located in proximity and contiguity with the middle ear, and a cartilaginous part, located in the pharynx and forming a valve-like slit. It has three main functions:

- the tube maintains a balanced air pressure between the ambient and the middle ear: by contraction of the levator veli palatini muscle and the tensor veli palatini muscle, the Eustachian tube briefly opens up during swallowing, chewing, yawning and sneezing, thus enabling air passage from the pharynx to the middle ear.
- when the slit is closed, usually during breathing and phonation, the middle ear is protected by both the loud sound transmission of a person's voice, and the physiological variation in pressure that occurs in the upper respiratory tract. In addition, the closure of the tube, protects the ear from the potential damage caused by biological, chemical or physical agents originating from the pharynx.
- lastly, the auditory tube provides production of mucus and mobile cilia that grant transport of material from the middle ear to the pharynx, and the valve-like mechanism enables a unilateral passage from the ear to the pharynx, but not the other way.

The last constituents of the middle ear are the mastoid cells, which the tympanic cavity is in communication with through the aditus and the antrum; the cells are air-filled cavities contained in the spongy bone of the mastoid process of the temporal bone, and the biggest of them, with a maximum diameter reaching up to 1 cm, is called the antrum. They have a pneumatic function, that lessens the direct damage caused by trauma on the temporal bone, and a regulatory function, which contributes to maintain an appropriate air pressure balance in the middle ear.

2.2.3 - The inner ear

The inner ear is represented by a series of cavities within the petrous segment of the temporal bone, forming the bony labyrinth; inside the latter, and conforming to its structure, there is the membranous labyrinth, which houses the organs of equilibrium and hearing. The bony labyrinth contains three major sections: the bony cochlea, the bony vestibule and the semicircular canals.

Communication to the osseous labyrinth passes through the oval and round windows, the cochlear aqueduct, the vestibular aqueduct (that helps fluid exchange and regulation between the perilymph and endolymph, and the cerebrospinal space and the endolymphatic sac, respectively), and the openings to the cranial cavity through which the nerve and vascular supply of the labyrinth enter. Figure 4 illustrates the main structures of each part of the ear.

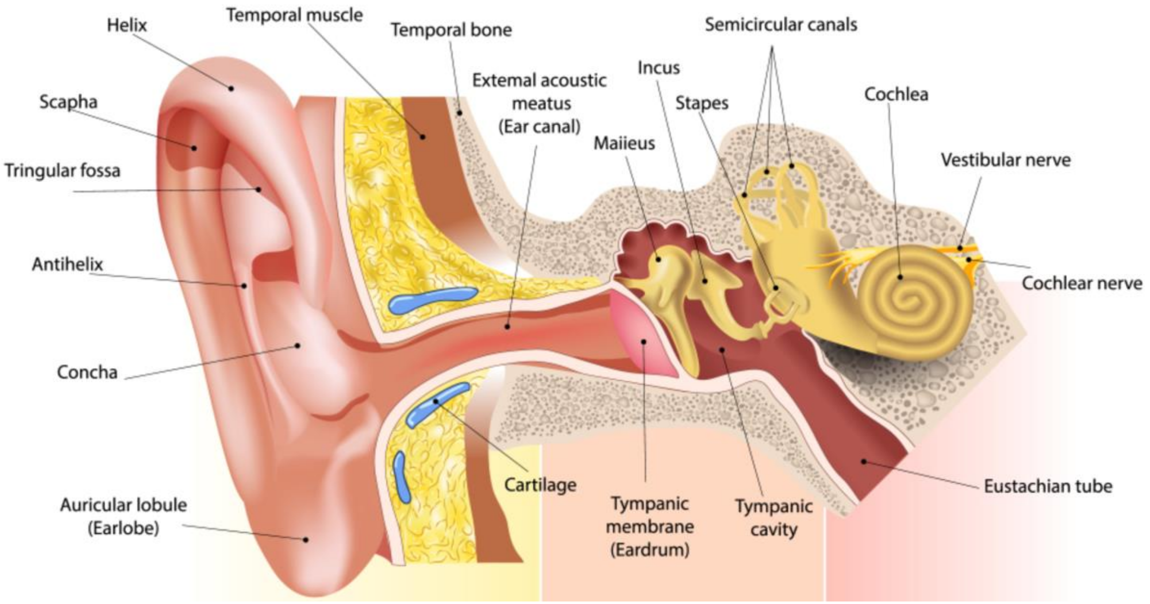

Figure 4. **Peripheral auditory system.** Schematized structures of the external ear (yellow band), of the middle ear (orange band) and of the inner ear (pink band) are reported.

<u>2.2.3.1 - The cochlea</u>

The cochlea is divided into a bony cochlea and a membranous cochlea. The bony cochlea is a snail-shaped structure that creates 2½ turns, with the basal one larger than the apical one, and that is coiled around its osseous central core, the modiolus. From the modiolus the spiral lamina, protrudes into the cochlea, and incompletely divides the canal into two compartments. The lower one is the scala tympani that opens up in the tympanic cavity through the round window; the upper one is the scala vestibuli that communicates through the oval window. The surface of the spiral lamina is embedded with small perforations on its lateral side, through which the fibers of the acoustic nerve (originating from the hair cell) can pass and form the trunk of the nerve (Figure 5).

The membranous cochlea comprises three ducts: the scala vestibuli (superior), the scala media (or cochlear duct, middle), and the scala tympani (inferior). The inferior part of the scala media is divided from the scala tympani by the basilar membrane, while its superior portion is separated from the scala vestibuli by Reissner's membrane. The organ of Corti is located on the surface of the basilar membrane, containing the hair cells responsible for the electromechanical transduction of sound vibrations into nervous impulses. Furthermore, on the basilar membrane there are up to 30.000 basilar fibers: they are rigid yet elastic structures, with their proximal extremity firmly fixed at the base of the modiolus, and their distal one free in the loose structure of the basilar membrane, so that they can vibrate in the medium fluid. From the oval window to the helicotrema the fibers progressively increase in length and decrease in diameter, so that, at the opening of the basilar turn we can find short and rigid fibers that better vibrate in response to high frequency sounds, while at the apex there are long and flexible fibers that better react to low frequencies.

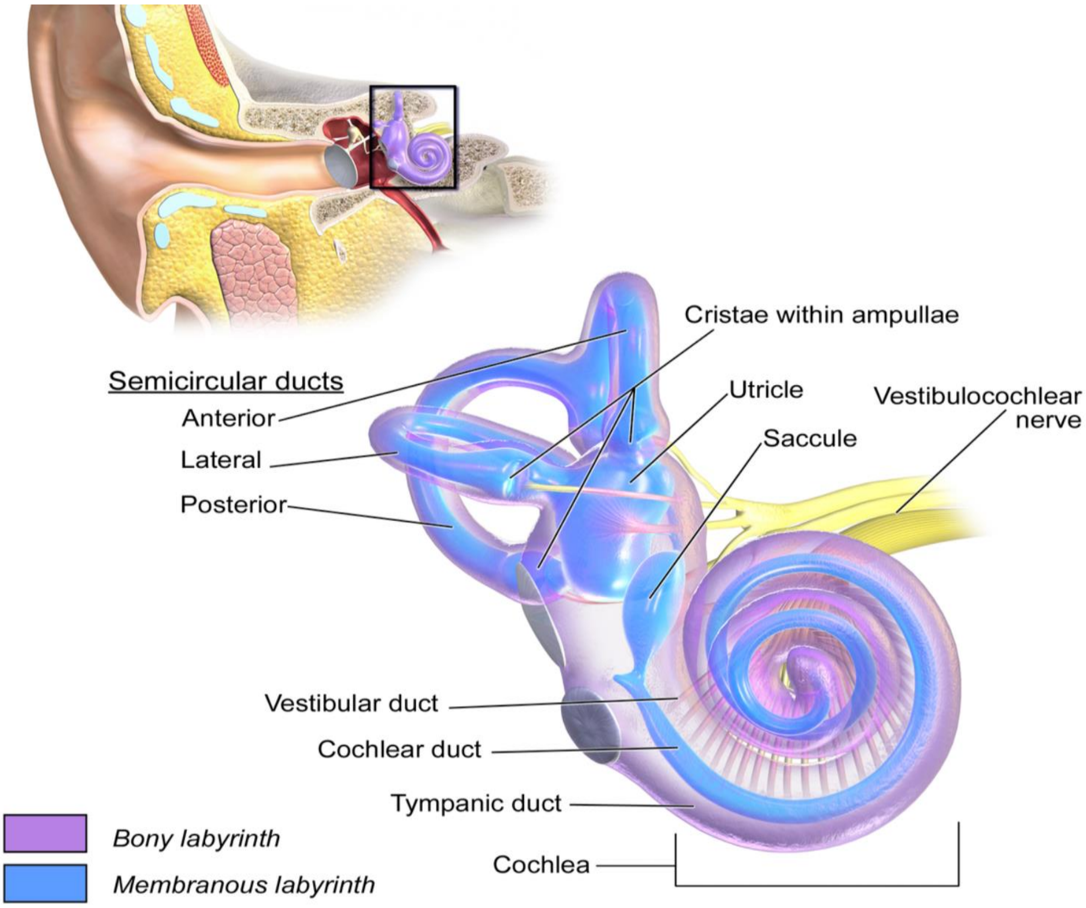

Figure 5. Cochlea structure.

This mechanism is explained by observing the profile of the “travelling wave” through the basilar membrane: soundwaves travel at different frequencies, and, when they hit the membrane, they put it into a weak vibration until they reach the part of the membrane with a frequency resonance equal to their own; in that point, the soundwaves get amplified and the membrane starts to vibrate flexibly, until the waves’ energy (called “travelling wave”) dies out. In such way, a sound wave can travel through the membrane up until it reaches its point of resonance. This mechanism will explain why the maximum wave amplitude of sound waves at around 8000 cycles per second resides at the base of the cochlea, while that of sound waves of 200 cycles per second is located near the helicotrema (Raphael & Altschuler, 2003).

At the peak of the cochlea there is a point of communication between the scala tympani and vestibuli, called helicotrema. The membranous system is a fluid-filled structure, where the scala tympani and vestibule contain perilymph, while the scala media is full of endolymph and cortilymph (Yost & Schlauch, 2001). Perilymph has the same chemical composition of cerebrospinal fluid, being low in potassium and high in sodium and with a 0mV electrical charge (similarly to the cortilymph), while endolymph, similar to intracellular fluid composition, has high potassium and low sodium levels, and a +80mV electrical charge. The ionic balance of the endolymph is maintained by the stria vascularis, a cell-rich vascular layer on the outer wall of the cochlea. The vestibular aqueduct contains the endolymphatic sac and endolymphatic duct and is believed to act as an overflow valve in case of excess of endolymph; the cochlear aqueduct, on the other hand, is a key factor in intracochlear hydromechanics, because, the cerebrospinal fluid can flow through to the scala tympani and vestibule, thus providing the pressure reference for the perilymph and, to a great extent, also to the endolymph (Reid et al., 1990).

The organ of Corti represents the endpoint of the peripheral acoustic system, by transducing in nervous impulses the vibration of the basilar membrane. The organ lies upon the basilar membrane, through all its length. It is made of sensory cells, supporting cells and the terminal plexus of the auditory nerve fibers. Specialized cells create a structural support for the organ, forming a rigid framework located on the basilar membrane. The most important ones are the inner and outer pillar cells; other supporting elements are the inner phalangeal cells and outer Deiters cells. These cells on one hand embrace the bottom part of the sensory cells and keep them in place, while, on the other, their long processes extend up to the top part of the sensory cells and, along with the apical extensions of the pillar cells, form the reticular lamina.

The reticular lamina is a flat plate that supports the apical portion of the sensory cells, and at the same time creates an important isolation between the organ of Corti and the endolymphatic space.

The actual sensory cells are represented by the inner hair cells (robust and flask shaped), located on the modiolus side, and outer hair cells (cylindrical and thinner), disposed on the opposite side and free of surrounding cells; they hold an electrical charge of -40 /-70 mV. The base of the cells is represented by the acoustic nerve fibers connections (terminal buttons), and their apex by stereocilia (or cilia).

Cilia are surrounded by pores that open up when the cilia are bent sideways, thus enabling the passage of potassium ions and starting the transduction process. This structure is sustained and coordinated by two sets of filaments: (A) the tip-links, bond one cilium to another, facilitating the opening and closing of the pores; (B) the cross-links, which are located on the sides of the cilia, and they enable the cilia to move in unison when stimulated.

Above the organ of Corti we find the tectorial membrane, a non-cellular structure with the properties of a gel, which serves a functional purpose of being a valid support to the cilia activity, while maintaining energetic neutrality due to the lack of cellular membranes (Figure 6).

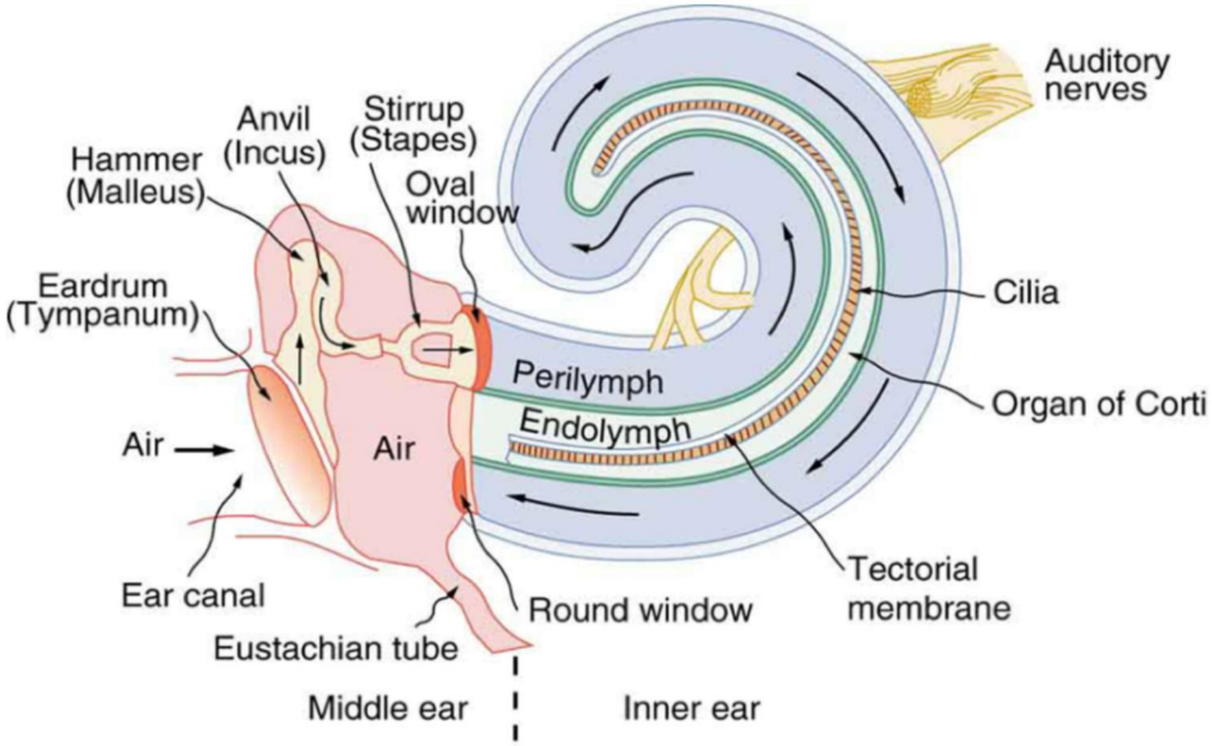

Figure 6. Internal structures of cochlea. Sensory receptors of hearing are hair cells (cilia), present on basilar membrane of cochlea. Sensory organs present on basilar membrane for hearing is formed by hair cells and the tissue is called Organ of Corti.

The tectorial membrane is connected with the cilia of the outer hair cells, and when a travelling wave passes through the basilar membrane two things can happen.

(A) The acoustic wave depresses the basilar membrane downward and the organ of Corti moves accordingly: the tectorial membrane pushes the stereocilia towards the limbus, causing the tip-links to close the pores. The result is a hyperpolarization of the hair cells.

(B) The acoustic wave thrusts the basilar membrane upward and the organ of Corti moves accordingly: in this case the tectorial membrane pushes the cilia away from the limbus, thus causing depolarization of the hair cells. Since the tectorial membrane is not linked to the cilia of the inner hair cells, these sensory transductors could be moving along with the fluid flow caused by the movement of the outer hair cells.

Hair cell depolarization is coupled with three cochlear potentials: the endocochlear/resting potential, the cochlear microphonic and the summating potential. The latter is followed by the action potential, produced by the auditory nerve. The endocochlear potential provides the main driving force for sensory transduction, is essentially a K+ diffusion potential, and is generated by the intermediate cells of the stria vascularis. The resting potential is created by the differential voltage between the +80 mV in the scala media and the -40 to -70 mV charge in the hair cells (Wangemann, 2002).

The cochlear microphonic is mostly created by the outer hair cells and increases or decreases proportionally to the intensity of the sound stimuli. It can respond to relatively high stimuli up until saturation, after which the potential decreases. The summating potential is generated by inner hair cells and follow the envelope of the stimulus. In contrast with the cochlear microphonic, the summating potential doesn’t saturate at high intensities and, on the contrary, it accommodates well to them.

Lastly, the action potential is created by the acoustic nerve, so it isn’t part of the cochlear potentials, but it is strictly associated with them and is a good estimate of behavioural hearing threshold (Musiek & Baran, 2018).

2.2.3 - The auditory nerve

The auditory nerve is one of the components of the VIII cranial nerve along with the vestibular nerve. The nerve is responsible for transmitting the auditory signals from the Organ of Corti to the cochlear nuclei within the brainstem and ultimately to the primary auditory cortex in the temporal lobe. Its fibers originate from the terminal buttons of the hair cells and pass through the habenula perforata, in the osseous spiral lamina, and reaches the Rosenthal’s canal, that hosts the spiral (cochlear) ganglion cells. The ganglion is constituted by two types of bipolar neurons: (A) type I neurons: they are large and myelinated, represent 90% of cochlear nerve population and their peripheral processes are connected to the inner hair cells; (B) type II neurons: they are smaller and unmyelinated, represent the remaining 10% of cochlear nerve cells and their fibers project to the outer hair cells. As a result, a single nerve fiber may innervate many outer hair cells, while many fibers may connect to a single inner hair cell.

The auditory nerve presents a tonotopic organization: high frequency fibers are situated on the outermost part of the nerve trunk, while low frequency fibers run in the innermost part of the nerve. The transduction apparatus is able to grant a rapid response in transferring the auditory information: the receptor potentials of specific hair cells and the following action potentials of the associated auditory nerve fibers can react to stimuli of up to 3 kHz in a one-on-one manner. This mechanism encompasses the so called "volley principle", that states that for sound frequencies between 500 Hz and (theoretically but debated) 5000 Hz cochlear neurons individually fire subharmonic frequencies of a sound being heard and collectively phase-lock to match the total frequency of the sound (Joris & Smith, 2008).

These rapid processes though seem to be unsuccessful in following frequencies above 3kHz, so the basilar membrane provides a "labelled-line" coding mechanism. In this case, the tonotopy of the cochlea is maintained throughout the ascending structure of the nerve, and thus specific information on the sound frequency is preserved. Since neurons are linked to inner hair cells in a one-on-one manner, auditory fibers transport information of just a little part of the whole auditory frequency spectrum. As a result, fibers associated with the upper part of the cochlea respond to higher frequencies while fibers connected to the basal part of the cochlea better react to lower frequencies. These cut-off frequencies represent the "tuning curves" of the auditory neurons and their lowest threshold is called "characteristic frequency". This is of great importance when considering that one of the most important features of cochlear implants is their replica of the tonotopic organisation of the cochlea and its nerve afferents (Purves et al., 2001).

2.3 - The central auditory system

The acoustic nerve is composed by the afferent nerve fibers, having body cell at the spiral ganglion of Corti, and by efferent nerve fibers. Together with the inferior and superior vestibular nerves, it forms the nerve vestibulocochlear, the VIII cranial nerve (Figure 7). It originates in the petrous rock of the temporal bone, crosses the internal auditory canal, comes out at the ponto-cerebellar corner, crosses the cisterna magna and penetrates the underside of the pons, where it reaches the ventral and the dorsal cochlear nuclei, from which the central acoustic pathway begins. Cochlear nuclei are organized tonotopically: adjacent neurons respond preferentially to progressive similar frequencies, forming map that gradually respond from higher to lower frequencies. From the ventral cochlear nucleus, fibers project bilaterally to the superior olivary complex, it is responsible for phase and sound intensity processing. From the dorsal cochlear nucleus fibers reach directly the inferior colliculus, which is also organized in a tonotopic manner, and it is responsible for lateral inhibition which allows for the separation of individual sounds within complex spectra. From the inferior colliculus an ascending path begins, ending in the medial geniculate nucleus of the thalamus, which has proved to be fundamental in various physiological processes of sound processing, as for example the novelty recognition, the sound localization and the processing of complex vocal communications (Winer et al., 2005).

The central acoustic pathway travels to the primary auditory cortex in the temporal lobe (Brodmann areas 41), again with a tonotopic organization. The incomplete crossing of the central acoustic pathway causes that each ear sends information to both primary auditory cortices. The secondary auditory cortex (Brodmann areas 41) surrounds the primary and receives information and sending them to the auditory association cortex, Brodmann area 22 and to other higher-order cortical areas, which guarantee the processing of the information necessary for the understanding of the language. Finally, the auditory areas are connected to the parietal lobe, which processes and interprets visual-spatial properties of the stimuli. The efferent cochlear pathways are made up of fibers originating from the superior olivary complex. Their purpose is mainly inhibitory, in order to reduce the sensitivity of the organ of Corti, in the case of a loud or disturbing noise.

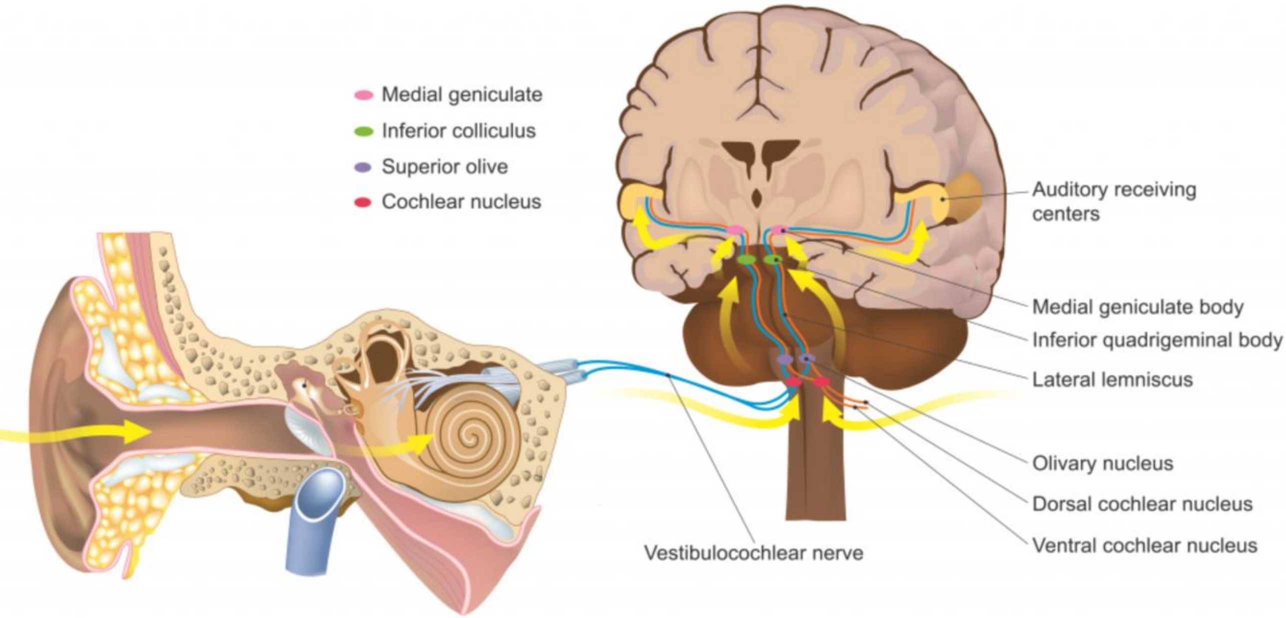

Figure 7. Central auditory pathway. Information from each ear and the cochlear nucleus is transmitted bilaterally to the auditory cortices.

2.4 - The proprieties of sounds

The understanding of speech requires a wide range of functions that are integrated in specific neural networks. The auditory system perceives speech as a sound, it analyzes its pitch, timbre and source location.

The pitch is the attribute that allows the sounds to be ordered in a scale from low to high (Krumbholz et al., 2005). Pitch is a feature of both simple and complex sounds, and consequently of the spoken language (Gelfer & Mikos, 2005). There are multiple theories describing how the auditory system identifies the pitch of a sound: spatial theories state that this ability directly depends from the neural tonotopic distribution (Cariani, 1999), whereas temporal theories start from the assumption that tonotopic coding only would be not enough, especially for sounds with a frequency lower than 200 Hz and for those with an high intensity, which stimulate large areas of the basilar membrane. They postulate that neurons respond to incident signals in one precise phase of the oscillatory cycle, a phenomenon known as phase-locking. The frequency would therefore be indirectly derived from the interval between two successive depolarizations, corresponding to the period of the wave (Cohen et al., 1997 Oxenham, 2018).

Timbre is the qualitative difference between two sounds having the same pitch, intensity and duration. It is a multidimensional parameter with spatial and temporal characteristics, dependent on the dynamics of its origin and by the distribution of energy in the sound spectrum (Bizley et al., 2010). The timbre makes the sound source identifiable, keeping it separate from any other sounds and is determined by the spectral composition of the sound, i.e., from the distribution of the energy of the different frequency components which compose the sound itself (Shamma, 2001). Pitch and timbre are characteristics identified entirely at the cortical level. From studies on patients with brain damage, it appears that alterations of the right auditory cortex impair the ability to identify pitch and timbre (Robin et al., 1990) of pure and complex tones (Samson et al., 2011). Damage to the left hemisphere changes the ability to analyze intact pure tones sent individually.

For the localization of the sound source the brain exploits the position of the ears on both sides of the head. Sound comes first and with the greatest intensity in the ear ipsilateral to the source. The difference between the quality of the sound perceived between the left and right side allows the CNS to localize the source. Moreover, the natural shape of the ear shields more the sounds originating from the back of the head, and it amplifies those coming from the front, allowing for accurate localization also in the anteroposterior direction.

Studies in patients with brain lesions and neuroimaging research attempted to identify the areas that are recruited for spatial localization of sound, and it seems that all the auditory network contribute to the sound localization, although the posterior part of the network is more active than the anterior ones (Brugge et al., 2001). In any area the neurons seem to respond predominantly to contralateral stimuli, for what concerns the analysis of the sound source (Schnupp et al., 2001).

2.5 - The understanding of language

In the second half of the 1800s Carl Wernicke states the importance of the left superior temporal gyrus (STG) for the understanding of the spoken language. In 1976, in an article titled Wernicke's region: where is it?, it is identified Wernicke's area, "area in which a lesion can impair the comprehension of language" (Bogen & Bogen, 1976). The definition does not originally have an anatomical value, but rather functional (Figure 8).

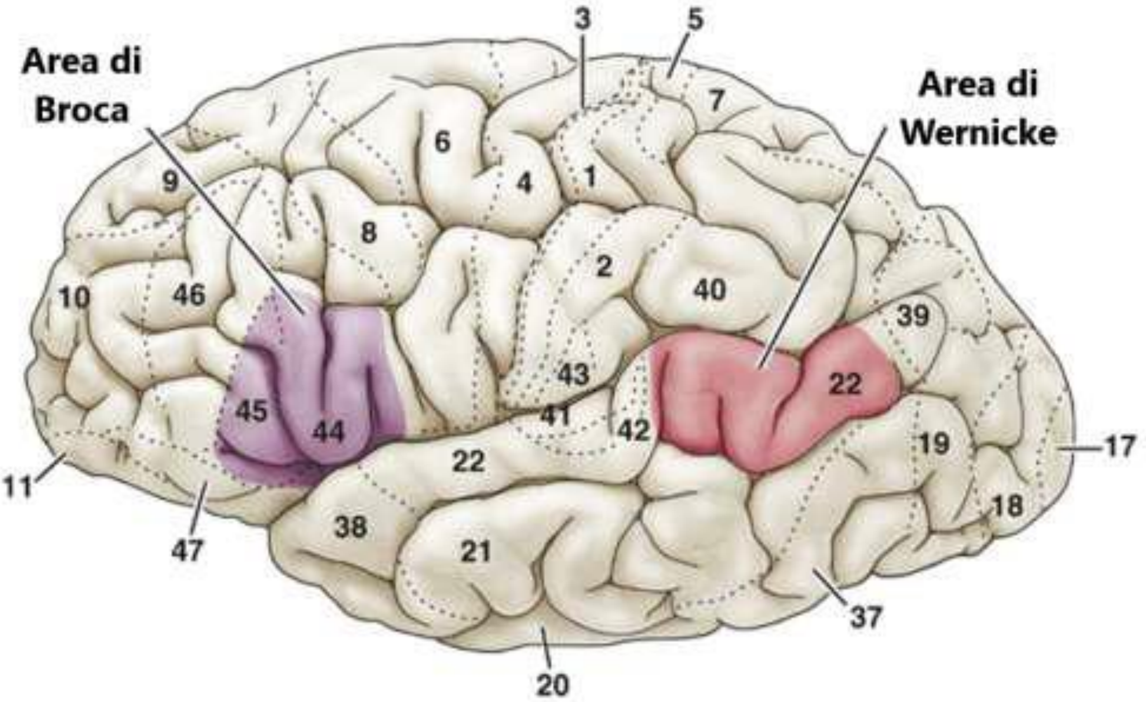

Figure 8. Wernicke and Broca's Area. These areas are the pivotal nodes of the language network.

Indeed, in literature the cortical zones involved in this complex function are multiple (Figure 9): in addition to the posterior STG (pSTG), also the supramarginal gyrus (SG), the middle temporal gyrus (MTG), the gyrus angular (AG) and the inferior temporal gyrus (ITG) have a pivotal role in speech perception and elaboration (Hertrich et al., 2020).

Nonetheless, the term "Wernicke's area" has taken on anatomical content until it is identified in the STG and the SG, respectively Brodmann areas 22 and 40 (Binder, 2015). It is now anyway demonstrated that other brain regions are involved in the understanding of the language. From studies on subjects with lesions of various causes extending to the cortical level, it has been demonstrated, for example, an alteration of comprehension ability in the case of a damages in the MTG, the AG, the anterior STG (aSTG) and the left prefrontal cortex (Thothathiri et al., 2012). Neuroimaging studies on patients with primary progressive aphasia and a severe impairment of language comprehension, have demonstrate an alteration of the anterior portion of the temporal lobe (Rogalski et al., 2011). From these findings it is possible to deduce that the impairment of the ability to understand the language can be the result of damage of different areas of the cerebral cortex (Binder, 2015).

Neuroimaging studies have also identified two phases that appear to lead to the understanding of language. The first consists in the mere analysis of the auditory signal in terms of pure phonemes, regardless of the real meaning of words. It is mainly performed by the aSTG bilaterally (Binder et al., 2000; Poeppel & Marantz, 2000; Hickok, 2012) and in which

Wernicke's area participates apparently only in the coding of the phonological profile and the form of the words (Pulvermüller, 2013). The second corresponds to the assignment of the meaning of the sound and it seems to occur in the AG, MTG, ventral temporal lobe, medial parietal cortex, medial and inferolateral prefrontal cortex (Binder et al., 2009). Furthermore, the inferior frontal gyrus (IFG), although useless to perception and to the assignment of meaning of single words, appears implicated in sentence comprehension (Mesulam et al., 2015).

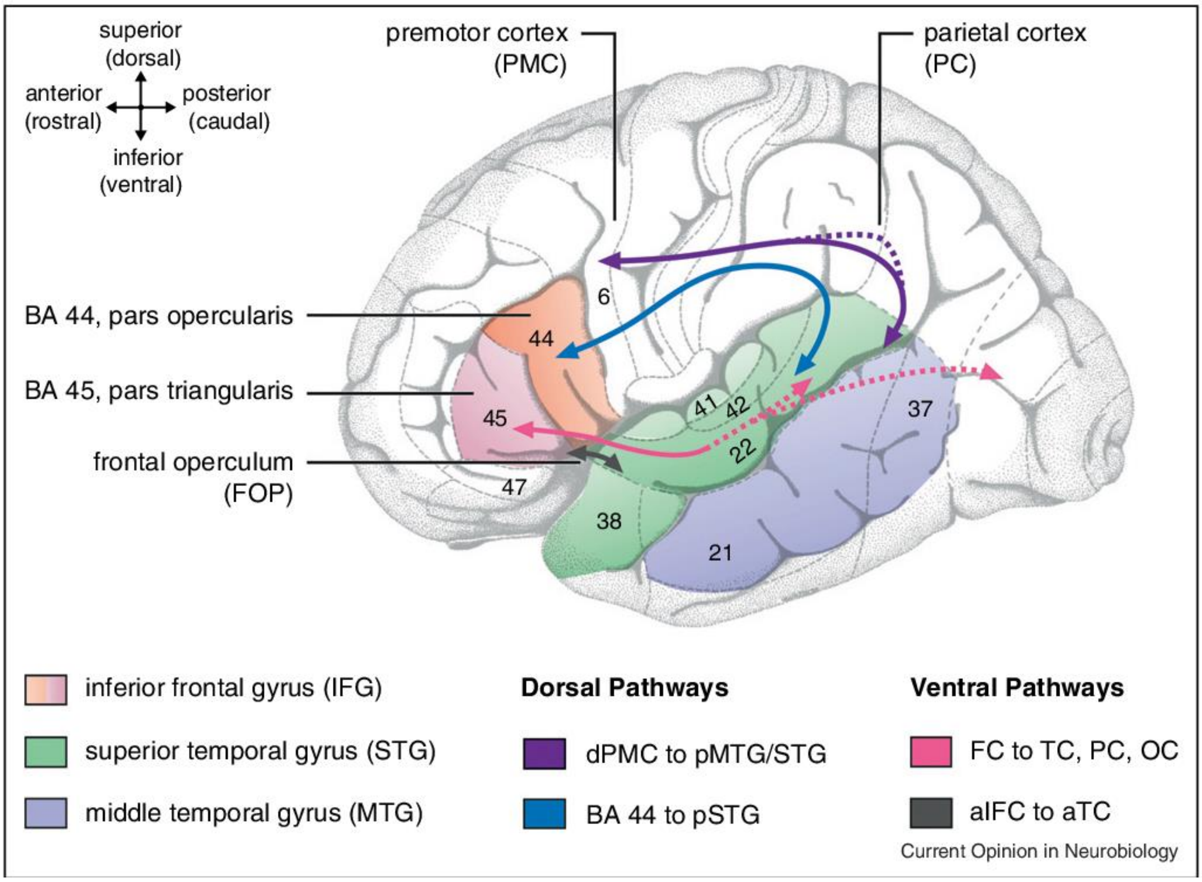

Figure 9. Language network brain regions and fiber tracts (schematic and condensed view of the left hemisphere). The dorsal pathway connecting dorsal premotor (dPMC) with posterior temporal cortex (pMTG/STG) involves the SLF III and/or the SLF II and the SLF-tp; the dorsal pathway connecting BA 44 with the posterior STG involves the AF. The ventral pathway connecting the frontal cortex (FC), that is, BA 45 and others, with the temporal (TC), the parietal (PC), and the occipital (OC) cortex, involves the IFOF (also called the ECFS); the ventral pathway connecting the anterior inferior FC (aIFC), that is, BA 47 and others, and the FOP, with the anterior TC (aTC), involves the UF.

Human voice represents a specific category that activates the auditory association cortex (Belin et al., 2000; Morillon et al., 2022), with left lateralization for sentence encoding (Albouy et al., 2020) and specific activation of the left STG, the supratemporal plane and the left hemisphere for voice perception (Rupp et al., 2022). An area corresponding to the superior temporal sulcus (STS) appears to be activated with a high degree of selectivity in human speech comprehension (Belin et al., 2000), as its activation increases accordingly to both the complexity of a sentence (Wilson et al., 2010) and the higher sequencing demands of a phrase (Pallier et al., 2011). The accuracy and the reaction time of participants' responses to complex questions change after inhibitory 1Hz rTMS targeting the left superior temporal sulcus, providing causal information on the central role of the posterosuperior part of the temporal gyrus in sentence comprehension (Kyriaki et al., 2020).

This chapter has described the normality of perceptual and cognitive processes concerning the elaboration of sound and language. In the next part, the pathologies that affect the ear and which can compromise the processing of sound and the reception of a verbal message will be presented. In addition, the most common methods for assessing the severity of damage to the peripheral system will be listed.

CHAPTER 3 - HEARING LOSS AND AUDIOMETRIC TESTS

Worldwide, 1.5 billion people suffer from significant and progressive lowering of the hearing threshold (Haile et al., 2021), and half of the elderly population have a significant hearing loss (HL) (Ford et al., 2018). Hypoacusis refers to a decrease in hearing ability, from mild forms up to a complete deafness. Normal hearing is defined as a subject capable of perceiving sounds with an intensity equal to or less than 20 dB for all frequencies of the tonal field. This limit refers to an audiometric threshold level at which usually there is no subjective sensation of hearing impairment. HL can be unilateral or bilateral, mild, moderate, or severe/deep. Unilateral complete loss of hearing is termed anacusis, the bilateral is cofosi.

Alteration of the peripheral auditory pathway changes the cortical representation of an acoustic stimuli. When neurons responsible for receiving signals to a certain frequency are no longer stimulated, the plasticity of the cerebral cortex change accordingly, and neurons of the same point in the tonotopic map begin to respond to the other frequencies of adjacent cells, with a reorganization of the tonotopic map, that occurs especially in cases of infantile deafness, or at least the loss of lateral inhibition (Dietrich et al., 2001). This results in difficulties in understanding the spoken language, which requires correct decoding of an acoustic signal (McCoy et al., 2005). Therefore, HL patients complain more difficulties in hearing in noisy environmental that masks the listening to the conversation, compared to peers with normal hearing (Hopkins & Moore, 2009). They also require greater cognitive efforts (Shinn-Cunningham & Best, 2008; Rönnberg et al., 2013), inevitably followed by central fatigue and asthenia, elements that contribute to the psychosocial distress of this category of patients (Kramer et al., 2006; Hornsby, 2013).

3.1 - Epidemiology

The pathology can arise at any age by compromising language development in children and causing serious relationship, occupational and psychological problems (Bainbridge & Wallhagen, 2014) in adults, with consequent reduction in the quality of life. The incidence in newborns is estimated be between 4 and 60 for every 1000 births and about 3% of children and adolescents develop hearing problems, with significant difference between social and economic status (Lasak et al., 2014). The prevalence in adults increases gradually with age and it is estimated that about 50% of people suffer from HL between 60 and 69 years (Agrawal et al., 2008) and 80% of over 85s (Lin & Albert, 2014). The severity of a similar problem in the elderly population is particularly evident when comparing groups of HL patients and normal hearing peers. The fists appear to have higher rates of hospitalization (Genther et al., 2013), falls (Lin & Ferrucci, 2012), dementia (Gallacher et al., 2012; Lin & Albert, 2014) and depression. In children, HL results in a lower level of education than peers with normal hearing and it correlates to a higher rate of unemployment in adults (Cunningham & Tucci, 2017). HL can be classified into conductive, sensorineural or mixed, on the basis the pathophysiology. Sensorineural or perceptive deafness is an expression of the load of the lesion to the sound transduction apparatus. Deterioration of the acoustic nerve leads to the so-called retrocochlear or neural HL, with a consequent alteration of the signal transmission (P. Z. Wu et al., 2019; Chester et al., 2021).

Hair cells are particularly susceptible to damage that are caused by different factors and their loss is permanent, since they do not possess ability to self-regeneration. In some cases the death of such cellular elements can determine the degeneration of spiral ganglion neurons, compromising the possibility to obtain therapeutic benefits from the placement of a cochlear implant (Cunningham & Tucci, 2017). Among the many forms of progressive sensorineural HL, there are two main forms: chronic acoustic trauma, characterized by decrease hearing ability caused by prolonged exposure to high-intensity noise, and the presbycusis. In terms of incidence, acoustic trauma is the second cause of HL in adults. The pathophysiology is unclear, but a mechanism of excitotoxicity due to exaggerated release of glutamate a due to repeated stimulation. The most damaged cells are those of the basal gyrus, dedicated to the transduction of frequencies between 3 and 6 kHz, that is the most amplified part by the external auditory canal. Presbycusis is due to the set of changes that occur in the load of the hearing system with advancing age. It is the most common form of HL, affecting with different grades any subject that over the age of 40, although usually it appears clinically evident only after 60 years. The specific causes are uncertain, but vascular disease, hyperlipidemia, chronic exposure to noisy environment and genetic predisposition seems to be involved (Eckert et al., 2021). The damage can be identified a t the level of the peripheral auditory system, of the central auditory system, or of both circuits simultaneously.

The main peripheral form is the strial, where the main cause is the degeneration of the stria vascularis, followed by a reduction in the endolymph potential, which compromises the property of hair cells (Yu et al., 2021).

The central deafness forms are characterized by the slowing down of the understanding of the spoken language and by a major difficulty to localize the sound source (Freigang et al., 2014). It can be a primitive form, but more frequently it is secondary to the loss of the hair cells. In addition to the reduced hearing sensitivity, what distinguishes this deficit is the major repercussions on the quality to understand the spoken language, especially in noisy environments.

Indeed, if the changes in the inner ear are better known and identifiable (Eckert et al., 2021) significant changes in the peripheral organ could affect specific brain areas in the left pSTG and in the STS that are pivotal for phonological encoding, syntactic processing, lexical-semantic processing, and syntax-sematic interface (Walenski et al., 2019). This maladaptive mechanism might compromise the cortical representation of an acoustic stimulus (Bidelman et al., 2020; Koops et al., 2020), such as human speech, contributing to the progressive deterioration of communication ability in deafness (Fortunato et al., 2016)

3.2 - Audiometric tests

3.2.1 - Pure audiometry

The test assesses the auditory threshold for pure tones, i.e., sounds with a pure frequency ranging from 125Hz to 12kHz frequency in octave steps. The exam is conducted in an audiological cabin and provides the possibility to investigate threshold for both ears bilaterally, in free field, or, more frequently, for the single ear.

3.2.2 - Speech audiometry

It is based on the administration of an acoustic messages, as for example a phrase, that the patient has to hear, to understand and to repeat. It allows to investigate for the level of speech intelligibility and therefore the impact of hearing impairment in interpersonal communication. It can be performed with headphones or in a free field, in silence or in competition with a background masking noise. The Matrix Sentence Test is usually chosen to investigate the speech audiometry in patients (Puglisi et al., 2015) and the name of the test derives from the array of words used to compose the sentences, that are randomly administered to the patient with disturbing noise, i.e. in competition. The subject is then invited to repeat the phrase. The matrix consists of a vocabulary of 50 common words of 2 to 3 syllables, from which test sentences were randomly generated (10 names, 10 verbs, 10 numerals, 10 adjectives, and 10 nouns). From this matrix (Table 1), semantically unpredictable sentences with fixed grammatical structure were randomly generated (e.g., “Sofia drags ten black pencils”). These features make the Matrix Sentence Test more reliable than the speech audiometry, because of the very high number of possible combinations effectively prevents learning phenomena that could distort the result (Puglisi et al., 2015).

It is an adaptive test, following each patient's response and based on its accuracy. The software automatically generates one more sentence that are easier or more difficult to understand. In general, it is preferable to fix the intensity of the backward noise to 65 dB, allowing the software to vary the volume of the sentences. The difficulty increases if the patient correctly repeats at least 3 out of the 5 words, otherwise, it is reduced. The process lasts about 4', with the administration of 20 sentences, necessary to identify the precise intensity of the words at which the subject understands 50% of the stimuli administered. The test result is called Signal Reception Threshold (SRT); it is expressed in dB, and it represents the difference between the intensity of the words and that of the backward noise. The average value is -6/-7 dB in healthy subjects (Puglisi et al., 2015), but HL patients can reach SRT even much higher than zero. The presence of the noise reproduces the normal environmental situations, thus allowing to evaluate the real threshold of perception of the subject.

Table 1. Italian Matrix Sentence Test. Here, the matrix of possible combination between words is represented.

Subject	**Verb**	**Numeral adjective**	**Direct object**	**Qualifying Adjective**
Andrea	cerca	Due	bottiglie	azzurre
Anna	compra	Quattro	macchine	belle
Chiara	dipinge	Cinque	matite	bianche
Luca	manda	Sette	palle	grandi
Marco	possiede	Otto	pietre	nere
Maria	prende	Nove	porte	normali
Matteo	regala	Dieci	scatole	nuove
Sara	trascina	Venti	sedie	piccole
Simone	vede	Poche	tavole	rosse
Sofia	vuole	Molte	tazze	utili

After having illustrated the types of HL and briefly mentioned of how HL might cause changes in the CNS, the techniques available today to treat HL will be discussed in the next chapter.

CHAPTER 4 - HEARING LOSS TREATMENT

As already mentioned, the physiological hearing capacities of a healthy subject ("normal hearing") allow the perception of sounds between 20 and 20,000 Hz. In some cases, pathological conditions lead to the reduction of hearing performance and therefore of perceptive abilities, which vary according to numerous factors. Depending on the etiology, temporary HL are generally treated through the use of antibiotics and anti-inflammatory cortisone or anti-inflammatory corticosteroids, but the possibility to restore physiological hearing it is almost impossible. Nowadays, methods that replace and compensate the HL are investigated, in order to attempt auditory restitution in all those conditions of infantile or adult sensorineural HL and to bring perceptive abilities back to optimal pre-pathological levels. Numerous hypotheses have been proposed by research, mainly deriving from the regenerative therapy of hair cells, through gene therapy, pharmacology or the use of stem cells, with the main purpose of regenerating the spiral ganglion neurons (Matsuoka et al., 2017), whose loss is a common cause of impaired hearing.

As a result of untreated HL, a person's professional and personal lives can be negatively impacted. To identify these effects, research shows that untreated hearing loss may result in the following effects:

- Avoiding social situations or withdrawing from them
- Memory impairment and difficulty learning new tasks
- Depression, fatigue, tension, and stress
- A reduction in job performance and earnings

The relationship between hearing loss and other serious health problems like dementia, diabetes, heart disease, depression, and fall rates in older adults has been studied extensively (Stahl, 2017; Ren et al., 2021). HL is becoming more of a topic of research as those who live with untreated HL patients are at greater risk for other physical and cognitive problems. Hearing aids and cochlear implants are the most commonly used and efficient device to treat HL, and they will be discussed in the following paragraphs.

4.1 - Removable hearing aids

Removable hearing aids (RHA) are generally the first choice for sensorineural or mixed HL. RHA are very effective in improving the patient's acoustic perception but only the 25% of the HL patients population benefit from its use (Walling & Dickson, 2012). Essentially, RHA is composed of microphone, amplifier, receiver, battery and intensity regulators. The microphone picks up the sounds and converts them into electrical signals. Sensitivity, selectivity, the range of frequencies to be amplified, can be modified according to the patient's needs. RHA can use mono or multidirectional microphones. The amplifier has dynamic characteristics, since sounds of lower intensity are more amplified than those of high intensity. The receiver converts the electrical signal of the amplifier, filters and sends it to the tympanic membrane.

Digital RHA offers the possibility to exclude the background noise, to adapt the device to the receptive properties of the environmental condition or to connect to other electronic devices. Every device can be fully customized by modulating the gain, the maximum output and the frequency range. Gain, expressed in dB, is the capability to amplify the input sound and it corresponds to the difference between the amplified output signal and the incoming signal. The gain is profoundly conditioned by the patient's audiometry threshold. The maximum output of the RHA is set to be below of the patient’s annoyance threshold, but it should be sufficient to guarantee an appropriate information reception. The choice of the frequency range allows to select the frequencies that need to be amplified, and it is mainly based on the patient’s audiogram.

In cases of bilateral HL, it is preferable to apply the prosthesis bilaterally. There is a wide variety of types of RHAs, adaptable to the patient’s need (Figure 10). The "pocket hearing aid" is the oldest form, and it is nowadays no longer used. It is a small pocket radio connected with earphones through a wire. This device is very visible and not very discreet, but it has a high amplification power, it is suitable for an extended frequency range, handy for subjects with compromised fine movements and it is affordable, remaining a viable option for patients suffering from severe-profound HL.

The "behind the ear" device is a type of RHA with instrumental components contained in a small semi-lunar structure which is positioned behind the auricle. In the case of a deficit of the high frequencies, a subtype called “open air fitting” can be used, it has reduced dimensions and it allows to reduce selectively the amplification of low frequencies, eliminating the sense of autophony. The Larsen effect is an annoying whistle that derives from the imperfect occlusion of the duct, and it is reduced thanks to an out-of-phase signal generated with respect to it by this RHS. BTE is usually chosen by children, because it results comfortable and practical, it is hardly visible and has a good amplification power.

The "in the ear" device, is an instrument with a shape modeled on the outline of the patient's external ear and positioned entirely in the concha of the auricle. It is less powerful than the BTE, and it is mostly indicated in moderate or mild HL. It is less visible and does not hinder the possibility of wearing other accessories, such as glasses.

The “in-the-canal” is modeled to the external ear canal, in the basin to the isthmus, that is the concentric narrowing in which the canal becomes composed of bone. This RHA has the advantage of being almost invisible and, moreover, it has a conformation that makes it more performing in the omnidirectional capture of sounds. It is more effective in correcting HL involving high frequencies. It requires careful hygiene of the external ear, as it can favor accumulations of cerumen that can easily block the ear canal. However, it does not reach great powers and generally it does not guarantee intensities higher than 80 dB. It is therefore indicated in mild to moderate HL and in individuals, especially the young, who could suffer the psychological and social impact of using a more visible device.

Finally, the "completely in canal" RHA is less visible compared to the previous one, due to its small size and it occupies the same position. It has a higher capacity of sound transmission, guarantees a more precise localization of the source noise and determines a lower risk of obstruction. However, the small size determines a minor amplification power, and it is in fact unsuitable for severe HL. It is also the most expensive form on the market.

Figure 10. RHA types. Here, the main RHA that are commonly used are shown. For a detailed description of each RHA see the paragraph above.

4.2 - Cochlear implants

Cochlear implant (CI) is a surgically neuroprosthetic device implanted in patients with a moderate to profound HL. CI has the aim to replace hearing organs that are no longer functioning and therefore allows an improvement in the hearing field and, consequently, in the quality of social, emotional and psychological life. It should be emphasized that all of this is possible only if the patient agrees to undergo a speech therapy rehabilitation process aimed at the correct use of the CI, through specific and gradual stimulation methods. The so-called "artificial cochlea" replaces the real one damaged in cases of profound sensorineural HL by positioning an array composed of 12 to 22 electrodes, surgically implanted in the cochlea, with the aim of restore the lost activity of the hair cells which transform the acoustic signal into an electrical stimulus (Macherey & Carlyon, 2014), thus replacing the analysis of sounds according to the parameters of intensity, frequency, timbre and duration of the signal. The intracochlear electrode system, together with the processor, a communication link and the multi-magnet assembly, constitutes the internal portion of the CI (Figure 11). Each electrode inserted in the cochlear gyrus codes for a specific signal frequency (following the tonotopic theory), bypasses the hair cells and stimulate the fibers of the cochlear nerve. The sounds, transmitted through the acoustic nerve, reach the auditory centers of the cerebral cortex.

Figure 11. Internal components of the CI. The cochlear implant is made by the electrode array (1) that guarantee the patient to understand sound and speech. The array is connected to processor (2) that receive input from a communication link (3) and a multi-magnet assembly (4) that allow user to capture sounds and safely undergo high resolution imaging. (In this photo: a MED-EL cochlear implant)

The external part of the CI it is made up of the processing unit (microphone and processor), the control unit (battery compartment and controls) and the transmission unit (external antenna and magnet), generally placed in the retroauricolar area (Figure 12).

Therefore, the external portion picks up the sounds perceived in the environment and converts the pressure variations of the sound wave into variations of the electrical signal, through the speech processor. The sounds are digitized and transmitted to the internal portion which decodes the digital signals into electrical impulses sent to intracochlear electrodes which stimulate the corresponding portions of the auditory nerve.

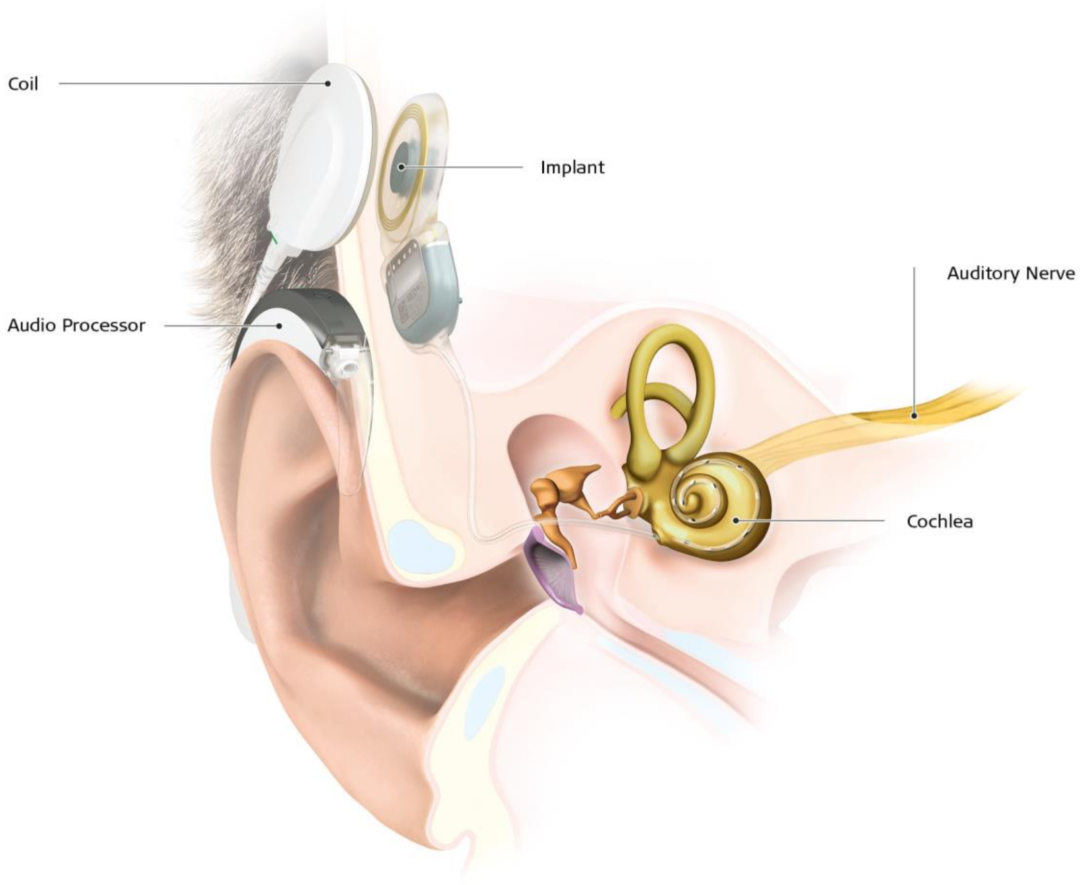

Figure 12. Location of the CI components. The figure shows how the cochlear implant is fixed to the bone. Moreover, the external components of the implant are represented

Auditory perception and data analysis by CI depend directly on the decoding strategies adopted for signal processing according to the individual needs of the subject. The activation, if not intraoperative, it takes place after a month (in compliance with the healing times) and a technician processes the acoustic signal of the new device, subsequently replaced and updated in the phases subsequent to the fitting, i.e., the progressive and periodic personalized adjustments of the CI over time given the flexibility of the stimulation parameters.

The hearing performance of CI patients is measured on the basis of hearing levels and their ability to understand speech. During the activation and in the following individual mapping sessions, the patient is subjected to audiometric, discrimination, identification, recognition and understanding tests, assessing abilities of reception of phonemes, of words, of sentences and of speech. Technicians and operators monitor the difference of results obtained in the audiometric and in the speech therapy tests administered at each meeting, register the feedback given by the patient and updates the cochlear mapping.

There are two main measurements to search for and set for each active electrode: the "minimum" (level T) and "maximum" (level C) comfortable levels (Lenarz, 2018); subsequently, to determine the subjective sound intensity, the balancing of the electrodes is carried out. The mapping procedure consists in choosing the characteristics of the strategy used and in determining the appropriate sites and levels of stimulation; it can take place with or without the patient's collaboration depending on age, previous sound experience and any associated pathologies; in all cases, the main aim is to obtain stimulation patterns as closer as possible to those of the patient’s need (Lipson et al., 2020). The chosen parameters, specific for each patient, are saved as a "map" and remain in the memory of the speech processor. The maps will then have to be updated in the subsequent fitting phases.

There is significant variability in the audiometric and speech performance in the adults CI patients (Anderson et al., 2017) due to innumerable auditory and extra-auditory variables (Nicastri et al., 2021). It is pivotal to assess all factors that can influence the intervention: the pathological history, the current health conditions, residual hearing and the etiology of the HL. Among the aspects to be taken into consideration for the prospect of post-operative success there is also the environment and the age of the patients, and last, an important role is played by the family, whose motivations must be carefully examined. It is also important to consider the history of HL, since it is now known that subjects who became deaf in the post-linguistic moment have a faster recovery following CI placement; but also, the age of the implant has to be considered: subjects implanted early and with a shorter duration of deafness have a greater chance of obtaining good results (Stropahl & Debener, 2017). The speed of recovery is influenced by the duration of HL and the improvement is greater in the case of a short interval between the HL and the intervention; in fact, numerous studies have shown the rapid neurocircuitry modification associated with the changes induced by auditory stimulation (Stropahl & Debener, 2017). Moreover, the quality of life is thus increased in the absence of worsening tinnitus (very often concomitant to cases of sensorineural deafness) (Bond et al., 2009). In addition to the variables that can directly affect the obtainable outcomes, some studies agree in stating that the benefits obtained from the positioning of an CI are greater in a silent environment than in the presence of background noise Moreover, it is now recognized that one-sided CI results in reduced ability to understand in a noisy environment (Mosnier et al., 2015). Bilateral intervention seems to increase the understanding and hearing abilities, with a more precise localization of the sound source in noisy conditions, leading to an improvement in the accuracy to distinguish speech from noise.

4.2.2 - Brain changes in CI patients

The link between hearing and the brain is bidirectional and the results in verbal comprehension gain totally depend on the neuroplastic modifications induced in the auditory cortex following the sensorial stimulation after the positioning of the CI. Neural plasticity consists in the possible modification of neuronal circuits and functions (mainly based on synaptic modifications) on the basis of experience-induced neural activities (Citri & Malenka, 2008). The phenomenon of cross-modal neuroplasticity is based on the concept that the areas of the brain that have been deprived from a specific sensory stimulation do not remain inactive, but rather can "reorganize themselves" and process information from other senses (Han et al., 2019). For example, if the auditory cortex is deprived of acoustic input prior to language development (preverbal deafness), the visual cortex may recruit areas of the auditory cortex for visual processing purposes (Campbell & Sharma, 2016). It is easy to understand that, in the case of missing or degraded auditory input, the other sensory afferents, including the visual ones, are more activated in order to compensate for the function (e.g., lip-reading ability).

Cortical changes induced by sensory deprivation have been found in deaf individuals; this is a consequence of a stimulation reduction in the corresponding cortical representation of the specific stimuli, therefore mainly at the level of the temporal lobe, but not limited to this in the case of HL (Sun et al., 2020). A longer duration of auditory deprivation corresponds to a greater reorganization and less ability to activate cortical auditory areas (Green et al., 2005). According to a study, the understanding abilities in CI patients depend on the different levels of activation of the left STG and of the IFG, that are recruited during speech. It thus demonstrates how the involvement of the left hemisphere, in addition to the primary auditory cortex, is crucial in order to adequately process and understand speech with CI (Mortensen et al., 2006).

Through neuroimaging methods, the cortical modifications of the acoustic pathways were analyzed in CI patients (Profant et al., 2014; Ponticorvo et al., 2019). Thanks to the use of CI, improvements in auditory attention and receptive language have been highlighted following speech therapy rehabilitation (Figure 13) (Pichora-Fuller & Singh, 2006), with a greater activation in the STG, the Wernicke's area, the left insula and the left fronto-superior gyrus (Pereira-Jorge et al., 2018). Despite the good results in plastic reorganization, many patients still show numerous difficulties in communication since speech requires numerous integrated neural functions (Bidelman et al., 2020).

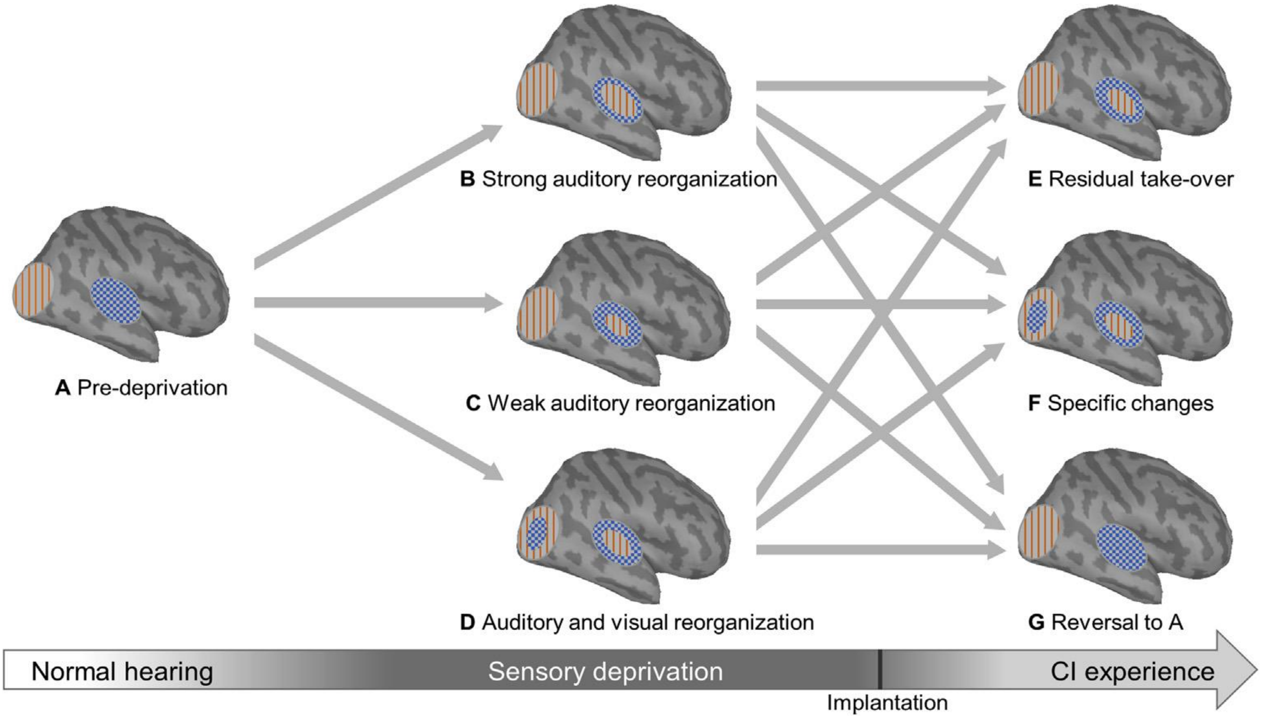

Figure 13. Brain network reorganization after CI implantation. Here, a possible reorganization given the hearing deprivation and consequent restoration with CI compared with the physiological condition is shown. (From Strophal et al., 2017).

HL has implications, not only in the linguistic-communicative skills but, in general, also in the patient's sociality, in the emotional and psychological domain. The HL patient is very often also depressed and isolated due to sound deprivation: numerous studies show that this condition is frequently associated with the elderly; hence, presbycusis often worsens the cognitive decline due to deafferentation and hearing deprivation, and additional conditions as psychological decay, anxiety and depression sum up in leading to isolation even in the family context (Castiglione et al., 2016). The detectable cognitive effects are based on the concept according to which central or peripheral auditory deprivation is connected with cognitive decline. HL reduces cortical stimulation, increases the effort needed to listen, consequently degrading the message; the possibility of the distraction increases, and the perceptual learning is reduced. All this entails an important cognitive load during data processing that "fatigues" the brain and reduces the attention and the cognitive resources available for other tasks (Lin & Albert, 2014). Social isolation could be one of the mechanisms through which the link between HL and brain alterations is substantiated: communication difficulties connected to hearing impairment can favor solitude, which must be considered a risk factor for cognitive disorders. The placement of an CI allows to limit the stages of decay (Mosnier et al., 2015) and it might prevent forms of dementia in the HL patient (Sarant et al., 2019); it also avoids the deterioration of the patient's quality of life, more or less associated with states of anxiety or depression (Yang et al., 2021). For these reasons, hearing rehabilitation must be considered pivotal, restoring adequate auditory inputs and reducing the cognitive overload caused by the HL and the possible physical and psychosocial consequences and to an increase in the score on the scales concerning the quality of life of the patient undergoing treatment (Castiglione et al., 2016).

4.2.2 - Speech assessment in CI patients

The speech evaluation has the aim to obtain information on the time of onset of HL, type and side of HL, date of the first prosthesis, time of initiation of speech therapy and rehabilitation approach. The evaluation detects the level of auditory perception in the patient prior to the intervention, including the assessment of perceptive skills and communicative-linguistic skills. Neuropsychological or psychological evaluation may be suggested, if necessary (De Filippis, 2002).

The assessment of perceptual-verbal skills conforms to the perceptual categories according to the hierarchical model of Erber (Ertmer, 2002):

- Detection: ability to differentiate between the absence and presence of sound (sound/silence). If this analysis is absent, the subsequent ones are not possible.
- Discrimination: ability to differentiate the equality or the difference between two verbal stimuli; it consists in the ability to analyze sound according to the parameters of frequency, duration and intensity.
- Identification: ability to identify a stimulus within a limited number of known stimuli in a closed set.
- Recognition: ability to recognize a sound in an open set without a visual aid.
- Understanding: correct answer to a question; after the auditory information has been heard, discriminated, identified and recognized, it will be understood by the integration in the CNS, with additional auditory and non-auditory information.

Thus, it consists of perceiving an auditory stimulus, cognitively processing it and providing an adequate response (Nicastro et al., 2017).

The assessment of these analytical skills in CI patients must be performed in the best different conditions: with or without lip reading, in quiet or with a background noise (Cocktail Party).

The evaluation precedes and follows the CI surgery. This consists of a series of supervision and mapping (fitting) meetings. The performance of the patients is influenced by other cognitive functions, such as selective attention and working memory: in hearing, the person needs to isolate the sound message from a noisy context or in conditions of multiple listening, keeps it active in working memory storage and, if necessary, compare it with other information in memory, before the response (Burdo et al., 1997).

4.2.3 - Speech therapy in CI patients

There is a central role also played by the type, quality, and frequency of habilitation-rehabilitation training, which must be administered not only in the speech therapy clinic, but also independently.(Pomaville & Kladopoulos, 2013). During the first year, the patient undergoes one or more cycles of speech therapy with specific frequency sessions alternating with mapping meetings, in order to support the recovery of verbal perception. In order to perform functional rehabilitation, it is very important to choose the electroacoustic parameters appropriately for the individual patient, with the aim of helping the subject to re-adapt to sound. This means that the complete recovery of hearing capacity is not possible only through the execution of the surgical intervention: the consequent duration of the rehabilitation process depends on the patient's compliance, willingness and collaboration to work in autonomy at home (Geers, 2004).

This continuous habilitation-rehabilitative intervention is performed through personalized perceptive-auditory training, which varies accordingly to the needs and to the abilities of the patient. The speech therapist needs to be well trained in order to: highlight difficulties; monitor perceptive performance and temporal evolution; check the proper functioning of the device; verify the correct application of therapy; perform counseling on device maintenance and care; propose strategies and verify their generalization and learning. Traditionally, in the perceptual-auditory training gradually the therapist adjust the difficulty of the proposed stimulations, starting from the listening of the environment sounds (Eshraghi et al., 2012).

In adults, the treatment is canonically divided into seven phases (Nicastri et al., 2021):

- the first familiarization with the new device: patient is informed about the functioning of the CI.
- the perception of environmental sounds begins, and it depends on the perceptual level of the patient that has been detected first evaluation (detection, discrimination, identification, recognition and understanding). The training is made through exercises with specific software, simulating sounds of daily life.
- the next phase is the training through phonetic segments (vowels, consonants, syllables) with discrimination and identification activities.

- then, the training with verbal material begins, in a silent or noisy context, using words and sentences. Implanted hypoacusis patients are more susceptible than those with normal hearing to the interference created by the presence of the background noise.
- the training continues with conversations on the phone. The ability to support telephone conversations is always difficult to achieve by CI patients. This is primarily associated with the narrowing of the frequency band (300-3400 Hz), but also with the absence of all the non-verbal component and with the presence of a possible interfering noise. For these reasons, telephone conversation training consists of real simulations, with the acquisition of pragmatic principles.
- in order to facilitate independent daily work, training with a software may be proposed in addition to that performed during the therapy sessions, order to maximize the treatment effects.
- generalization phase: it is the final step of the treatment and consists in the daily application of what has been learned during the speech therapy; this is possible only through the involvement of the patient's family collaboration and adapting the environment where the patient lives.

In general, it is important to pay attention to the changes, asking the patient for information regarding the perception of new sounds within their daily life, or of unpleasant noises. Even minimal progress is needed to maintain the motivation of the patient.

3.4.3 - Executive functions and listening effort in CI patients

The term executive functioning refers to a set of high-order neurocognitive skills necessary for identifying, processing, planning, and completing daily tasks (Diamond, 2013). Working memory, inhibitory control and cognitive flexibility are the executive functions core skills. In addition, there are a number of higher level neurocognitive skills that are dependent on executive functions, including the ability to process information, plan an action course, organize materials, and solve problems (Gioia et al., 2010).

A period of rapid growth occurs in the prefrontal cortex in early childhood (Best et al., 2009), that is followed by a period of maturation during adolescence, and is accompanied by decline in the late years of life (Best et al., 2009). It has been suggested that hearing ability is crucial to the development of the executive function in childhood because auditory deprivation is associated with disorganization of developing cortical pathways (Sharma et al., 2007). These studies have provided support for the hypothesis that executive functions can be measured using performance and questionnaire-based assessments in CI patients, that provide sound input but degraded sensory input, demonstrate significant deficits in executive functions compared with their normal hearing peers (Castellanos et al., 2015).

A significant association between HL severity and the degree of cognitive declines has been found, as well as an increased incidence of clinically significant cognitive impairment among adults with impaired hearing (Lin & Ferrucci, 2012). Studies have not specifically examined the cognitive efficiency in CI patients with severe-to-profound HL. In contrast to patients with mild-to-moderate hearing loss, CI patients generally experience a longer duration of auditory deprivation than those with mild-to-moderate HL.

The executive functions of CI patients and adults with normal hearing have been compared only a few times, and most of the studies have used performance measures of working memory (Lyxell et al., 2003; Tao et al., 2014). Working memory skills in CI patients were compared to age-matched normal hearing peers, using digit span and serial recall of monosyllabic words tasks. While digit span accuracy scores and response times were similar between groups, serial recall accuracy scores were significantly lower among CI patients than controls (Moberly et al., 2017).

The neurocognitive functions of adult CI patients and normal hearing peers were evaluated using nonauditory tasks assessing global intellectual abilities, cognitive ability, inhibition concentration, and controlled fluency (Moberly et al., 2016). The tasks were visually presented to assess global intellectual abilities, cognitive ability, inhibition concentration, and controlled fluency. In all tasks except working memory where CI patients performed significantly worse than controls, neurocognitive functions were similar between groups. According to these results, CI patients may have lower executive functions than their normal hearing counterparts, particularly when performing tasks that require working memory (Moberly et al., 2016). The understanding executive functions in adult CI users will allow for a better understanding of the role auditory input plays in maintaining executive functions skills in adults, and conversely, the detrimental effects of not having auditory input for clinical populations with hearing loss, and the relationship between executive functions and speech recognition outcomes in this clinical population.

Listening effort is the voluntary allocation of mental resources, in order to overcome obstacles during the completion of a task in which listening occurs and is strictly connected to executive functions functionality, especially with the working memory ability (Pichora-Fuller & Singh, 2006). To effectively extract the intended meaning of speech, listeners must match the rapid incoming acoustic stream with stored representations of words and phonemes. When speech is acoustically degraded, it becomes harder to identify sounds accurately: the listener is provided with less information, which reduces the quality of speech cues and increases the likelihood of errors. The grade of the listening effort associated with the detection of the stimulus varies accordingly with the abilities of the listener, the clarity of the external signal, and the characteristics of the acoustic environment (Denes & Pinson, 2015). The increase in acoustic challenge, as illustrated in Figure 14, causes a listener's cognitive demand to increase, which ultimately leads to an increase in listening effort modulated by the listener's motivation.

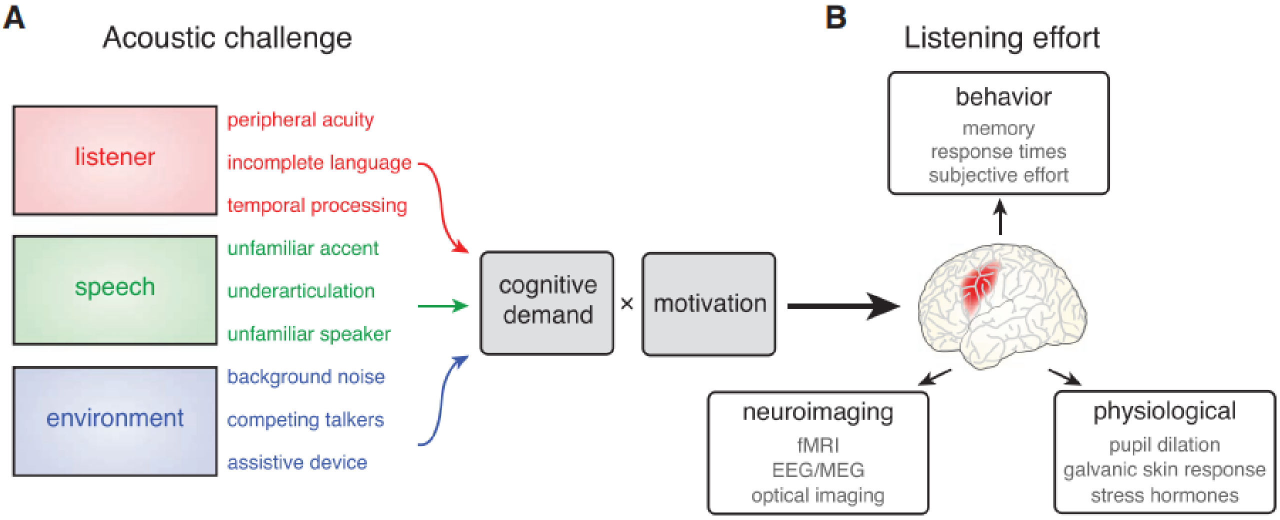

Figure 14. Listening Effort. As a result of individual hearing ability as well as external acoustic characteristics (including speech quality and background noise), listeners experience an overall acoustic challenge. (Note only a subset of these conditions are addressed directly in the main text.) Acoustic challenge increases cognitive demand, which is one of the primary factors contributing to listening effort (modified by motivation). When speech does not easily match a listener's expectations, additional neural processing is frequently required. Functional brain imaging can be used to measure increases in listening effort, as they are reflected in physiological responses outside the brain and often result in measurable differences in behavior. (From Peelle; 2017).

This listening effort is forced to rely more heavily on cognitive systems when listening to an acoustically degraded speech signal, as for example in the case of HL. Hearing-impaired listeners' performance improve when processing time is increased compared to hearing-normal listeners' performance, indicating that these patients are subject to a greater degree of cognitive challenge (Wingfield et al., 2006). A growing number of studies indicate that cognitive factors generally play a significant role in explaining individual differences in speech understanding that cannot be attributed to differences in standard audiometric performance only (Akeroyd, 2008).

Although care must be taken when using neuroimaging to study auditory function due to the acoustic noise generated by the scanner, it is possible to obtain data regarding neural responses to speech (Peelle, 2014). In order to identify neural correlates of the listening effort, brain activation difference was compared in a group of participants when listening to a degraded speech and to a clean speech (Davis & Johnsrude, 2007). Authors found an increased activation in the left temporal cortex, IFG, and premotor cortex for degraded speech using a correlational approach with sentences that parametrically varied in intelligibility (Davis & Johnsrude, 2007).

In the next chapter, the results of the feasibility study performed on cochlear implants will be shown. These implants were stimulated with rTMS protocols, in order to verify their subsequent structural and functional integrity, and hence their potential resistance to a rapid magnetic field variation.

CHAPTER 5 - FEASIBILITY OF rTMS IN COCHLEAR IMPLANTS

According to currently operating safety guidelines, the presence of a CI is being considered an absolute contraindication for experiments and/or treatments with TMS (Rossi et al. 2009; 2021). So, the first step is to verify the possibility that a new generation of MED-EL CI - that are compatible with stable magnetic fields as they can be used within MRI scanner – are not damaged when exposed to rapidly varying magnetic fields as those generated by single pulses and low and high-frequency trains of rTMS. This is a pre-requisite for exploiting rTMS as an adjunct therapy to speech therapy for promoting reacquisition of speech perception after the cochlear implant.

5.1 - Research rationale

CI patients can acquire the linguistic skills to engage a good telephone conversation, while others only develop basic reading skills (N. L. Cohen et al., 1993). As aforementioned, the reacquisition of language skills after the CI positioning, may take up to six months or more depending on individual characteristics (Kral & Sharma, 2012). Other patients with may require longer rehabilitation period. The most relevant factor associated to a successful improvement of language abilities is related to neural plasticity mechanisms (McKay, 2018).

As explained in detail, rTMS has the potential to cause long-term neuroplasticity effects in the CNS (Ziemann, 2004) and might be a valid method in CI patients for a faster acquisition of linguistic skills. According to the last available international safety guidelines for the use of rTMS in clinical practice and research (Rossi et al., 2009, 2021), the presence of a CI is an absolute contraindication to the use of any TMS protocol, because the magnetic/electric fields induced by TMS can cause a malfunction or can damage the electronic components of CI, consequently preventing clinical investigations, research or therapeutic interventions to be carried out in these subset of patients.

More recently, a new generation of CI has been developed by MED-EL: these are theoretically more resistant to external perturbations, such as those due to exposure to intense magnetic fields. These devices are compatible with the magnetic field of MRI scanner up to 1.5 Tesla (T). However, one major difference discerns between the static magnetic field of an MRI, compared to that induced by a TMS device, which rapidly varies in few hundreds of milliseconds. Hence, whether these CI are resistant also to such kind of perturbations is still unknown.

Two MED-EL cochlear implants with titanium housing were tested for their integrity as well as their ability to receive forces after exposure to low frequency (1Hz) and high frequency (10Hz) trains of rTMS. Parameters of stimulation exceeded all the upper limits suggested for a safe use in humans (i.e., the combination of frequency, intensity, number of pulses, and inter-training intervals) (Rossi et al., 2009, 2021). Furthermore, two different TMS devices were used, each with a figure-of-eight coil, and a maximum output of either 2.2 T or 3.2 T. No previous studies investigated TMS effects on CI devices directly; therefore, the results may provide insight into the feasibility of targeting specific cohorts of CI patients with rTMS.

5.2 - Methods and results

As part of the assessment of the feasibility of the proposed approach, both the electrical/magnetic compatibility of the implants as well as the effects that will be elicited on the patient were taken into consideration. During rTMS, the implant's robustness was verified under the worst possible working conditions: parameters of stimulation reached conditions that are incompatible with the standard clinical application of TMS. It was important to consider two aspects of the proposed approach to provide a comprehensive evaluation: electrical and mechanical compatibility with safety requirements.

5.2.1 - Experiment 1 - Induced voltage with single-pulses

As shown in figure 15 (left panel), the considered implants (MED-EL Synchrony) embed an antenna consisting of five spirals with a diameter of approximately 22 mm. A mock-up device comprised of five copper spirals wrapped around a 22 mm diameter thermoplastic polymer cylinder in ABS (acrylonitrile butadiene styrene) was designed to evaluate the effects of the generated magnetic field without directly exposing the implant to it. It is noteworthy that only the outermost spiral of the cochlear implant has a diameter of 22 mm, while the rest have a smaller area. Thus, we over-dimensioned the active area considering 5 spirals with minimum 22 mm diameter. Firstly, we mapped the induced voltage in the self-made antenna to verify the portion of the TMS coil with the highest magnetic induction. To reconstruct the induced current, an ABS 3Dprinted grid was positioned on the figure-of-8 cooled TMS coil (Ates EB-Neuro, with a maximal output of 3.2 T). The grid consisted in a grating of 1 cm spaced bars (2 mm thickness). The grid positioned on the TMS coil is reported in figure 15 (right panel). To measure the magnetic induction, we moved horizontally and vertically the antenna probe with 1 cm step in accordance with the grill resolution.

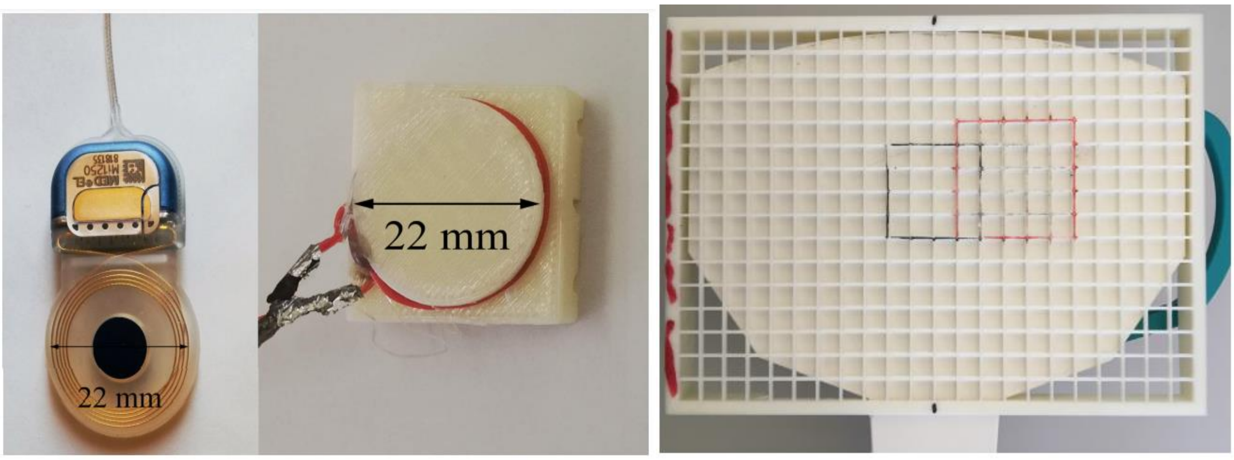

Figure 15. Experiment 1. Left panel: one of the MED-EL cochlear implants used in the study and the mock-up exploited for the preliminary experimental evaluation. Right panel: The thermoplastic polymer grid in ABS (acrylonitrile butadiene styrene) used for precisely positioning the probe.

The experiment was repeated using both a 30x30 mm and a 40x40 mm antenna to increase the resolution of the mapped field up to 5 mm. The probe coil was positioned parallel to the TMS coil surface at a distance of 1 cm. and the induced voltage was measured with a Tektronix TDS3012 oscilloscope for each position of the coil in the grid with three single-pulse stimulations from the TMS machine at 100% of the maximal stimulators' output (MSO). Figure 16 presents the average of the three measures. This figure consists of two panels (the central panel and the right panel, using the 30x30 mm and 40x40 mm grids, respectively).

Fig. 3 (left panel) illustrates the theoretical hypothesis concerning the magnetic field generated by the TMS coil as follows:

- the zone between the two toroids has the highest intensity, oriented parallel to the horizontal axis (parallel to the coil surface).
- (ii) The field has a lower intensity at the centre of each toroid, but the lines are perpendicular to the plane.

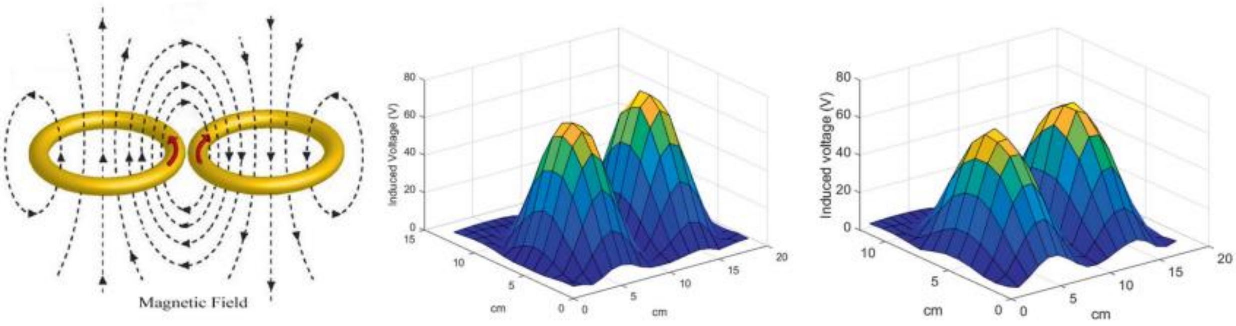

Figure 16. Experiment 1 - induced voltage. Left panel: the theoretical direction of the magnetic field generated by the two toroids inside the coil. The induced voltage mapped with a 30 30 mm and 40 40 mm grid are reported in the central and right panel, respectively.

If the CI is laid horizontally, the induced current is higher at the center of the toroids than it is at the surrounding areas because the induced voltage depends on the trigonometric sine of the angle between the coil and the magnetic field. For some positions, the magnetic field generated more than 70 Volts (V) in the CI antenna, as a result of these acquisitions. In the former condition (30x30 mm base), we observed that the induced voltage reached a peak of 74,6 V, and an average of 74,4 V. This exceeds the breakdown voltage guaranteed by the company for safe operation of the device, which is 70 V. We confirmed this observation by placing a Mi1200 Synchrony CI (serial number 750617) on the coil surface and stimulating it with MSO. The product was electrically damaged as a result. During the failure analysis performed by the manufacturer, it was discovered that the rectifier diodes within the power supply circuit were broken. As a result, the rectifier diodes in the inductive loop antenna have most likely been overloaded as a result of the strong signal received.

5.2.2 - Experiment 2 - Copper shielding

The copper shield protects the cochlear implant even when the MSO is lower than 100% in real application scenarios of rTMS treatment. A copper plate (40x40x5 mm) was added between the antenna and the TMS coil, in order to keep the induced voltage within a wider safety range (being more than seven times under the limit is a good practice). To protect the CI from undesired voltage inductions in real usage (with patients), the copper shield will be placed over it. Moreover, in this case, we considered and evaluated the worst possible situation, which was a perfectly centered cochlear implant within 1 cm of the highest magnetic field induction point. The magnetic field induction was reduced 90% in all tested positions. We show data of the acquisitions in figure 17. The induced voltages were all below 8.3 V, eight times below the safety limit. As a consequence of the copper layer's dimensions, we moved only one antenna probe in the grid. As a consequence, we confirmed that the copper layer does not affect the magnetic shape field.

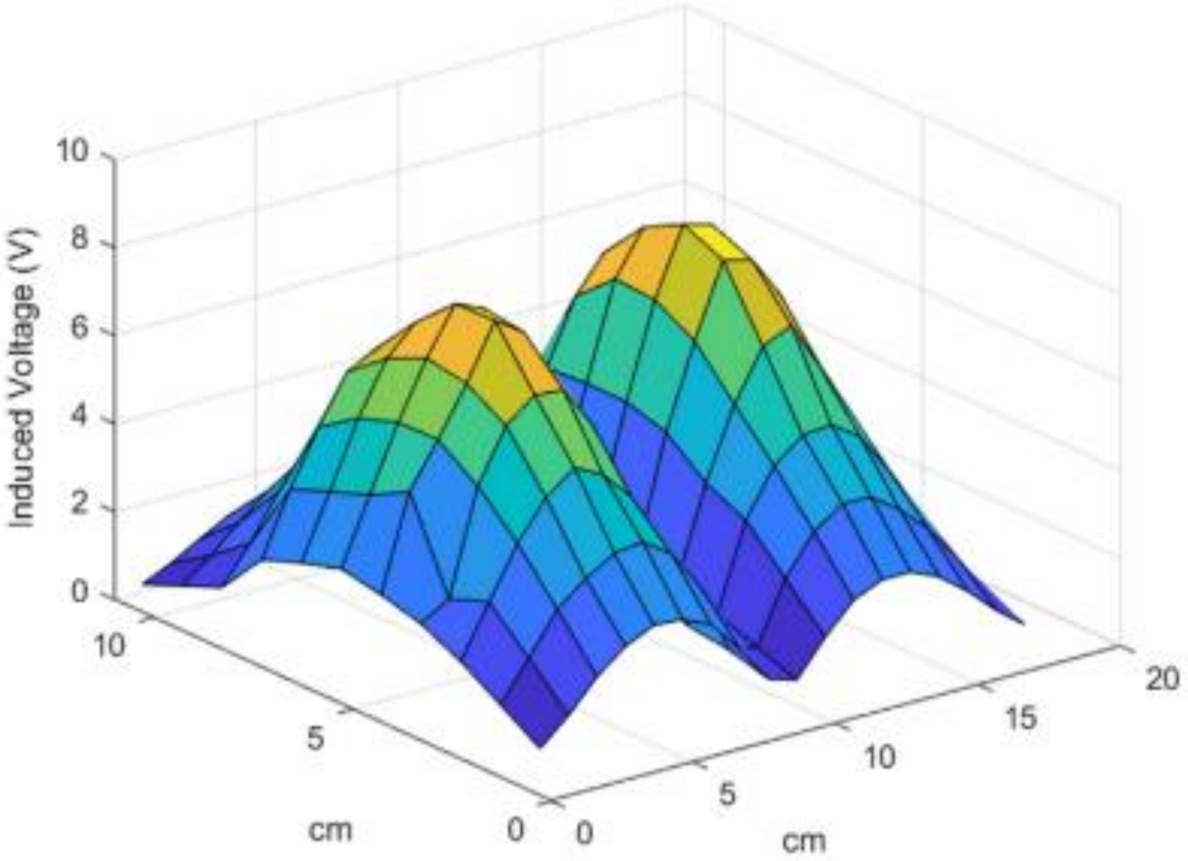

Figure 17. Experiment 2 - induced voltage with a copper shield. The voltage induced in the antenna with a copper plate inserted between the antenna and the coil.

In order to accomplish this, an additional probe was added, as shown in figure 18. In this configuration, three spirals were wrapped around a cylinder with a diameter of 2 cm, with spirals perpendicular to the coil surface at the maximum magnetic field. In this position, such a configuration maximizes the induced current into the antenna, simulating a real brain stimulation. Note that the number of spirals was reduced to three for practical reasons. In order to prevent damage to the measurement instruments, we reduced the system inducing capability at this point since the magnetic field strength is the strongest. As a result, the ability to measure and analyse magnetic field effects was not influenced. The recorded waveform was visually compared in figure 18 (right panel) in which the presence of the copper plate did not affect the magnetic field generated.

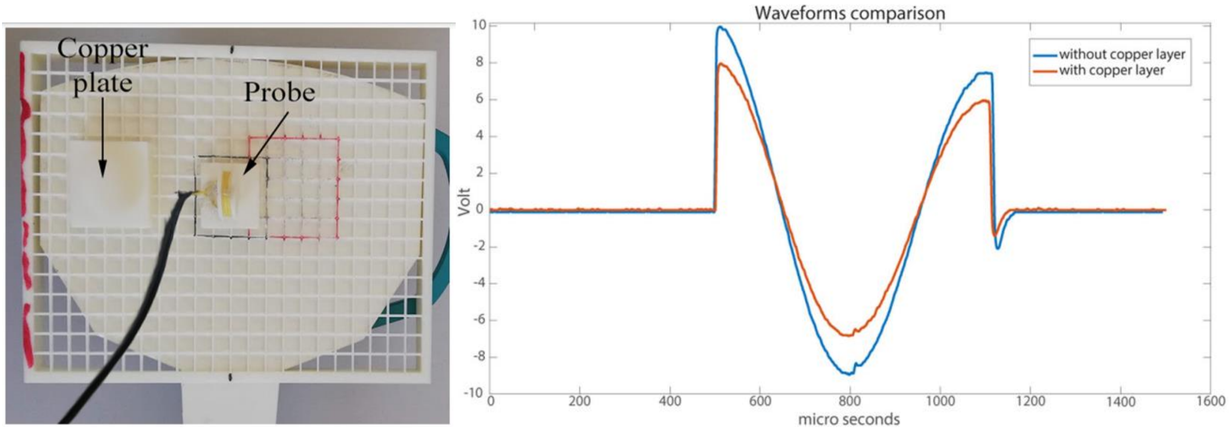

Figure 18. Experiment 2 - induced voltage with/without copper shield. The induced voltage in a perpendicular antenna made of 3 spirals. In the upper panel the grid, the sensing antenna and the copper layer are reported. In the lower panel, the waveforms generated by the Transcranial Magnetic Stimulation (TMS) are reported in red and blue using the TMS with and without the copper plate, respectively. It is worth noting that the waveforms have the same profile, thus the same effect. The marked difference in amplitude is due to the presence of the copper layer.

Furthermore, we examined the interference with the copper plate in all possible positions over the TMS coil. This experiment mimicked a real-life clinical scenario, where the exact position of copper shielding is unknown in advance. The copper plate (40x40x5 mm) was moved horizontally and vertically with 1 cm steps, covering all the grid, by placing a probe antenna (4 spirals 1 cm radius) perpendicular to the TMS coil center. In each grid position, we delivered three single pulse TMSs with a biphasic impulse (same intensity and intensity as above), recording the induced voltage in the probe placed in the center of the TMS coil (simulating the patient's brain). Figure 19 clearly illustrates that the copper layer did not significantly alter the TMS effect, indeed we observed a variation of 0.3 volts.

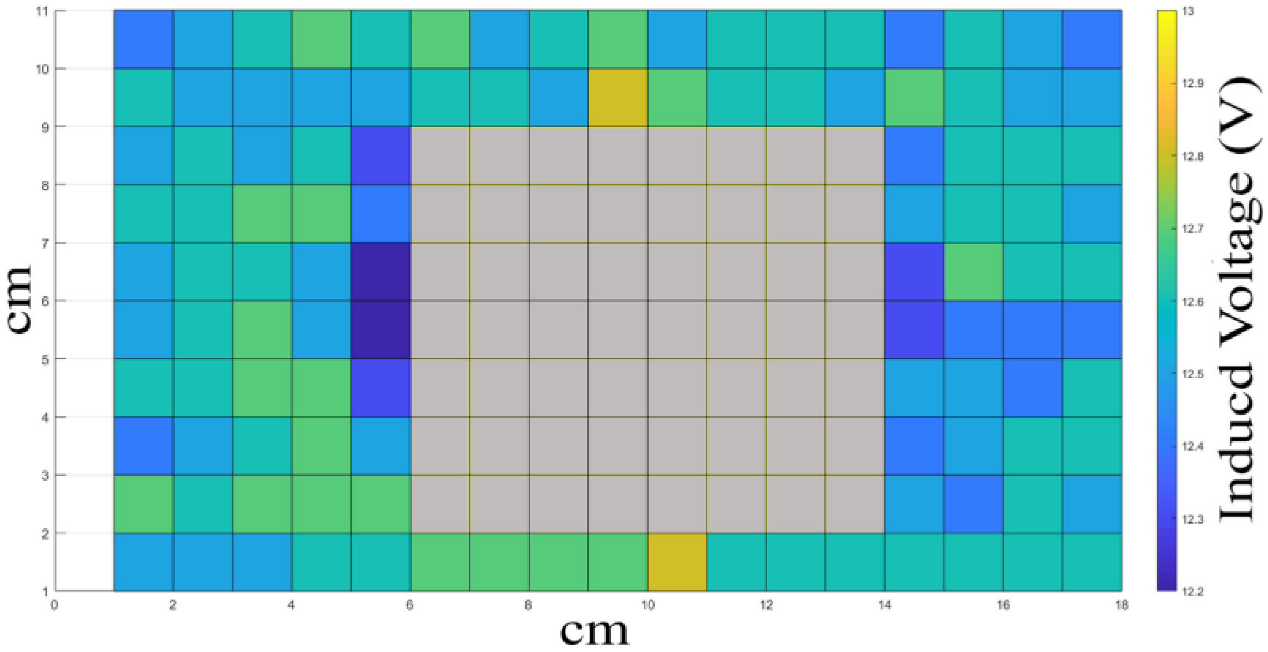

Figure 19. Experiment 2 - induced voltage scheme. Squares represent the position in which the copper plate was positioned. The color of the square indicates the voltage induced in the coil positioned in the center of the coil. Gray squares represent unavailable measures since the zone was occupied by the probe coil and there was no space for correctly positioned the copper plate.

5.2.3 - Experiment 3 - rTMS with real implants

Real and functioning CIs were used as a final step to assess the implant's capability to be used with rTMS stimulations. In the experiment, five titanium-housed cochlear implants were used by MED-EL: two Mi1000 models (Concerto, serials 565312 and 552878) and three Mi1200 models (Synchrony, serials 723229, 750617 and 740255). The electrode pathway was not incised during testing, so all tests were conducted in air. Two types of stimulators were used: Magstim Super-Rapid, which had a maximum output of 2.2 T, and Ates EB-Neuro, which had a maximum output of 3.2 T, both connected to a standard figure-of-eight coil with a cooling system. All stimulation sessions were conducted at 100% MSO. A low frequency stimulation protocol of 1 Hz was applied for 30 minutes (1800 pulses) followed by a high frequency stimulation protocol of 10 Hz, trains of 4 seconds, inter-train intervals of 8 seconds, and 1800 pulses per train. It is reasonable to consider these stimulation parameters are unsafe for humans since both frequencies/intensities and lengths exceed the upper limits of published safety tables (Rossi et al., 2009). On a phantom plastic head, the CIs were positioned on the retroauricolar surface, and the coils were held in contact with the titanium chases. Two Concertos with serial numbers 565312 and 552878 were used in this experiment. Both groups received 10 Hz rTMS using the Magstim stimulator, with the former receiving 1 Hz rTMS.

For the purpose of verifying the influence of TMS-induced magnetic fields on implant properties, all tested implants were sent to MED-EL for electronic post-checking: (i) if is possible that the strong time-varying magnetic field induced by TMS could damage the inductive receiver and the circuitry within the cochlear implant due to the resonance frequency of the inductive link coil; (ii) local oscillator frequency generated in an ASIC (Application Specific Integrated Circuit) within the implant. This is the time base for all cortical implants internal signal processing, as well as the stimulation signal. (iii) the electrodes are connected to the circuitry generating the stimulation signal, the induced magnetic field in TMS may cause currents in the electrode paths, influencing or damaging the circuitry; (iv) measurement of impedance telemetry. Since the impedance telemetry circuitry is connected to the electrodes' channels, the TMS induced magnetic field will generate currents in the electrodes' paths. No damage or defect was found on any of the implants, regardless of the stimulation protocols used.

5.2.3 - Experiment 4 - Induced forces

In addition, we considered possible electromagnetic stimulation-induced forces on the CI. TMS coils generate magnetic field pulses that exert attractive force on ferroelectric objects and repulsive force on nonferromagnetic conductors (Rossi et al., 2009). Thus, TMS can result in forces on the CI that can potentially cause it to move. Induced forces on ferromagnetic objects tend to be larger than those on nonferromagnetic conductors. Titanium skull plates are nonferromagnetic, low-conductivity, and have radial notches that reduce induced force. As a result of our experiments, we investigated the compatibility of the aforementioned CI with TMS stimulations.

To achieve this, we utilized a ballistic pendulum principle as a basis for our system. An impulse can be indirectly measured using this approach (the integral of a force over a time interval). The effect of TMS's magnetic field on an CI can be better explained by measuring the impulse rather than the force. Figure 20 illustrates the position of a device on one of the ends of a PVC pipe (internal radius 16 mm, external radius 18 mm) that is housed in a 3D printed ABS support. A 500 CPR encoder (Agilent HEDS-9140) was connected to the other end of the pipe. Three different rods with the following characteristics were used:

rod 1: length 25 cm, weight 41 grams (rod: 22 g, CI support: 11 g, implant 8 g).
rod2: length 50 cm, weight 62 grams (rod: 43 g, CI support: 11 g, implant 8 g).
rod3: length 120 cm, weight 123 grams (rod: 104 g, CI support: 11 g, implant 8 g).

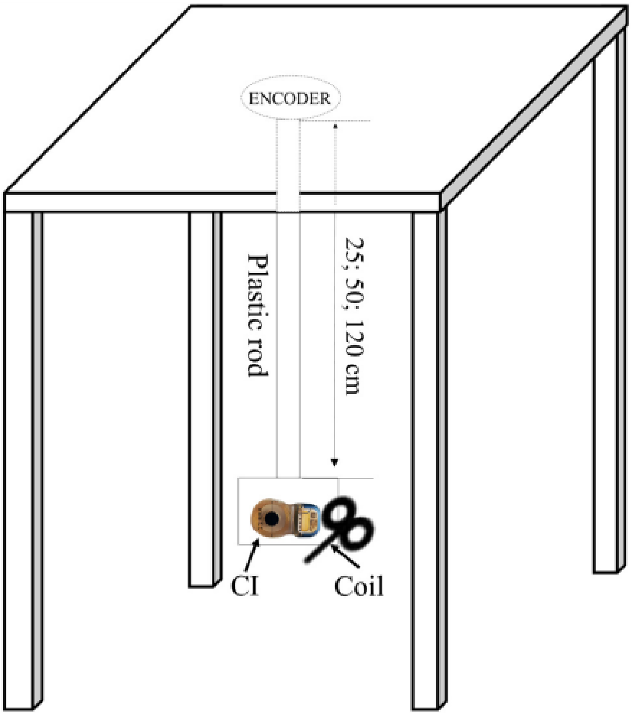

Figure 20. Experiment 4 – induced forces. Setup for the experimental evaluation for evaluating the induced forces. In the left panel the pendulum with 120 cm of rod, in the right panel the 50 cm version.

Using Labview software, sensor measurements was acquired at 100 kHz. The encoder has two quadrature outputs and a third index output, so variation has a resolution of 0.18. To verify the assumption that the distance between the sensor and the stimulation point ensures the absence of interference and magnetic disturbances in measurement, a series of magnetic pulses were generated. TMS coil was positioned 10 mm away from implanted electrodes during the experiment. Based on the following considerations, such a distance was chosen: (i) the tested distance was the best compromise when it came to positioning the coil during clinical stimulation of auditory cortices; (ii) when induced forces are applied to the CI, it allows for free swing and/or oscillation, which cannot otherwise be observed if the coil is directly connected to the CI; (iii) the CI was as close as possible in order to maximize the induced magnetic field and to investigate the forces induced by TMS magnetic fields.

Two different evaluations were conducted. The former used a single pulse width 100 percent of the MSO to stimulate the CI, while the latter used a train pulse of 10 Hz for two seconds (both using the Ates EB-Neuro coil with its maximum output of 3.2 T). In Fig. 7, a video is provided as Supplementary Material that illustrates the experimental setup used for each scenario. Ten trials were conducted. It was observed (and recorded) that the pendulum moved during a stimulation with a rod of 50 cm with an angle of 0.18. The recorded motion was considered an outlier due to external factors such as windage, environmental vibrations, etc., as it corresponded to the encoder's resolution and occurred only once. Based on these results, it was concluded that the TMS induced forces on the CI are negligible.

5.2 - Discussion

This study demonstrated that TMS and rTMS can be used in proximity/contact with new generation CI without causing a malfunction or significant forces that could potentially result in the device being displaced, when is normally positioned at the temporoparietal region of the patient's head and is fixed to soft tissues. It appears, however, that additional tools are required to maintain the implant within an acceptable range of electromagnetic safety. As part of our proposal, a small copper plate will be positioned over the CI so that it is shielded from the electromagnetic field generated by the TMS coil. The copper plate will become heated rapidly as a result of repetitive TMS stimulation. It is necessary to use a simple heat sink in order to avoid replacing the copper shield or interrupting the treatment. We used an ABS shell to enclose the copper layer in such a way as to prevent excessive copper temperature. In this manner, the patient was not irritated by the copper temperature.

Moreover, the direct stimulation of the device using the Ates EBNeuro stimulator, capable of reaching an MSO of 3.2 T with the figure of eight coil, damaged the internal circuitry of a previous cochlear implant used for testing purposes. There is no doubt that these data are reasonably applicable to all combinations of stimulation used in clinical and research studies due to the fact that they have been obtained with stimulation parameters (intensity, frequency, and timing) exceeding the upper limits of safe TMS use in humans (Rossi et al., 2009). In spite of the absence of damage to the internal device circuitries when the induced magnetic field is derived from impulses, it is vital that the CI, which is attached to the soft tissue of the patient's skull, is not affected by the forces resulting from the impulse. As a matter of fact, the magnetic field pulse generated in the coil may exert attractive forces on ferromagnetic objects and repulsive forces on non-ferromagnetic conductors (Rossi et al., 2009, Rossi et al., 2021).

Consequently, rTMS can result in forces on head devices, particularly if positioned superficially as CI, which could potentially displace them. Using a high-resolution ballistic pendulum, we measured the momentum induced by the CI. In spite of an unfavourable situation in terms of stability, TMS pulses (or trains of pulses) allowed the measurement of negligible forces. Since the device is anchored to the tissue of the patient, it is reasonable to assume that such forces are absent or, at worst, are insufficient to dislodge it once anchored. Although we did not directly measure the currents generated by the electrodes connected to the CI during the TMS pulses, an experimental mock-up device was used to overestimate these currents. As a result of the safety protection action of rectifier diodes, this possibility cannot occur in real-life situations.

Therefore, it is not possible to theoretically cause damage to CI receptors or unpleasant auditory sensations by induced currents in the intracochlear electrodes. In clinical and research terms, current results open the possibility of using traditional single-pulse TMS in patients with CI, whenever neurophysiological investigations are required. Furthermore, they provide the basis for neuromodulatory rTMS applications on auditory cortices following CI placement, possibly with the aim of promoting plasticity mechanisms that will aid the recovery process toward earlier and better speech perceptions. The use of rTMS prior to CI may remain an effective method of improving both short- and long-term outcomes. Clinical trials of this kind are currently being conducted at Siena University Hospital.

The current study has published in Clinical Neurophysiology in March 2021 (Mandalà et al., 2021). The next chapter will show the results of a rTMS study that was conducted on a sample of patients with sensorineural deafness and RHA, stimulating the auditory association cortex, with the aim of improving speech perception skills of participants and testing the feasibility of the stimulation protocol, before applying rTMS in CI patients.

CHAPTER 6 - rTMS IN PATIENTS WITH HEARING AIDS

Before initiating the study combining rTMS of the auditory cortex with speech therapy for boosting speech perception recovery in patients with cochlear implants, we tested a similar rTMS protocol in patients with hearing aids, with the aim to verify whether promoting neuroplasticity in auditory networks could be a worth hypothesis to be then exploited in CI patients.

Thus a 5-days rTMS protocol targeting the posterior superior part of the temporal gyrus (in the superior temporal sulcus, it has been applied in order produces a long-term reduction of SRT in HL patients wearing RHA and improves their ability to hear a sentence in a background noise context.

6.1 - Research rationale

By using RHA, patients with HL can improve their symptoms and enhance cognitive performance, with a general amelioration of the users' receptive language (Pichora-Fuller & Singh, 2006). As a result of the correct use of RHA for one year in patients with HL (Pereira-Jorge et al., 2018), BOLD signals were found to be increased in the left STG, Wernicke's area, left insula, and left superior frontal gyrus (BA 40/41, BA22, BA13 and BA8).

Although the correct use of RHA has been shown to result in these beneficial changes, many patients still exhibit substantial communication difficulties (Bidelman et al., 2020). As aforementioned, understanding of the spoken language requires a wide range of integrated neural functions and abilities, from the right processing of sound signals to assigning meanings to the sounds themselves.

rTMS promote short and long-term changes in cortical plasticity and it seems that the technique is highly effective for treating tinnitus, that results from maladaptive plasticity of the auditory pathways (Schoisswohl et al., 2019). In addition, rTMS was compared with traditional corticosteroid therapy and hyperbaric oxygen therapy in a group of patients experiencing sudden sensorineural hearing loss. In Zhang and Ma (2015), rTMS significantly improved hearing function and reduced tinnitus perception (Zhang & Ma, 2015).

Consequently, rTMS may improve the communicative skills of people suffering from HL by stimulating brain areas linked to sentence comprehension. The target area was chosen on previous research findings: based on activation likelihood estimation (ALE) analyses, some brain areas around the primary auditory cortex - particularly those located in the left posterior STG, have been shown to play an important role in phonological encoding, syntactic processing and prediction, lexical-semantic processing and syntactic interfaces (Walenski et al., 2019). A high degree of selectivity has been found in the activation of the STS during human voice hearing (Belin et al., 2000).

6.2 - Materials and Methods

6.2.1 - Study protocol

A randomized, double-blind, sham-controlled study was conducted at the University Hospital in Siena, Italy, among 22 right-handed HL patients wearing RHA, 17 males and 5 females (mean age 63.1 ± 13.3 years). The following inclusion and exclusion criteria were established: a previous diagnosis of chronic and worsening HL corrected by RHA; normal cognitive functioning; a minimal corrected score of the Mini Mental State Examination (MMSE) of >24. Exclusion criteria were a prior diagnosis of epilepsy, pacemakers, or other implanted electromedical devices (Rossi et al., 2021). Furthermore, patients with other neurological or psychiatric conditions were excluded from the study. A written informed consent form was completed by all patients before participation in the study. The study was approved by the Local Ethic Committee under the protocol code "Brainsight 21-24".

Participants were randomly assigned to a real stimulation group (Active group: 12 participants; 3 females, mean age: 59.4 ± 22.4) and a control group receiving a placebo stimulation (Sham group: 10 participants; 2 females, mean age: 67.4 ± 13.3). Following the removal of the HA, rTMS was performed using an air-cooled figure-of-eight coil oriented tangentially to the head with the STM9000 device (Ates-EBNeuro). An area that is recruited during voice listening (Belin et al., 2000), which is located closely above the posterior portion of the left superior temporal sulcus (MNI coordinates: -62; -40; 10), was targeted by a neuronavigation system (BrainNET, EBneuro Ltd, Florence, Italy). Each patient's exact location was determined by using the Colin 27 Average Brain, Stereotaxic Registration Model template.

Five sessions of rTMS were administered daily to all patients. In each session, 1800 pulses were delivered at 100% intensity of the individual RMT, with an inter-train interval of 4 seconds, at a frequency of 10 Hz, in trains of 2 seconds duration. Patients and experimenters wore earplugs throughout the procedure. An electromyograph (NeMus 2, EBneuro Ltd, Florence, Italy) triggered by the TMS pulses was used to determine the stimulation intensity prior to each visit. Patients were asked to remain awake and keep their eyes open during stimulation sessions. In accordance with guidelines (Rossini et al., 2015), RMT was defined as activation of the right first dorsal interosseous (FDI) of the right arm in response to a single TMS stimulus in the left primary motor cortex. Active electrode weas placed over the FDI muscle belly, reference electrode was placed on the metacarpophalangeal joint of the index finger, and ground electrode was placed on the wrist. Designed to produce a current flow directed from the back of the scalp to the front of the scalp in order to elicit consistent responses, the coil was placed tangentially to the scalp at a 45° angle to the midline. With a placebo air-cooled figure-of-eight coil (Ates-EBNeuro), only superficial scalp skin was stimulated for placebo purposes. As a result, the Sham rTMS protocol resulted in the same acoustic and sensory activation sensation as the Active rTMS protocol, but the cortical neurons were not exposed to the electric field.

6.2.2 - Audiological performance

To evaluate the participants' audiological performance, the Italian Matrix Sentence Test and Pure Tone Audiometry were administered in an audiometric cabin before (T0), immediately after (T1), and one week after the end of treatment (T2). Test sentences were generated by randomly selecting words from a list of 50 common words of two to three syllables (10 names, 10 verbs, 10 numerals, 10 adjectives, and 10 nouns). The patient was presented with semantically unpredictable sentences with fixed grammatical structures (e.g., "Marco takes four yellow balls") and a background noise was played in the background. The sound pressure level was set at 65 dB, and the signal-to-noise ratio was initially set at zero dB. For minimizing learning effects, both with and without RHA, each test list consisted of 20 different sentences, and two training lists preceded each test list. The software determined the speech level of the next sentence by analysing the number of words correctly repeated in the previous sentence and determined a SRT, at which 50% of the words were correctly repeated. The Italian Matrix Sentence Test is considered accurate and reliable based on its 0.2 dB standard deviation across test lists, as well as 0.6 dB test-retest reliability (Puglisi et al., 2015).

The patients' hearing threshold levels at different frequencies were identified using Pure Tone Audiometry, a method for determining the presence and severity of HL (Kapul et al., 2017). To determine patients' hearing thresholds for each frequency (0.25, 0.5, 1, 2, 3, 4 kHz), a pure tone was delivered, and its intensity was progressively reduced or increased. As part of Pure Tone Audiometry, the pure tone average (PTA) was calculated as the mean of each patient's hearing thresholds at each of the four main frequencies (0.5, 1, 2 and 4 kHz). The tests were conducted in the free field, using headphones, with and without RHA (Figure 21).

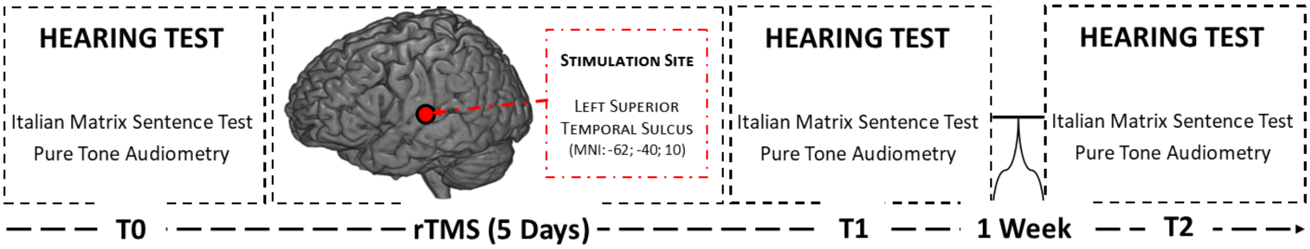

Figure 21. Experimental Design of the study. At T0, T1, and T2 participants' SRT and PTA were measured with Italian Matrix Sentence Test and Pure Tone Audiometry, respectively. Between T0 and T1, HL patients underwent 5 days of rTMS treatment delivered on the left superior temporal sulcus (between Brodmann area 22 and Brodmann area 42).

6.2.3 - Statistical Analysis

A single outlier was removed from the analysis because its performance differed more than two standard deviations from the mean of the participants. Data from 21 patients were analysed statistically (Active group: 12 participants; 3 females, mean age: 59.4 ± 22.4 Sham group: 9 participants; 2 females, mean age: 68.2 ± 13.9). The raw SRT and PTA data were normalized by time points and groups (see Table 1). Two repeated measures ANOVA analyses (ANOVARM) were conducted on normalized data, either with or without RHA, to determine the impact of time and group on SRT and PTA.

- The analysis includes three time points (T0, T1, T2) and two groups (Active, Sham).
- Analysis of long-lasting effects: [Factors: Timepoint (2 levels: T1, T2) and Group (2 levels: Active, Sham)].

6.3 - Results

6.3.1 – Safety and feasibility

Except for mild and transient numbness in the skin area below the stimulation site and periodic activation of the ipsilateral facial muscles, the rTMS procedure was well tolerated by the patients. No side effects were reported.

*6.3.2 - **SRT** - patients without RHA*

a) Analysing changes in performance on the Italian Matrix Sentence Test (Figure 22) across time points revealed the main effect of the Timepoint factor (F(2,18)=8.530; p=.002), showing a lower SRT at T1 as compared to T0 (p=.004) and at T2 as compared to T0 (p=.003). A trend toward a significant interaction between Timepoint and Group factors was noted (F(2,18)=3.061; p=.072). According to the Bonferroni-adjusted significance test for pairwise comparisons, the Active group performed significantly better at T2 than at T0 (p=.002) and at T2 than at T1 (p=.006).

b) A main effect of the Timepoint factor was detected (F(1,19)=5.302; p=.033) in the Italian Matrix Sentence Test (Figure 2). In the Bonferroni corrected post-hoc analysis, a significantly lower SRT was found at T2 for the Active group only compared to T1 (p=.002). There was a significant interaction between Timepoint and Group factors (F(1,19)=5.605; p=.029).

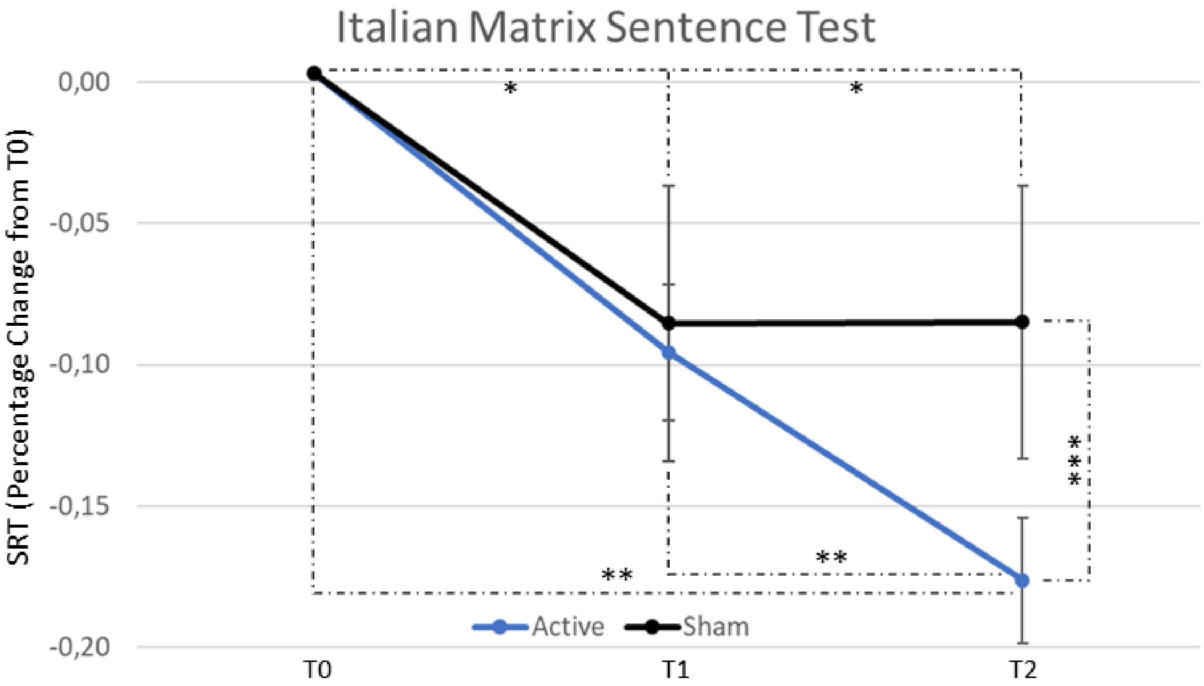

Figure 22. Italian Matrix Sentence Test results (patients not wearing RHA). Comparing all time points, a general reduction of SRT in both groups (Active and Sham) was found at T1 that was maintained at T2 (*). Observing T2, a different pattern of SRT change is noticeable between groups and a strong trend toward a significant interaction between Timepoint and Group factors was also found in the analysis (p=.072). Post-hoc analysis revealed a higher performance at T2 compared to T0 and at T2 compared to T1 in the Active group only (**). Analysis comparing T2 with T1 confirmed a significant difference between the two groups, with a significant lower SRT at T2 compared to T1 in the Active group only (***).

6.3.3 - SRT - patients wearing RHA

The same analyses were performed in patients wearing RHA and no significant changes were found (p>.05 comparing Timepoint and Group factors).

6.3.4 - PTA

No significant main effects or interactions between factors were found for all tests performed, either with or without RHA. (p>.05 comparing Timepoint and Group factors).

6.4 - Discussion

The present study demonstrated the feasibility of rTMS in improving auditory perception in chronic HL patients, demonstrating that it is a viable intervention in the view of the possible exploitation to help patients with CI to foster the after-implant period of speech therapy. In addition to being safe, free of side effects, and having relatively long-lasting beneficial effects, the treatment program proved to be very effective. A controlled double-blind, parallel groups study demonstrated that 5 days of real rTMS to the left auditory association cortex improved SRT performance in HL patients without affecting the PTA.

In the superior temporal gyrus and adjacent brain areas, the primary and association cortices of the left side of the brain are closely related to those that govern receptive language function (Friederici, 2017). As a result of damage to these cortical nodes or their associated white matter tracts, fluent aphasia syndrome can develop. Usually, spoken language remains intact, but receptive speech ability is impaired (Friederici, 2017). As a result of damage to the STG, the STS, and the MTG, a reduced ability to make grammatical judgment has been observed (Wilson & Saygin, 2004). This is supported by the finding that rTMS on the left STG resulted in an increase in verbal comprehension ability in chronic stroke patients with fluent aphasia (Versace et al., 2020).

However, HL impairs the functional connectivity between the auditory association cortex and brain regions within the auditory network and other large-scale networks (Bonna et al., 2021). Aside from the difficulty of perceiving sounds, it also makes it difficult for you to receive and process complex phrases, particularly in an everyday context with background noise (Shepherd & Hardie, 2001). While RHA may improve sound reception and lead to significant improvements in patients' daily lives, some deficits remain, especially with regard to speech perception in noisy environments, as a result of maladaptive plasticity of the auditory cortex (Bidelman et al., 2020; Butler & Lomber, 2013).

Because the effects of rTMS are known to occur in the entire network involving the cortical rTMS target (Jung et al., 2020; Ridding & Rothwell, 2007), treatment with rTMS may have restored a more physiological processing of speech perception networks. Both the Sham and Active groups experienced a long-term decrease in SRT. In line with literature, which reports a learning effect between consecutive uses of the Italian Matrix Sentence Test due to recurrent words during sentence presentation (Nuesse et al., 2019), this outcome was partially expected, but the significant difference in performance between the two treated groups is likely due to the real rTMS intervention, as it apparently occurred at the time of T2 sampling, well after the end of the treatment phase. A dedicated neuroimaging investigation could provide information about the neural underpinnings of the delayed improvement in speech perception in the active group.

There is some uncertainty as to why no significant results were found when RHA was worn by the patients. As a result, it is plausible that small variations in the size and shape of the hearing aids as well as how they are worn in the ear canal could contribute to bias in the evaluation during test/retest. Consequently, finding a significant result without the device is not only satisfying, but probably more physiologically relevant. The improvement of speech perception in noise, however, does not appear to be consistently associated with RHA adaptation, owing to the higher levels of processing of complex auditory stimuli and the possibility that RHA may result in lower discrimination performance due to its increased amplification and pre-processing of sounds (Cubick et al., 2018).

The improvement of speech perception, even without the use of hearing aids, could have significant implications for hearing loss as well as associated diseases. Even in early stages of Alzheimer's disease, patients have been shown to have significant difficulty understanding speech in a noisy environment (Ralli et al., 2019). Three main theories have been proposed regarding the relationship between Alzheimer's disease and deafness (Stahl, 2017; Ren et al., 2021). The common cause theory: both diseases are the result of a unique process (Godyń et al., 2016); the cascade process theory: it has been suggested that deafness plays a role in preventing cortical stimulation from being received, leading to social withdrawal, depression, and cognitive decline (Goman et al., 2017); excessive cognitive load theory: the brain effort required to maintain cognitive function in the setting of memory loss may divert cognitive resources from normal brain networks, resulting in structural/functional brain changes, impaired cognition, and dementia (Lin & Albert, 2014). rTMS should be investigated in the future to determine whether it can slow the progression of AD by improving deafness in the early stages.

It may be critical to find new therapeutic tools to improve HL impairment even though the relationship between these two disorders remains unclear. In the Italian Matrix Sentence Test, patients in the active group demonstrated improved recognition and repetition of complex sentences, suggesting that combined treatment with RHA and rTMS can partly counteract the maladaptive aspects of brain plasticity caused by deafness and improve speech comprehension skills significantly, especially those needed to understand a sentence in a noisy environment. The mechanism should only affect the SRT without altering the PTA. As a result, we did not expect any change in the PTA, since the peripheral part of the auditory pathway was not the target of our treatment and it had already been compensated for by using the RHA appropriately.

The study has certain limitations: as this study did not examine the impact of TMS on alternative brain nodes involved in syntactic information processing, future studies could investigate the role of these nodes. Additionally, future studies may examine how different NIBS methods, such as transcranial electrical stimulation, modulate the response of the entire auditory brain network responsible for receiving the verbal message by modeling individualized stimulation of the patient's brain. In this study, network-level changes were not examined; however, EEG and fMRI methods could provide further insight into the neurobiological changes underlying the behavioral benefits resulting from rTMS. In addition, the effect of contemporary speech therapy could also be considered to examine the potential effects of combining multiple treatments.

We have demonstrated that multiple rTMS sessions are a valid method of treating language comprehension deficits of complex sentences in HL patients, thereby improving their quality of life, a novel neuromodulatory application of rTMS that has not been previously explored.

Results of this study are under review evaluation in the Clinical Neurophysiology journal. The results shown in this chapter, together with the safety study carried out on CI (Chapter 5), therefore gave the possibility to start the experimentation on patients with CI. The preliminary results of this study phase will be shown and discussed in the next, last chapter.

CHAPTER 7 - rTMS IN PATIENTS WITH COCHLEAR IMPLANTS

7.1 - Study rationale

A 5-days rTMS protocol targeting the posterior superior part of the temporal gyrus - specifically on the left STS between Brodmann areas 22 and 42 - produces a long-term reduction of SRT in RHA patients and improves their ability to hear a sentence in a background noise context (Neri et al., submitted). This brain region is pivotal during speech listening and comprehension (Belin et al., 2000). This study took the results of Zhang and Ma (2015) concerning the application of rTMS in subjects with sudden deafness. Specifically, in this case, 20 sessions of rTMS at 1 Hz were administered at the level of the temporoparietal junction ipsilaterally to the pathological ear, with the aim of preventing maladaptive cortical reorganization (Zhang and Ma, 2015).

These results and those of Rossi et al. 2021 of the safety of TMS on CI have been taken as rationale base for a new study in CI patients. Auditory verbal comprehension skills are lower in CI patient, especially in a noisy environment. It was hypothesized that the application of rTMS immediately preceding speech therapy (ST) treatment should bring benefits to the speech comprehension in CI patients.

The presented results have to be considered as preliminary, because the study is still ongoing, after the necessary temporary stop due to the pandemics. Thus, these findings are discussed based on descriptive results. However, preliminary statistical analyses are also reported, understanding the sample size does not allow yet a meaningful interpretation of these promising results. The prevision is to reach a final sample of 34 patients (G-Power software: effect size: 0.40; power: 0.8).

7.2 - Materials and methods

7.2.1 - Participants

The participants in the study are subjects with CI patients, implanted and followed up at the otolaryngology clinic of the Siena Hospital “Le Scotte). The selected population was heterogeneous for various parameters, including age, gender, cause and type of HL, with respect to linguistic development (pre, peri and post verbal), time since diagnosis, period between the onset of deafness and placement of the CI, surgery and speech therapy following diagnosis, presence of RHA contralateral to the implant, implanted ear (right-left), previous placement of a RHA.

Inclusion criteria: the inclusion criteria concern several parameters: in particular, adult patients with unilateral CI compatible with TMS pulse (Mi1200 Synchrony MED-EL model) and positioned from at least six months, subsequently subjected to speech therapy treatment, from which discrete results emerged in comfortable listening situations (e.g., quiet, with a familiar voice and/or two-voice interaction), stabilized over time but with reported and objectified difficulties in speech-in-noise reception ability, multi-voice conversations and/or reproduced voices.

Exclusion criteria: the exclusion criteria follow the general guidelines for safety in the use of rTMS (Rossi et al., 2009): patients with electrical devices (besides the CI), with a high possibility of inducing epileptic seizures, etc., were excluded from the trial. Further criteria concern the CI, in particular models that are not compatible with the stimulation, and the methods and outcomes of treatment, respectively not having undergone speech therapy and/or an unstable result afterwards.

A total of 9 patients were enrolled (mean age: 57,5; SD: 18,5; 5 females):

- SBJ_1: F.E.; M; 73 y/o.

Diagnosis: Menière's syndrome, sensorineural deafness.

Unilateral right CI, implanted in June 2020 and wearer of left RHA.

Standard operation under general anesthesia, associated with right labyrinthectomy and insertion of all electrodes in the scala tympani of the cochlea.

Activation one month after surgery.

- SBJ_2 P.M.; F; 69 y/o.

Diagnosis: profound bilateral deafness due to otosclerosis (for 25 years) with worsening of left hearing loss.

Unilateral right CI, implanted in November 2019.

Standard operation under general anesthesia, associated ossification of the basal gyrus of the cochlea and, therefore, reamed. Insertion of all electrodes into the tympanic ramp of the cochlea.

Activation one month after surgery.

- SBJ_3 B.V.; F; 32 y/o.

Diagnosis: long-standing bilateral congenital sensorineural hearing loss (connexin-26) in the absence of benefit from RHA. History of recurrent ear infections and family history of HL.

Unilateral left CI, implanted in January 2021 and wearer of right RHA.

Surgery under general anesthesia with difficult identification of chest structures, and, therefore, necessary removal of the incus and cochleostomy. Insertion of all electrodes into the tympanic ramp of the cochlea.

Activation one month after surgery.

- SBJ_4 G.V.; F; 29 y/o.

Diagnosis: preverbal deafness from meningitis from 11 months. Complete remnant in the contralateral ear.

Unilateral left CI, implanted in April 2019 (no previous RHA stimulation).

Standard procedure under general anesthesia with insertion of all electrodes into the cochlea.

Activation one month after surgery.

- SBJ_5 N.G.; F; 62 y/o.

Diagnosis: varicella zoster virus (VZV).

Unilateral right CI, implanted in May 2017 and wearer of left RHA.

Standard procedure under general anesthesia with insertion of all electrodes into the cochlea.

Activation of CI one month after surgery.

- SBJ_6 C.S.; M; 63 y/o.

Diagnosis: Streptomycin-induced HL at age of 12.

Unilateral left CI, implanted in May 2017.

Standard procedure under general anaesthesia with insertion of all electrodes into the cochlea.

Activation of CI one month after surgery.

- SBJ_7 T.D.; M; 42 y/o.

Diagnosis: congenital bilateral preverbal deafness.

Unilateral left CI implanted in September 2021 and wearer of right PA.

Standard operation under general anaesthesia and insertion of all electrodes in the tympanic ramp of the cochlea.

Activation of CI one month after surgery.

- SBJ_8 P.A.; M; 75 y/o.

Diagnosis: long-standing bilateral congenital sensorineural hearing loss

Unilateral right CI implanted in September 2020 and wearer of right PA.

Standard operation under general anaesthesia and insertion of all electrodes in the tympanic ramp of the cochlea.

Activation of CI one month after surgery.

- SBJ_9 V.M.; F; 76 y/o.

Diagnosis: chronic otitis.

Unilateral left CI implanted in September 2018.

Standard operation under general anaesthesia and insertion of all electrodes in the tympanic ramp of the cochlea.

Activation of CI one month after surgery.

7.2.2 - Study protocol

Participants were randomly assigned to the active stimulation group (Active: 5 participants; mean age:60,6; SD:17,4; 3 females) or to the control group receiving placebo stimulation (Sham: 4 participants; mean age:53,7; SD:21,8; 2 females). Subjects underwent rTMS in 5 consecutive daily sessions, immediately followed by ST treatment. This period was preceded (T0) and followed immediately (T1), one week after treatment (T2), and 6 months after the end of the treatment (T3), by the administration of audiometric, cognitive and speech evaluation tests, to verify the performance at timepoints and look to possible changes in the patients' hearing and cognitive abilities. Italian Matrix Sentence Test, speech test of Icare protocol (*I care*, Florence, 1995) and Paced Auditory Serial Addition Test (PASAT)(Tombaugh, 2006) were chosen to assess for audiometric, speech and cognitive abilities respectively (Figure 23). The patients underwent EEG acquisition in all evaluation sessions, but the results will not be discussed in this work.

A cooled a figure-of-eight 8 coil was used for the stimulation, placed tangent to the scalp with an STM9000 device (Ates-EBNeuro), positioned in correspondence with the left STS (between area 22 and 42 according to Brodmann) which was identified using neuronavigation techniques (BrainNET, EBneuro Ltd, Florence, Italy) including stereotaxic recording.

In the Sham stimulation, the magnetic field only produces acoustic and sensory scalp stimulation, preventing activation of superficial cortical neurons, the subject perceives the sensation of being stimulated, to make the participant "blind" to the type of condition used. Sham stimulation was performed using an instrument similar to that of Active rTMS, whose coil however has a conformation determining the surface dispersion of the magnetic field. The placebo has the scope of verifying that the possible observed effects are dependent by the real stimulation. For this to occur, the patients of Sham group were unaware of the fact that they were not receiving effective stimulation and therefore the coil was be positioned in the same location as that of an Active stimulation (Loo et al., 2018).

The daily stimulation frequency was set at 10 Hz, for 20 minutes for five consecutive days, in trains of 2s duration and an intertrain interval of 4s. Throughout the stimulation, patients and experimenters wore earplugs to protect ear from coil discharge noise. The stimulation intensity was set at 100% of the individual RMT, that was assessed before each stimulation session by recording muscular responses through electromyograph (NeMus 2, EBneuro Ltd, Florence, Italy) according to international standards (Rossini et al., 2015), involves a motor response recorded by electrodes positioned at the level of the metacarpophalangeal joint of the index finger and wrist.

The stimulation modality was conducted double-blind: the subject and the evaluators were not aware of the type of stimulation administered (Active or Sham) in order not to influence the participant, the therapist, the evaluation or the treatment and then the outcomes. Only after the data analysis, experimenters aware of the type of stimulation administered to the individual subject (table 2 for details).

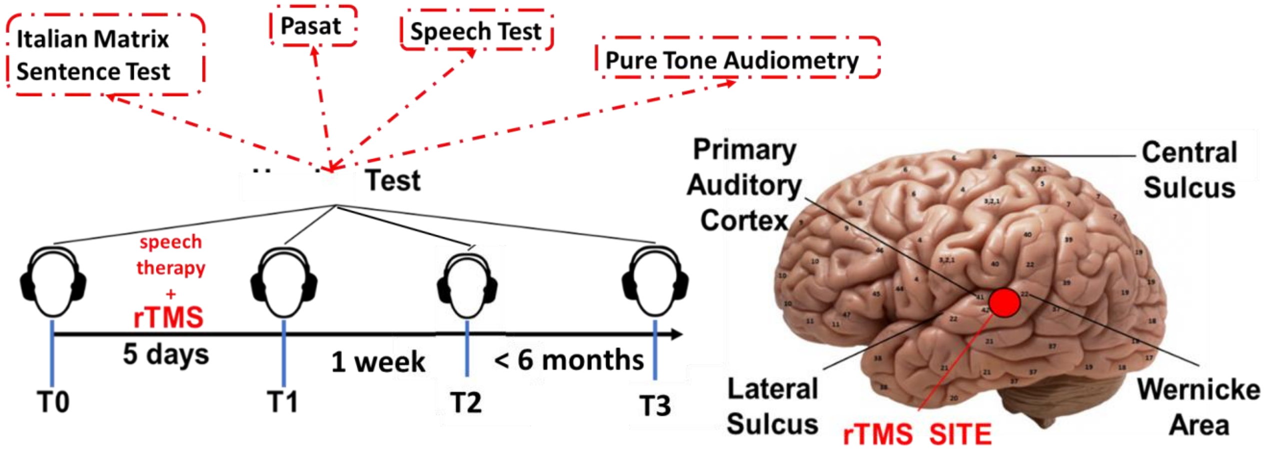

Figure 23. Protocol of rTMS + ST in patients with CI. Patients with unilateral right or left unilateral CI were selected. The same area treated on patients with RHA prostheses was stimulated (posterior portion of the left STS (MNI coordinates: -62; -40; 10), but the work was expanded by adding an hour of ST after each rTMS session. Data on 9 patients were collected (5 performed Active rTMS and 4 Sham rTMS). In addition to the matrix and audiometric tests, these patients carried out the speech tests and PASAT before the intervention (T0), immediately after the treatment (T1), one week later (T2) and within 6 months of the intervention (T3).

Table 2. CI patients. Randomization of the rTMS condition (Active and Sham) between 9 participants.

Active rTMS	**Sham rTMS**
SBJ_1: M; 73 y/o; right CI	SBJ_2: F; 69 y/o; right CI
SBJ_3: F; 32 y/o; left CI	SBJ_4: F; 29 y/o; left CI
SBJ_5: F; 62 y/o; right CI	SBJ_7: M; 42 y/o; left CI
SBJ_6: M; 60 y/o; left CI	SBJ_8: M; 75 y/o; right CI
SBJ_9: F; 76 y/o; left CI	

7.2.3 - Speech assessment

The evaluation protocol used (I care, Florence, 1995) aims to determine the patient's speech ability by administering different tests. The auditory functions to be evaluated and specified in the processing of receptive communication are detection, prosodic discrimination, identification, recognition and understanding.

The tests were administered with auditory modality, with a female speakerphone, in the absence of reproduced voices, with shielded mouth. Tests were performed in a silent room and with a background white noise 7 dB lower than the target stimulus, simulating cocktail party (CP) effect and requesting an higher listening effort (Miller, 2016).

5 subtests for adults have been selected:

- Vowels recognition.
- Intervocalic-consonants identification ("phonemic confusion matrix").
- Disyllabic words recognition.
- Sentences recognition.
- Questions comprehension.

7.2.4 - Audiometric assessment

The patients enrolled in the study underwent audiological evaluation through the Italian Matrix Sentence Test. The validity of this tool, now gold-standard consists in the possibility of evaluating ecological verbal comprehension in conditions of background noise since it is the only test capable of simulating the real hearing difficulties encountered in everyday life (listening effort), which is not characterized by a silent environment, but, on the contrary, is immersed in natural and/or artificial sounds and noises (see specific paragraph for details).

7.2.5 - Neuropsychological assessment

PASAT was administered with the association with environmental noise, to assess working memory (WM) of patients. The PASAT was developed with the aim of evaluating the effects of a traumatic brain injury on cognitive functioning and is one of the most used tests by neuropsychologists in order to evaluate working memory functioning and is useful in finding difficulties in cognitive processing (speed and flexibility) of auditory information in patients with a wide variety of syndromes (Tombaugh et al., 2006). Age and gender are variables to consider in the analysis of the results, together with non-cognitive factors that could influence the performance of the patients and the results obtained; these are: fatigue, depression, sleep disturbances, anxiety, and systemic pathologies (Brooks et al., 2011). Likewise, it is sensitive to the training effect, since patients often have a worse initial performance than subsequent ones due to lack of familiarity (Tombaugh et al., 2006). For this reason, patients of the study have trained the task for 10 minutes before the real evaluation started.

A series of 60 numbers is presented in the auditory modality presentation with a background noise 7 dB lower than the target stimulus to increase the listening effort in the task

(Miller, 2016). The patient's task was to sum the last two numbers continuously. Two different interstimulus intervals between stimuli were chosen: 3000ms and 2200ms. The score corresponds to the total of the correct answers given by the patient. PASAT 3000ms was used as training in each visit and only the PASAT 2200ms performance was analyzed.

7.2.6 - Speech therapy

The ST was carried out on the basis of the speech evaluation results: the letters/words/speech discrimination, identification, recognition and understanding were trained, depending on the weak and the strong points of each patient. The ST was performed by means of speakerphone and a female voice, with the mouth shielded, in a quiet and/or in a noisy environment and with the CI ON mode only (the temporary removal of the contralateral RHA was requested).

Activities on "discrimination":

- Same/different word sounds; in this case pairs of words diversified by different syllabic lengths are presented, signaling their equality or diversity (repetition is not required).
- Prosodic discrimination of sentences; in this case different sentences are presented for different prosody. The patient is asked to discriminate the type of sentence, whether affirmative, interrogative, or exclamatory.

Activities on "identification":

- Disyllabic and trisyllabic words in closed list; the patient identifies the word and chooses it among the alternatives provided in a progressively increasing way (2, 3, 4 and 6 alternatives).
- Foreign words (common in Italian language) in progressive closed list (2, 3, 4 and 6 alternatives).
- Identification exercises with cognitive effort; in this case the patient performs the previously presented identification activities but with fatigue, i.e., during the execution of a double task (patient listens to the words and identifies them, in the meantime participant has to carry out another exercise on a paper or on the computer).
- Identification exercises with background noise.

Activities on "recognition":

- Repetition of words with a shared category; in this case the category to which the words belong is anticipated to the patient.
- Repetition of words with a shared phoneme in this case the initial phoneme is anticipated to the patient).
- Repetition of words in the open list, i.e., in the absence of clues.

- Repetition of words in a cognitive fatigue task; in this case the patient listens to the words and repeats them; at the same time, it is subjected to another exercise using paper or computer material.
- Repetition of words with background noise.
- Repetition of short and complex sentences.
- Repetition of short and complex sentences in a cognitive fatigue task; in this case the patient listens to the sentences and repeats them; at the same time, it is subjected to another exercise using paper or computer material.
- Repetition of sentences with background noise.
- Speech tracking; this activity is defined as "the ability to recognize with continuous speech", that is, the exact repetition, word for word, of a passage read by the therapist.

Activities on “understanding”:

- Answering questions.
- Guided conversation; dialogue between therapist and patient regarding a shared topic starting from topics more familiar to the subject up to less known ones.

7.3 - Results

For each test, a table with the single scores and a representative graph with the mean of the two groups (Active, Sham) and the timepoints (T0, T1, T2, T3) are reported. Explorative (due to the small sample size) statistical analyzes have been conducted between groups (Active, Sham) and timepoints (T0, T1, T2), using repeated measures ANOVA.

7.3.1 - Speech assessment

In the following section, the performance of the "I care" protocol is reported (Table 4, 5, 6, 7, 8 and Figure 24, 25, 26, 27, 28). The scores obtained (total and individual) are divided according to the method of administration: in quiet (Q) or with a background noise (CP: Cocktail Party).

No significant difference or trend has been observed between timepoints (F(2,6)=,823; p=.484) or interaction between timepoints and group (F(2,6)=,051; p=.950) in the vowels recognition test in quiet.

No significant difference or trend has been observed between timepoints (F(2,6)=,019; p=.982) or interaction between timepoints and group (F(2,6)=,338; p=.726) in the vowels recognition test in CP.

Table 3. Vowels recognition test scores. Performance change from T0**.** Single score of participants, mean and standard error (*SE*) are reported. **Q**: in quiet; **CP**: with a background noise. **= subject did not participate at the evaluation session.

	Vowels recognition							
	T0 - Q	T0 - CP	T1 - Q	T1 - CP	T2 – Q	T2 - CP	T3 - Q	T3 - CP
SBJ_1_Active	0.00	0.00	0.05	0.25	0.05	0.19	0.05	0.25
SBJ_2_Sham	0.00	0.00	-0.05	0.00	-0.20	-0.21	-0.05	-0.05
SBJ_3_Active	0.00	0.00	-0.16	-0.29	0.00	0.06	**	**
SBJ_4_Sham	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
SBJ_5_Active	0.00	0.00	0.33	0.00	0.33	0.00	**	**
SBJ_6_Active	0.00	0.00	0.00	-0.11	-0.50	-0.21	0.00	-0.05
SBJ_7_Sham	0.00	0.00	0.19	0.06	0.25	0.12	0.13	0.18
SBJ_8_Sham	0.00	0.00	0.11	0.00	0.11	-0.06	**	**
SBJ_9_Active	0.00	0.00	0.05	0.05	0.05	0.05	**	**
Active: mean; *SE*	0.00 *(±0.00)*	0.00 *(±0.00)*	0.06 *(±0.06)*	-0.02 *(±0.07)*	-0.01 *(±0.11)*	0.02 *(±0.05)*	0.03 *(±0.01)*	0.10 *(±0.05)*
Sham: mean; *SE*	0.00 *(±0.00)*	0.00 *(±0.00)*	0.06 *(±0.04)*	0.01 *(±0.01)*	0.04 *(±0.07)*	0.03 *(±0.05)*	0.03 *(±0.03)*	0.04 *(±0.04)*

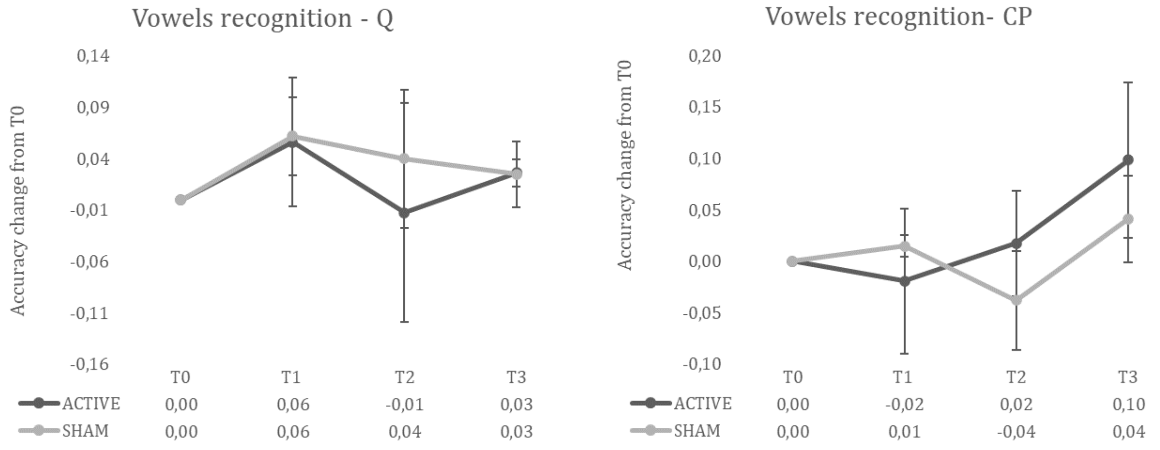

Figure 24. Vowels recognition test results. Performance change from T0 in quiet (*left; Q*) and with a background noise (*right; CP*).

No significant difference or trend has been observed between timepoints (F(2,6)=2.346; p=.177) or interaction between timepoints and group (F(2,6)=1.857; p=.236) in the disyllabic words recognition test in quiet.

No significant difference or trend has been observed between timepoints (F(2,6)=1.884; p=.232) or interaction between timepoints and group (F(2,6)=1.485; p=.299) at disyllabic words recognition test in CP.

Table 4. Disyllabic words recognition test scores. Performance change from T0. Single score of participants, mean and standard error (SE) are reported. **Q**: in quiet; **CP**: with a background noise. **= subject did not participate at the evaluation session.

	Disyllabic words recognition							
	T0 - Q	T0 - CP	T1 - Q	T1 - CP	T2 – Q	T2 - CP	T3 - Q	T3 – CP
SBJ_1_Active	0.00	0.00	0.00	0.75	0.10	0.38	0.30	0.20
SBJ_2_Sham	0.00	0.00	0.45	0.40	0.45	0.40	0.64	0.64
SBJ_3_Active	0.00	0.00	0.10	2.00	0.30	2.00	**	**
SBJ_4_Sham	0.00	0.00	0.25	-0.11	0.19	0.00	0.06	0.00
SBJ_5_Active	0.00	0.00	0.14	0.56	-0.07	0.11	**	**
SBJ_6_Active	0.00	0.00	-0.40	0.00	-0.30	0.00	-0.70	-0.60
SBJ_7_Sham	0.00	0.00	0.31	-0.18	0.15	-0.18	-0.23	0.15
SBJ_8_Sham	0.00	0.00	0.00	0.22	0.33	0.33	**	**
SBJ_9_Active	0.00	0.00	0.00	0.45	0.54	0.82	**	**
Active: mean; *SE*	0.00 *(±0.00)*	0.00 *(±0.00)*	-0.03 *(±0.08)*	0.75 *(±0.27)*	0.11 *(±0.11)*	0.66 *(±0.29)*	-0.20 *(±0.25)*	-0.20 *(±0.20)*
Sham: mean; *SE*	0.00 *(±0.00)*	0.00 *(±0.00)*	0.25 *(±0.07)*	0.08 *(±0.10)*	0.28 *(±0.05)*	0.14 *(±0.10)*	0.16 *(±0.16)*	0.26 *(±0.12)*

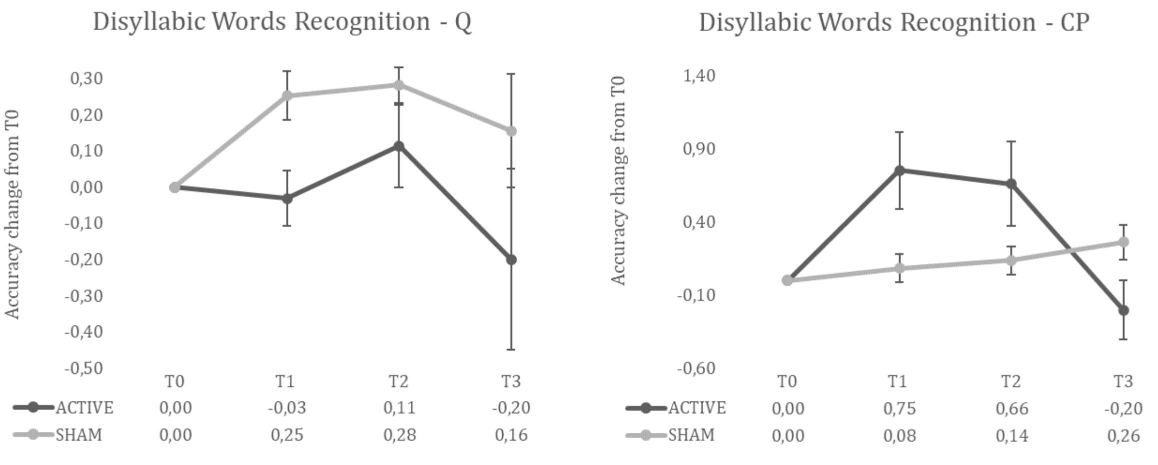

Figure 25. Disyllabic words recognition test results Performance change from T0 in quiet (*left; Q*) and with a background noise (*right; CP*).

No significant difference or trend has been observed between timepoints (F(2,6)=1.792; p=.245) or interaction between timepoints and group (F(2,6)=2.431; p=.169) in the questions comprehension test in quiet.
No significant difference or trend has been observed between timepoints (F(2,6)=2.099; p=.204) or interaction between timepoints and group (F(2,6)=2.837; p=.136) in the questions comprehension test in CP.

Table 5. Question comprehension test scores. Performance change from T0. Single score of participants, mean and standard error (SE) are reported. **Q**: in quiet; **CP**: with a background noise. **= subject did not participate at the evaluation session.

	Questions comprehension							
	T0 - Q	T0 - CP	T1 - Q	T1 - CP	T2 – Q	T2 CP	T3 - Q	T3 - CP
SBJ_1_Active	0.00	0.00	0.00	-0.15	0.00	0.00	0.00	-0.05
SBJ_2_Sham	0.00	0.00	0.18	0.18	0.12	0.12	0.12	0.12
SBJ_3_Active	0.00	0.00	0.13	1.00	0.00	0.89	**	**
SBJ_4_Sham	0.00	0.00	0.00	0.00	0.00	0.00	-0.25	-0.25
SBJ_5_Active	0.00	0.00	0.00	0.46	0.12	0.38	**	**
SBJ_6_Active	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
SBJ_7_Sham	0.00	0.00	0.00	0.00	0.00	0.00	-0.35	-0.05
SBJ_8_Sham	0.00	0.00	0.07	-0.09	0.13	-0.09	**	**
SBJ_9_Active	0.00	0.00	0.33	0.82	0.33	0.82	**	**
Active: mean; *SE*	0.00 *(±0.00)*	0.00 *(±0.00)*	0.09 *(±0.05)*	0.43 *(±0.18)*	0.09 *(±0.05)*	0.42 *(±0.15)*	0.00 *(±0.00)*	-0.03 *(±0.01)*
Sham: mean; *SE*	0.00 *(±0.00)*	0.00 *(±0.00)*	0.06 *(±0.03)*	0.02 *(±0.04)*	0.06 *(±0.03)*	0.01 *(±0.03)*	-0.16 *(±0.09)*	-0.06 *(±0.07)*

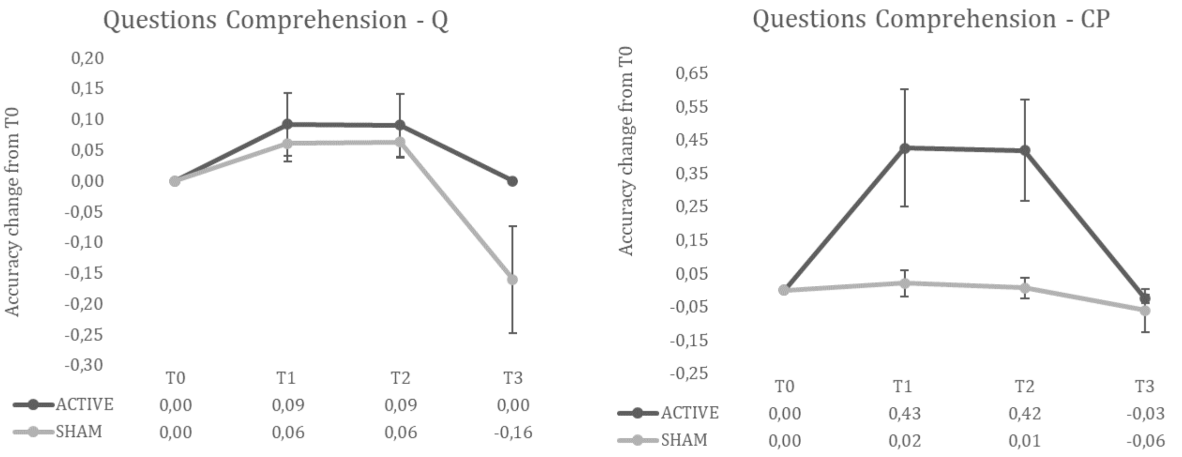

Figure 26. Question comprehension test results. Performance change from T0 in quiet (*left; Q*) and with a background noise (*right; CP*).

No significant difference or trend has been observed between timepoints (F(2,6)=.811; p=.488) or interaction between timepoints and group (F(2,6)=.335; p=.728) in the sentences recognition test in quiet.

No significant difference or trend has been observed between timepoints (F(2,6)=2.031; p=.212) or interaction between timepoints and group (F(2,6)=.472; p=.645) in the sentences recognition test in CP.

Table 6. Sentences recognition test scores. Performance change from T0. Single score of participants, mean and standard error (SE) are reported. **Q**: in quiet; **CP:** with a background noise. **= subject did not participate at the evaluation session.

	Sentences recognition							
	T0 - Q	T0 - CP	T1 - Q	T1 - CP	T2 – Q	T2 – CP	T3 - Q	T3 - CP
SBJ_1_Active	0.00	0.00	0.03	0.08	-0.16	0.05	0.02	0.07
SBJ_2_Sham	0.00	0.00	0.23	1.20	-0.25	0.80	0.15	0.87
SBJ_3_Active	0.00	0.00	1.00	2.10	1.00	3.60	**	**
SBJ_4_Sham	0.00	0.00	0.00	0.05	0.00	0.02	-0.12	-0.46
SBJ_5_Active	0.00	0.00	0.14	0.13	0.16	0.20	**	**
SBJ_6_Active	0.00	0.00	-0.36	0.16	-0.36	-0.11	-0.36	0.37
SBJ_7_Sham	0.00	0.00	0.03	-0.03	0.05	0.00	0.08	0.05
SBJ_8_Sham	0.00	0.00	0.06	0.00	0.15	0.06	**	**
SBJ_9_Active	0.00	0.00	0.30	1.31	0.43	1.46	**	**
Active: mean; *SE*	0.00 *(±0.00)*	0.00 *(±0.00)*	0.22 *(±0.18)*	0.75 *(±0.32)*	0.21 *(±0.19)*	1.04 *(0.55)*	-0.17 *(0.09)*	0.22 *(0.08)*
Sham: mean; *SE*	0.00 *(±0.00)*	0.00 *(±0.00)*	0.08 *(0.04)*	0.30 *(0.21)*	-0.01 *(±0.06)*	0.22 *(±0.14)*	0.04 *(0.05)*	0.15 *(0.24)*

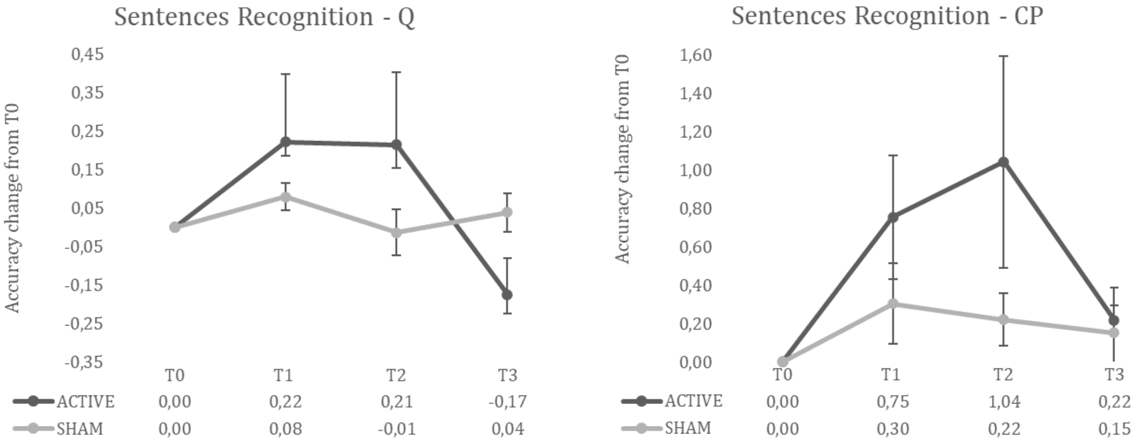

Figure 27. Sentences recognition test results. Performance change from T0 in quiet (*left; Q*) and with a background noise (*right; CP*).

No significant difference or trend has been observed between timepoints (F(2,6)=1.201; p=.364) or interaction between timepoints and group (F(2,6)=.156; p=.859) in the intervocalic-consonants identification test in quiet.

No significant difference or trend has been observed between timepoints (F(2,6)=.184; p=.837) or interaction between timepoints and group (F(2,6)=.543; p=.607) in the intervocalic-consonants identification test in CP.

Table 7. Intervocalic-consonants identification test scores. Performance change from T0. Single score of participants, mean and standard error (SE) are reported. **Q:** in quiet**; CP:** with a background noise. **= subject did not participate at the evaluation session.

Intervocalic-consonants identification

	T0 - Q	T0 - CP	T1 – Q	T1 - CP	T2 - Q	T2 - CP	T3 - Q	T3 - CP
SBJ_1_Active	0.00	0.00	0.23	0.25	-0.08	-0.08	-0.15	-0.15
SBJ_2_Sham	0.00	0.00	0.00	-0.22	-0.09	0.56	0.64	0.55
SBJ_3_Active	0.00	0.00	-0.80	-0.40	1.40	0.40	**	**
SBJ_4_Sham	0.00	0.00	0.00	-0.11	-0.06	-0.06	-0.17	-0.39
SBJ_5_Active	0.00	0.00	-0.10	-0.20	-0.10	-0.20	**	**
SBJ_6_Active	0.00	0.00	0.00	0.00	0.00	-1.00	1.11	1.11
SBJ_7_Sham	0.00	0.00	-0.10	-0.08	0.10	-0.17	0.14	0.05
SBJ_8_Sham	0.00	0.00	0.80	0.00	1.20	0.14	**	**
SBJ_9_Active	0.00	0.00	1.00	1.80	1.25	2.40	**	**
Active: mean; *SE*	0.00 *(±0.00)*	0.00 *(±0.00)*	0.07 *(±0.23)*	0.29 *(±0.31)*	0.49 *(±0.27)*	0.30 *(±0.45)*	0.48 *(±0.31)*	0.48 *(±0.31)*
Sham: mean; *SE*	0.00 *(±0.00)*	0.00 *(±0.00)*	0.18 *(±0.15)*	-0.10 *(±0.03)*	0.29 *(±0.22)*	0.12 *(±0.11)*	0.20 *(±0.14)*	0.07 *(±0.17)*

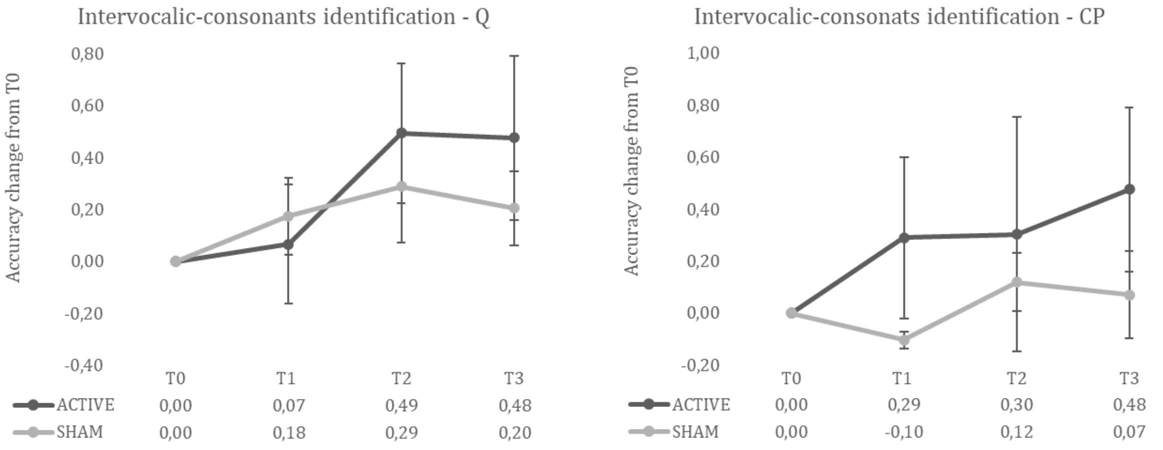

Figure 28. Intervocalic-consonants identification test results. Performance change from T0 in quiet (*left; Q*) and with a background noise (*right; CP*).

7.3.2 - Audiometric assessment – Italian Matrix Sentence Test and Pure Audiometry

No significant difference or trend has been observed between timepoints (F(2,6)=.1.919; p=.277) or interaction between timepoints and group (F(2,6)=1.833; p=.239) in the Italian Matrix Sentence Test.

Table 8. Italian Matrix Sentence Test scores. Performance change from T0. Single score of participants, mean and standard error (SE) are reported. *= OUTLIER VALUE, excluded from mean value. **= subject did not participate at the evaluation session.

	Italian Matrix Sentence Test (SRT value)			
	T0	T1	T2	T3
SBJ_1_Active	0.00	0.98	1.18	-6.27
SBJ_2_Sham	0.00	-1.00	1.00	-4.79
SBJ_3_Active	0.00	-6.20	*	**
SBJ_4_Sham	0.00	1.96	1.74	0.22
SBJ_5_Active	0.00	-9.03	-8.51	**
SBJ_6_Active	0.00	-8.11	-8.59	-6.68
SBJ_7_Sham	0.00	-2.31	-4.82	-8.67
SBJ_8_Sham	0.00	-1.41	-2.62	**
SBJ_9_Sham	0.00	0.42	1.89	**
Active: mean; *SE*	0.00 *(±0.00)*	-4.39 *(±1.54)*	-3.51 *(±1.69)*	-6.48 *(±0.10)*
Sham: mean; *SE*	0.00 *(±0.00)*	-0.69 *(±0.65)*	-1.17 *(±1.09)*	-4.41 *(±1.58)*

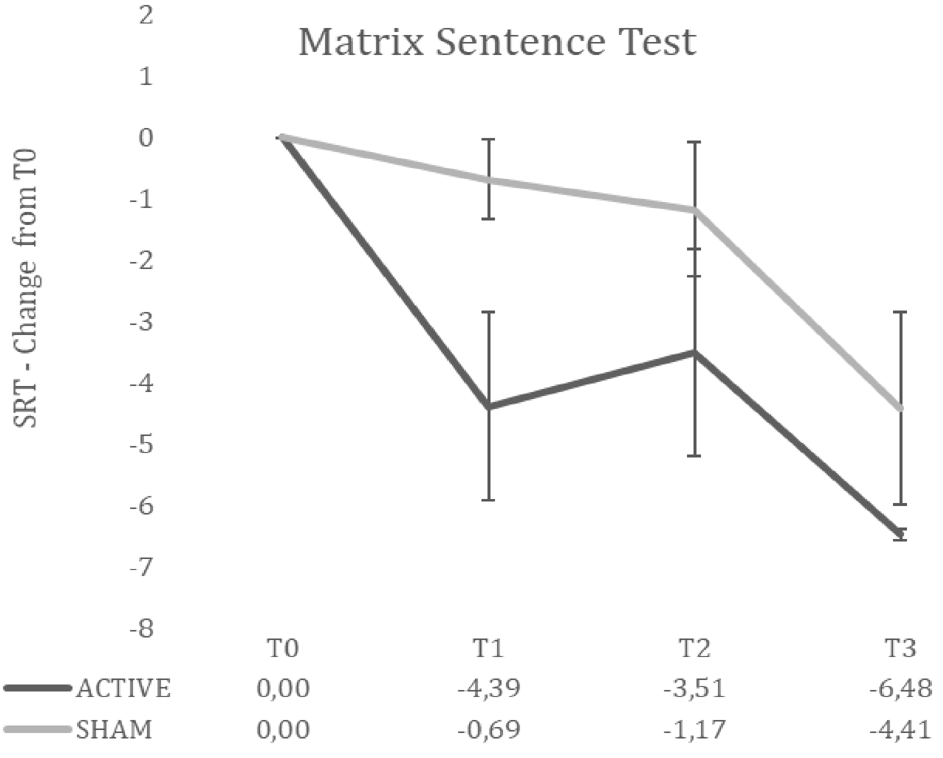

Figure 29. Italian Matrix Sentence Test results. Performance change from T0.

No significant difference or trend has been observed between timepoints (F(2,6)=.1.407; p=.316) or interaction between timepoints and group (F(2,6)=1.637; p=.271) in the Pure Audiometry.

Table 9. PTA scores. Performance change from T0. Single score of participants, mean and standard error (SE) are reported. *= OUTLIER VALUES, not considered in mean. **= subject did not participate at the evaluation session.

Pure Audiometry (PTA value)				
	T0	T1	T2	T3
SBJ_1_Active	0.00	0.10	-0.04	0.07
SBJ_2_Sham	0.00	0.04	0.02	0.04
SBJ_3_Active	0.00	-0.06	0.03	**
SBJ_4_Sham	0.00	-0.16	-0.09	0.22
SBJ_5_Active	0.00	-0.09	0.03	**
SBJ_6_Active	0.00	-0.05	*	-0.01
SBJ_7_Sham	0.00	*	-0.22	-0.43
SBJ_8_Sham	0.00	0.00	-0.04	**
SBJ_9_Sham	0.00	-0.08	0.11	**
Active: mean; *SE*	0.00 *(±0.00)*	-0.03 *(±0.03)*	0.03 *(±0.01)*	0.03 *(±0.02)*
Sham: mean; *SE*	0.00 *(±0.00)*	-0.04 *(±0.04)*	-0.08 *(±0.03)*	-0.05 *(±0.12)*

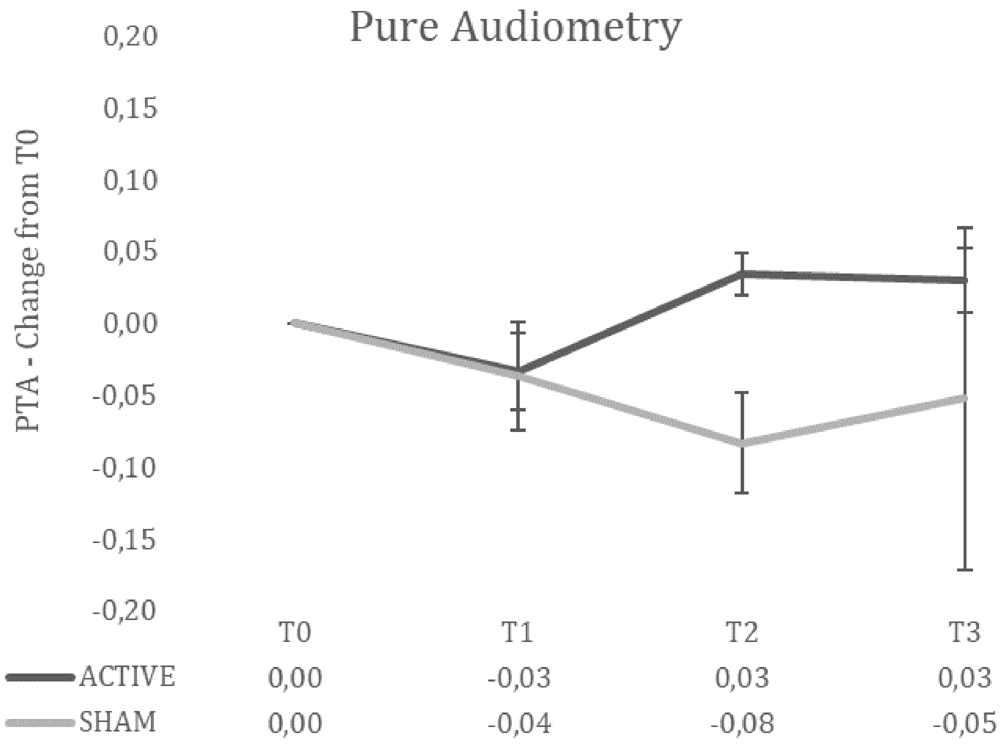

Figure 30. PTA results. Change of performance from T0.

7.3.3 - Neuropsychological assessment - PASAT

A significant difference between timepoints (F(2,6)=6.344; p=.033) has been observed without interaction between timepoints and group (F(2,6)=1.388; p=.320) in the PASAT 2200ms. However, only a significant difference in the Active group has been found between T0 and T1 (p=.021), running post hoc.

Table 10. PASAT 2200ms scores. Performance change from T0. Single score of participants, mean and standard error (SE) are reported. **= subject did not participate at the evaluation session.

	PASAT 2200ms			
	T0	T1	T2	T3
SBJ_1_Active	0.00	0.16	0.16	0.08
SBJ_2_Sham	0.00	0.11	0.12	0.03
SBJ_3_Active	0.00	0.15	0.11	**
SBJ_4_Sham	0.00	-0.02	-0.03	-0.01
SBJ_5_Active	0.00	0.00	0.00	**
SBJ_6_Active	0.00	0.11	0.02	0.09
SBJ_7_Sham	0.00	0.00	-0.03	-0.11
SBJ_8_Sham	0.00	0.07	-0.05	**
SBJ_9_Sham	0.00	0.25	0.25	**
Active: mean; *SE*	0.00 *(±0.00)*	0.13 *(±0.03)*	0.11 *(±0.04)*	0.08 *(±0.01)*
Sham: mean; *SE*	0.00 *(±0.00)*	0.04 *(±0.02)*	0.00 *(±0.03)*	-0.03 *(±0.02)*

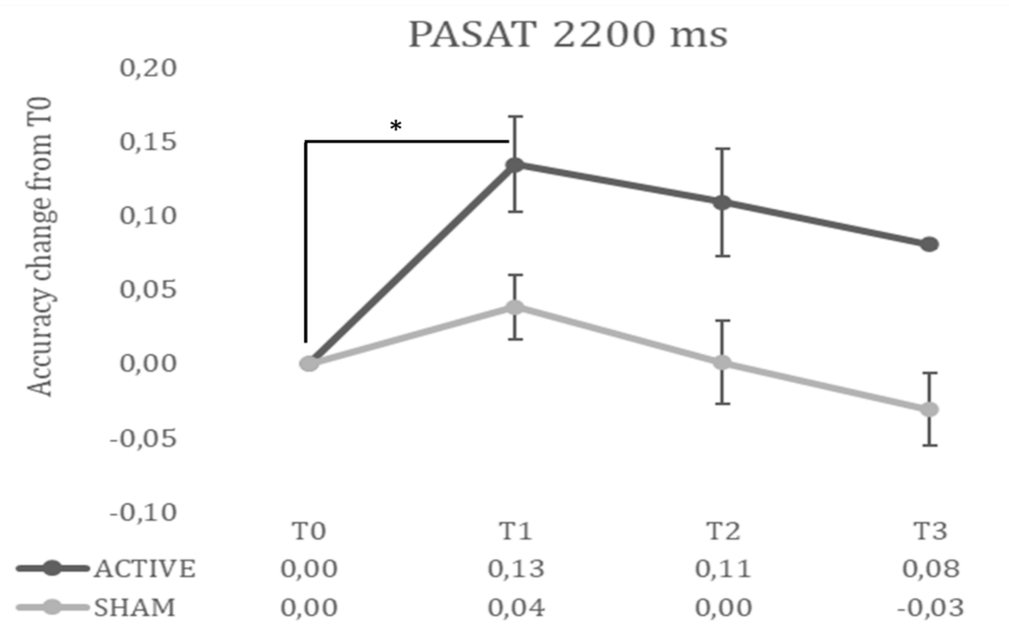

Figure 31. PASAT task(2200ms) results. Performance change from T0. *=post hoc revealed a significant change between T1 and T2 for Active rTMS group.

7.4 - Discussion

The rTMS protocol has confirmed to be safe, feasible and applicable in CI patients. The reported stimulation side effects are minimal, transient, and comparable to those encountered in the majority of other rTMS works (tingling, facial muscle movements during the delivery of magnetic stimuli, mild headache and discomfort). No patient reported negative effects on auditory perception or pain at the implant site at the end of single sessions and at the end of the treatment.

Statistical analysis conducted between T0, T1 and T2 showed no difference between groups, probably due to the small sample size. The low number of participants is a strong limitation of the results that will be discussed. No analysis was run on T3, because only 5 patients participated to the last assessement and the data collection on the remaining participants is still in progress. Thus, the discussion will focalize on the pattern diversity observed descriptively in the graphs that are reported in the results section.

The graphs shown patterns of an overall and homogeneous improvement of speech perception abilities in HL patients treated with real TMS versus those who were treated with placebo rTMS. In particular, this pattern is detectable in the real rTMS group at T1 and T2 compared to T0 in the tests carried out with the presence of a background noise in all evaluations (speech, audiological and neuropsychological assessments).

Speech evaluation results between timepoints demonstrated a pattern of improved ability to understand speech in a noisy environment especially in 4 out of 5 Icare protocol tests: in the questions comprehension, in the sentences recognition, in the disyllabic words recognition and in the intervocalic consonants recognition task. In line with the previous result, a marked improvement in the ability to understand sentences was observed in the Matrix Sentence Test in patients that underwent Active rTMS compared to those of the Sham stimulation. The results obtained in the neuropsychological evaluation (PASAT 2200ms) confirm the positive performance trend of the subjects of the Active stimulation group.

It appears that HL patients who undergo real rTMS coupled with ST become more able to detect an auditory stimulus in the presence of background noise. These participants become more skilled in receiving and elaborating a question (questions comprehension test), in hearing and comprehend words (disyllabic words test), in understanding and repeating sentences (matrix sentence test, sentences recognition) in hearing a group of phonemes (intervocalic consonant recognition test). Moreover, HL patients of Active rTMS seem to be more adept at keeping information in mind and performing operations on it, as can be seen looking to PASAT

2200ms task, which evaluates the working memory. As previously specified, the test was made more challenging by adding the background noise.

Tests with a background noise require high cognitive resources and the subject must remain concentrated and make a great listening effort (Peelle, 2018) in order to perform them effectively.

Commonly, in everyday life a person need to pay attention to auditory stimuli in the presence of acoustic noises that degrade the auditory input (Van Engen & Peelle, 2014). Background noise, competing speech, or foreign accents can all pose acoustic challenges. The auditory signal that reaches a listener's perceptual system is less fidelity when hearing is impaired, even when it is perfectly clear. Listeners' comprehension at an acoustic level is therefore challenged by external and internal sources of interference. In order to extract the intended meaning from speech, listeners must match the rapid incoming acoustic stream with stored representations of words and phonemes. As a result of acoustically degraded speech, it becomes more difficult to correctly identify sounds: less information is available to the listener, which leads to less quality speech cues and an increase in errors (Mattys et al., 2012).

The listening effort refers to the amount of resources or energy that a listener uses to meet cognitive demands (Peelle, 2018). The Framework for Understanding Effortful Listening was proposed in a recent consensus paper, which addressed a variety of complex topics related to spoken communication and listening effort (Pichora-Fuller et al., 2016). In this work the listening effort is defined as "the deliberate allocation of mental resources toward overcoming obstacles in goal pursuit while carrying out a task, with listening effort particularly relevant to tasks involving listening." The work emphasizes the distinction between the demands of a listening situation and the listening effort an individual puts forth.

Several studies have found that listening to speech that is more difficult to understand due to degradation (noise-vocoded) (Wild et al., 2012) or masking by noise (Zekveld et al., 2011) increases activity in working memory and auditory attention regions. This kind of study assumes that regional variations in blood oxygen levels reflect changes in brain network recruitment for cognitive processing related to tasks.

While listening to degraded speech, specific brain networks are active: the cingulo-opercular network, as well as the core speech networks that include the left medial gyrus, superior temporal gyrus, and inferior frontal gyrus. In addition, there are networks in the premotor cortex associated with verbal working memory and other general cognitive functions (Peelle, 2018) .

As previously discussed, the close connection between hearing and the cognitive system is now, and a lack of auditory input, this has negative consequences on other functions. The explanation associated with it can be found in the model of brain interconnections: auditory input not only stimulates the portion of the acoustic cortex, but also the other areas connected with it (Slade et al., 2020), determining, therefore, a generalized ignition of the brain. On the contrary, in the absence of an auditory stimulus, the possibilities of activating other areas are limited. The results obtained in the various studies suggest the presence of a strong "sensory-cognitive connection" and underlines the importance of audiological rehabilitation to also allow an increase in cognitive abilities (Karawani et al., 2018).

It has been found that the speed of cognitive processing (and in particular the role of working memory) is associated with the perception of speech in a noisy environment, hypothesizing that with the use of substitute devices the hearing, consequently increases the acoustic signal and, therefore, decreases the need to decipher what has been heard and therefore reduces the cognitive "burden" (or cognitive load, a term used to indicate the brain activity necessary to understand and recognize a voice) (Martini et al., 2014). These "neural resources" which are saved in the face of adequate auditory inputs, can be exploited for the purpose of improving cognitive performance, in particular, working memory and neural processing (Karawani et al., 2018).

Active rTMS on the auditory association area associated with the ST might have caused a reorganization of the auditory network circuits and the pattern of improvement of working memory and speech perception in the real stimulation group seem to support this hypothesis. These preliminary results must of course be confirmed by enlarging the sample. Furthermore, other areas of the auditory network play a fundamental role in the speech perception, and a future work might involve the stimulation of a different area than that of the present study. furthermore, 5 days of treatment may not be sufficient to guarantee stability of the effect and a longer program may bring out more consistent results.

However, for the first time rTMS was performed on a sample of HL patients with CI, conducting a double-blind, randomized study and the results reported so far suggest that real rTMS combined with ST is more effective than placebo rTMS combined with ST. Results of the current ongoing investigation, especially if conformed at T3 evaluation point, will help to move rTMS treatment to the lab boundary into a useful real-life translation of this innovative approach.

CONCLUSIONS

The cochlear implants tested are resistant to magnetic pulses delivered by a TMS device. HL patients with removable hearing aids significantly improves their speech perception abilities following 5-day rTMS to the auditory association cortex. Patients with profound HL and cochlear implants show a pattern of improvement in speech perception and working memory following treatment with rTMS associated with ST. These improvements in patients with HL could be related to a long-lasting reorganization of the brain auditory network after the rTMS treatment.

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