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rTMS of the auditory association cortex improves speech intelligibility in patients with sensorineural hearing loss

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HIGHLIGHTS

- Ear-brain pathway responsible for speech perception is altered in hearing loss.
- rTMS protocol directed to the auditory association cortex might restore its functionality.
- Improvements of speech perception are observed after 5 days of rTMS in deaf patients.

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ABSTRACT

Objective: Sensorineural hearing-loss (SHL) is accompanied by changes in the entire ear-brain pathway and its connected regions. While hearing-aid (HA) partially compensates for SHL, speech perception abilities often continue to remain poor, resulting in consequences in everyday activities. Repetitive transcranial magnetic stimulation (rTMS) promotes cortical network plasticity and may enhance language comprehension in SHL patients.
Methods: 27 patients using HA and with SHL were randomly assigned to a treatment protocol consisting of five consecutive days of either real (Active group: 13 patients) or placebo rTMS (Sham group: 14 patients). The stimulation parameters were as follows: 2-second trains at 10 Hz, 4-second inter-train-interval, and 1800 pulses. Neuronavigated rTMS was applied over the left superior temporal sulcus. Audiological tests were administered before (T0), immediately after (T1), and one week following treatment completion (T2) to evaluate the speech reception threshold (SRT) and the Pure Tone Average (PTA).
Results: In the context of a general improvement likely due to learning, the treatment with real rTMS induced significant reduction of the SRT and PTA at T1 and T2 versus placebo.
Conclusions: The long-lasting effects on SRT and PTA observed in the Active group indicates that rTMS administered over the auditory cortex could promote sustained neuromodulatory-induced changes in the brain, improving the perception of complex sentences and pure tones reception skills.
Significance: Five days of rTMS treatment enhances overall speech intelligibility and PTA in SHL patients.

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1. Introduction

The auditory system of a healthy adult can detect sounds with an intensity greater than 20 dB across the entire frequency range between 20 and 20000 Hz (Purves et al., 2001). The sounds are transformed into electrical signals within the cochlea and transmitted bilaterally to the brainstem nuclei, to the medial geniculate nucleus, to the thalamus, and to the cortex (Peterson et al., 2022). The neural pathway contains crossing fibers at each synaptic level, owing to the central auditory system necessity to acquire and analyze both contralateral and ipsilateral information (Felix et al., 2018).

Globally, roughly 1.5 billion individuals experience significant and progressive hearing impairment (Haile et al., 2021), and approximately half of the elderly population has notable sensorineural hearing loss (SHL) (Ford et al., 2018). SHL can be categorized into degrees of mild, moderate, severe, and profound (Alshuaib et al., 2015), and commonly arises from the irreversible damage of cochlear hair cells and auditory neurons (Wu et al., 2019; Chester et al., 2021). This impairment becomes particularly evident in everyday life situations, when the understanding of speech is required in noisy environments (Lee, 2013). These scenarios, which additionally necessitate greater cognitive effort (Rönnberg et al., 2013), can result in a quick feeling of cognitive fatigue and feebleness, which may contribute to psychosocial and occupational nuisance, common in SHL patients (Hornsby, 2013).

Pathological alterations in the inner ear are well-established (Eckert et al., 2021). However, modifications in the peripheral organ may impact specific brain regions in the left posterior superior temporal gyrus that play a crucial role in phonological, syntactic and lexical-semantic processing (Walenski et al., 2019). This mechanism may negatively affect the cortical representation of an acoustic stimulus (Bidelman et al., 2020; Koops et al., 2020), such as human speech, leading to the progressive decline of communication skills in deaf persons (Fortunato et al., 2016).

The human voice is a distinct stimulus that activates the auditory association cortex (Belin et al., 2000; Morillon et al., 2022), with left-side lateralization for sentence encoding (Albouy et al., 2020). Furthermore, voice perception activates the superior temporal sulcus, the supratemporal plane and the superior temporal gyrus (Rupp et al., 2022). An area corresponding to the superior temporal sulcus is highly activated during speech comprehension in humans (Belin et al., 2000). Its activation increases with sentence complexity (Wilson et al., 2010) and greater sequencing demands of a phrase (Pallier et al., 2011). The accuracy and reaction time of participants' responses to complex questions are worsened following the application of inhibitory 1 Hz repetitive transcranial magnetic stimulation (rTMS) targeting the left superior temporal sulcus (Kyriaki et al., 2020). This result provides causal evidence of the crucial involvement of the posterosuperior part of the temporal gyrus during a sentence comprehension.

Neuroimaging techniques disclosed changes in the cortical part of the auditory pathway in SHL individuals, revealing significant alterations in several neural circuits (Profant et al., 2020). The accumulating evidence of brain connectivity changes within the auditory network of these patients has led to the emergence of the concept of "central presbycusis" (Gates, 2012). This is a complex multifactorial process involving both age-related factors and various pathologies that have the potential to impact the auditory system as a whole (Humes et al., 2012). Neuroimaging studies have demonstrated that SHL decreases the blood flow and the thickness of gray matter in brain regions responsible for auditory processing (Profant et al., 2014; Ponticorvo et al., 2019). Changes in the brain function and structure can result in specific alterations in event-related potentials (ERPs), that represent a response to speech signals (Bidelman et al., 2017). Support vector machine classifiers can be used to differentiate between individuals with and without deafness, by examining particular changes in the ERPs morphology (Mahmud et al., 2020).

SHL patients can enhance their auditory perception using either wearable hearing aids (HA) or cochlear implants. Improvements in attention and receptive language abilities have been associated with the use of HA, especially after undergoing speech therapy rehabilitation (Pichora-Fuller and Singh, 2006). After one year of correctly using HA, SHL patients showed increased functional magnetic resonance imaging (fMRI) signal in specific brain regions including the left superior temporal gyrus, Wernicke's area, left insula, and left superior frontal gyrus (BA 40/41, BA22, BA13, and BA8, respectively) (Pereira-Jorge et al., 2018).

Although the appropriate use of HA can promote plastic reorganizations beneficial to the patients, many of them continue to experience significant challenges with communicative abilities (Bidelman et al., 2020). The comprehension of spoken language entails an array of integrated neural processes, that cover the correct interpretation of sound signals to the allocation of the meaning to sounds themselves.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation (NIBS) technique, widely applied in the treatment of psychiatric and neurological disorders (Rossi et al., 2009; Lefaucheur et al., 2020). It is believed to induce short and long-term changes in cortical plasticity (Klomjai et al., 2015). In the domain of hearing disorders, rTMS has been utilized to alleviate tinnitus (Langguth et al., 2008), which is a maladaptive plasticity disorder of the auditory pathways (Schoisswohl et al., 2019; Liang et al., 2020). Furthermore, in a cohort of patients suffering from sudden sensorineural hearing loss, rTMS yielded significantly greater recovery from auditory dysfunction and reduced tinnitus perception in comparison to conventional corticosteroid therapy or hyperbaric oxygen therapy (Zhang and Ma, 2015).

Based on these assumptions, rTMS treatment may be effective in patients with SHL. Therefore, a double-blind, randomized, sham-controlled, age-matched rTMS study was conducted among patients with chronic and worsening SHL, who were using HA. The study only included SHL participants who reported difficulty with speech understanding, particularly in noisy environments. It was hypothesised that applying multiple sessions of excitatory rTMS on the superior temporal sulcus, which is a brain area related to sentence comprehension, could bring beneficial effects on the communicative abilities of SHL patients, especially in a noisy environment.

2. Materials and methods

2.1. Participants

Twenty-seven right-handed patients with mixed causes of SHL and wearing removable bilateral HA (19 males and 8 females; mean age: 63.5 ± 13.9) were enrolled for a double-blind, age-matched, randomized, sham-controlled study at the Otolaryngology Clinic of the University Hospital in Siena, Italy. Inclusion criteria comprised a prior diagnosis of moderate to severe presbycusis SHL corrected through bilateral HA; high level proficiency in HA usage (minimum 1 year of daily use); normal cognitive function and a corrected Mini Mental State Examination (MMSE) score above 24. Exclusion criteria were, according to TMS guidelines: a prior diagnosis of epilepsy, pacemaker wearers, or individual with other implanted electromedical devices (Rossi et al., 2021). Patients with neurological or psychiatric conditions other than SHL were excluded. All participants were fully informed about the study objectives and signed the informed consent form before taking part. The study adhered to the guidelines of the Declaration of Helsinki, and was approved by the local ethics committee (protocol code: Brainsight 21/24).

2.2. rTMS treatment

Participants were randomly allocated to a real stimulation group (Active group: 13 participants; 4 females, mean age: 60.4 ± 21.8) and a control group who received a placebo stimulation (Sham group: 14 participants; 4 females, mean age: 63.3 ± 13.4).

rTMS was administered by utilizing an air-cooled figure-of-eight coil set tangentially to the head using an STM9000 stimulator (Ates-EBNeuro) after the removal of HA for safety reasons (Rossi et al. 2021). The stimulation site was situated above the posterior part of the left superior temporal sulcus, between BA 22 and 42 (Montreal Neurological Institute (MNI) coordinates: –62; –40; 10), and corresponding to the auditory association cortex which is recruited during voice listening (Belin et al., 2000). The electric field on the brain was estimated using SIMNIBS software, employing a standard template with MNI coordinates (Saturnino et al., 2019). The coil handle was oriented towards the back to induce current from the posterior-to-anterior direction. The targeting accuracy was monitored in real-time using a neuronavigation system (BrainNET, EBneuro Ltd, Florence, Italy). The precise localization was determined in each patient using the Colin 27 Average Brain, Stereotaxic Registration Model template (Holmes et al., 1998).

All participants underwent five consecutive daily sessions of rTMS. The stimulation frequency was set at 10 Hz, with 2-second trains duration and an inter-train interval of 4 seconds. In each session, a total of 1800 pulses was delivered at 100% intensity of the individual resting motor threshold (RMT). Mean RMT across treatment sessions for the Active group and Sham groups was 60% and 61.8% of maximum stimulator output, respectively. RMT was determined for each visit using an electromyograph (NeMus 2, EBneuro Ltd, Florence, Italy), triggered by TMS pulses. RMT was defined for the left primary motor cortex (M1) "hot spot", where single TMS stimulus had a 50% probability of eliciting a motor response of ~50 µV in the right first dorsal interosseous (FDI) muscle (Rossini et al., 2015). The muscular activity was measured by placing the active electrode over the FDI muscle belly and the reference on the metacarpophalangeal joint of the index finger, while the ground electrode was positioned on the wrist. To ensure consistent responses, the coil was positioned tangentially to the scalp and angled at approximately 45° from the midline, producing a current flow from the back to the front of the scalp.

Placebo stimulation was conducted using a placebo air-cooled figure-of-eight coil (Ates-EBNeuro) which stimulated solely the superficial skin of the scalp, thus eliciting an indistinguishable scalp sensation compared to the real stimulation. During the procedure, patients and experimenters wore earplugs. Participants were instructed to keep their eyes open and remain awake throughout the stimulation session.

2.3. Audiological assessment

Before, immediately following, and one week after the treatment conclusion (T0, T1 and T2 respectively), Italian Matrix Sentence Test and Pure Tone Audiometry were performed in an audiometric shielded cabin in order to evaluate the audiological performance of the participants.

The Italian Matrix Sentence Test consists of a vocabulary of 50 common words (10 names, 10 verbs, 10 numerals, 10 adjectives, and 10 nouns). Randomized sentences with a predetermined grammatical structure such as "Sofia drags ten black balls" were presented to the patient in a free field with background noise interference. The noise level was initially set at 65 dB, with a signal-to-noise ratio of 0 dB. Each test list comprised 20 sentences, and it was preceded by two training lists, in order to minimize the learning effect. Based on the previous sentence word accuracy, the software assessed the speech level of the following sentence and estimated the speech reception threshold (SRT), at which 50% of the sentence was repeated correctly. The Italian Matrix Sentence Test exhibits a 0.2 dB standard deviation of the SRT and a test–retest reliability of 0.6 dB, rendering it an accurate and reliable tool (Puglisi et al., 2015). The test was carried out twice in each assessment, the first time without HA and the second time with HA.

Pure Tone Audiometry is commonly used to determine the presence and severity of SHL (Kapul et al., 2017). Patients were exposed to a pure tone directed randomly to either the right or left ear. The intensity of the sound was then adjusted to identify the hearing thresholds for each frequency (0.25, 0.5, 1, 2, 3, 4 KHz). The pure tone average (PTA), which is the mean of patients' hearing thresholds at the four main frequencies (0.5, 1, 2 and 4 kHz) in Pure Tone Audiometry was calculated. The test was conducted inside a soundproof room, without HA in free field and with headphones, and lastly with HA (Fig. 1).

2.4. Hearing performance analysis

One participant who significantly deviated from the mean of the group by more than two standard deviations in the SRT was excluded from the analysis. As a result, statistical analysis was conducted on twenty-six remaining patients (Active group: 13 participants; 4 females, mean age: 60.4 ± 21.8 and Sham group: 13 participants; 4 females, mean age: 63.5 ± 13.9). Table 1 provides information on each participant.

To evaluate the significant change of performance between the baseline and subsequent assessments, the absolute change between T2 and T1 with T0 was calculated (for raw SRT and PTA

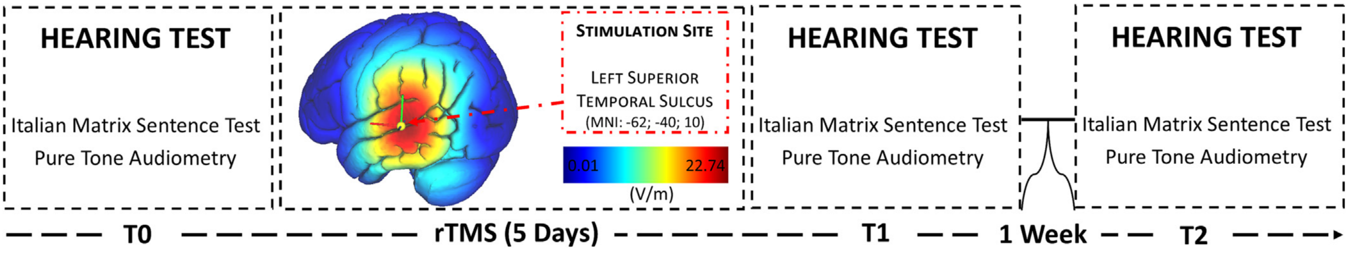

Fig. 1. Experimental Design of the study. At T0, T1, and T2 participants' SRT and PTA were measured with the Italian Matrix Sentence Test and the Pure Tone Audiometry, respectively. Between T0 and T1, HL patients underwent 5 days of rTMS treatment delivered on the left superior temporal sulcus (between Brodmann area 22 and Brodmann area 42). The estimation of the magnitude of the primary electric field given by TMS pulses is shown (Electric field vector, unit: V/m).

Table 1
Information on each patient is reported. The table displays demographic details for each patient including age and sex, along with the etiology and degree of their hearing loss, the hearing aid type, and the date of the first usage of the device.

Active rTMS group								
Participant	Age	Sex	HL etiology	HL degree	HA type	HA - date of first use	HA side	MMSE
Patient 1	44	M	Presbycusis	Moderate	BTE	2019	bilateral	30
Patient 3	92	M	Presbycusis	Severe	BTE	2013	bilateral	30
Patient 4	47	M	Presbycusis	Severe	BTE	2020	bilateral	30
Patient 9	43	F	Presbycusis	Moderate	BTE	2018	bilateral	30
Patient 10	46	M	Presbycusis	Moderate	BTE	2019	bilateral	30
Patient 11	48	F	Presbycusis	Severe	BTE	2019	bilateral	30
Patient 15	43	M	Presbycusis	Moderate	BTE	2020	bilateral	30
Patient 16	93	M	Presbycusis	Severe	BTE	2012	bilateral	30
Patient 13	43	M	Presbycusis	Severe	BTE	2020	bilateral	30
Patient 19	45	F	Presbycusis	Severe	BTE	2021	bilateral	30
Patient 18	90	M	Presbycusis	Severe	BTE	2020	bilateral	30
Patient 21	89	M	Presbycusis	Moderate	BTE	2018	bilateral	30
Patient 24	62	F	Presbycusis	Moderate	BTE	2021	bilateral	30
Sham rTMS group								
Participant	Age	Sex	HL etiology	HL degree	HA type	HA - date of first use	HA side	MMSE
Patient 2	77	F	Presbycusis	Moderate	BTE	2019	bilateral	30
Patient 5	71	M	Presbycusis	Moderate	BTE	2020	bilateral	30
*Patient 6	60	M	Presbycusis	Severe	BTE	2019	bilateral	30
Patient 7	65	M	Presbycusis	Moderate	BTE	2018	bilateral	30
Patient 8	40	M	Presbycusis	Severe	BTE	2021	bilateral	30
Patient 12	59	M	Presbycusis	Severe	BTE	2021	bilateral	30
Patient 14	80	M	Presbycusis	Severe	BTE	2016	bilateral	30
Patient 17	71	F	Presbycusis	Severe	BTE	2019	bilateral	30
Patient 20	63	M	Presbycusis	Severe	BTE	2020	bilateral	30
Patient 22	88	M	Presbycusis	Severe	BTE	2010	bilateral	30
Patient 23	60	M	Presbycusis	Moderate	BTE	2022	bilateral	30
Patient 25	53	M	Presbycusis	Moderate	BTE	2021	bilateral	30
Patient 26	55	F	Presbycusis	Severe	BTE	2021	bilateral	30
Patient 27	44	F	Presbycusis	Severe	BTE	2018	bilateral	30

[*] Patient excluded from the analysis; HL = hearing loss; HA = hearing aids; BTE = behind the ear hearing aids.

data from evaluations of the Italian Matrix Sentence Test and at the Pure Tone Audiometry, see Table 2). To investigate significant changes in SRT and PTA performance among different time points and groups, a repeated measures analysis of variance (ANOVA^{RM}) was carried out on patients with and without HA: [Factors: Timepoint (3 levels: T0, T1, T2) and Group (2 levels: Active, Sham)].

An analysis between the age of the Active and the Sham group was conducted, to determine whether the variable had an impact on the results. To this end, an independent samples t-test was run, using age as the independent variable and Active/Sham rTMS as the grouping variable.

3. Results

The entire procedure was generally well tolerated with no significant adverse effects reported, except for mild numbness below the stimulation site (67% of patients) and transient activation of the ipsilateral facial muscles during the pulse delivery (100% of patients).

A Mauchly's test was conducted to verify the sphericity of the data. The assumption of sphericity was confirmed in the SRT data without HA ($X^2(2) = 4.04$, $p = .132$), but not when wearing HA ($X^2(2) = 12.023$, $p = .002$). In this case, a Greenhouse-Geisser correction was applied ($\varepsilon = 0.711$). Regarding the PTA performance, sphericity was also confirmed for tests conducted in the free field (right side: $X^2(2) = 1.27$, $p = .528$; left side: $X^2(2) = 1.96$, $p = .374$; threshold level: $X^2(2) = 2.47$, $p = .290$). Sphericity was violated in tests conducted using the headphones for sounds directed to the left ear, right ear, and for the threshold level. A Greenhouse-Geisser correction was applied ($\varepsilon = 0.579$; 0.563; 0.722 for the right ear, left ear, and the threshold level respectively).

A significant main effect of the Timepoint factor was observed in the Italian Matrix Sentence Test conducted without HA ($F_{(2,48)} = 11.202$; $p < .001$). The overall SRT was lower at T1 compared to T0 ($p = .032$) and at T2 compared to T0 ($p = .001$). Additionally, a significant interaction between the Timepoint and Group factors was found ($F_{(2,48)} = 13.722$; $p = .046$). The Bonferroni-adjusted significance test for pairwise comparisons showed that the Active group had significantly higher performance at T2 compared to T0 ($p < .001$) and at T2 compared to T1 ($p = .017$) (Fig. 2-A). The analysis was repeated on the same patients wearing HA. in this case, a significant main effect of Timepoint factor was highlighted ($F_{(1.42,\ 34.11)} = 7.17$; $p = .002$), with an higher performance at T1 compared to T0 ($p = .032$) and at T2 compared to T0 ($p = .001$). No interaction between factors ($p > .05$) was observed (Fig. 2-A).

When analysing the change in PTA in a free field, a main effect of the Timepoint factor was found for sounds directed to the right ear ($F_{(2,48)} = 7.76$; $p = .001$). The PTA was lower at T2 compared to T0 ($p = .002$) and at T2 compared to T1 ($p = .024$). A significant interaction was found between Timepoint and Group factors ($F_{(2,48)} = 3.525$; $p = .037$), with the Active group showing a significant reduction of the PTA at T2 compared to T0 ($p < .001$) and at T2 compared to T1 ($p = .040$). No significant main effect or interaction was found for sound directed to the left ear ($p > .05$).

A significant main effect of Timepoint factor was found for PTA performance change using headphones with sounds directed to the left ear only ($F_{(1.65,\ 39.71)} = 5.692$; $p = .010$) with an higher performance at T2 compared to T0 ($p = .022$). No interaction between factors was found. Lastly, no significant change was found between time points by examining the remaining Pure Tone Audiometry tests performed while wearing HA ($p > .05$).

Table 2
Mean and standard deviation (*SD*) raw values of the speech reception threshold (SRT) and of the pure tone average (PTA) in both groups and time points in SHL patients.

		SRT – without HA		
		T0	T1	T2
Active rTMS	Mean	13.79	11.61	9.72
	SD	*10.17*	*10.84*	*9.04*
Sham rTMS	Mean	0.10.9	9.7	9.7
	SD	*10.4*	*0.10.7*	*0.10.2*
		SRT – with HA		
		T0	T1	T2
Active rTMS	Mean	0.77	0.11	0.04
	SD	*2.57*	*3.01*	*3.04*
Sham rTMS	Mean	1.5	1.2	0.00
	SD	*3.9*	*0.3.5*	*3.1*
		PTA – without HA - Free Field - Right Side		
		T0	T1	T2
Active rTMS	Mean	73.17	71.25	69.04
	SD	*11.53*	*11.24*	*11.48*
Sham rTMS	Mean	75.40.	75.77	74.60
	SD	*11.69*	*12.03*	*12.86*
		PTA – without HA - Free Field - Left Side		
		T0	T1	T2
Active rTMS	Mean	73.56	73.02	72.12
	SD	*9.81*	*10.02*	*10.82*
Sham rTMS	Mean	77.48	76.23	76.54
	SD	*8.36*	*8.00*	*9.23*
		PTA – without HA - Headphones - Right Side		
		T0	T1	T2
Active rTMS	Mean	57.69	57.31	56.44
	SD	*10.82*	*10.79*	*11.05*
Sham rTMS	Mean	62.12	60.85	59.75
	SD	*14.19*	*14.07*	*14.09*
		PTA – without HA - Headphones - Left Side		
		T0	T1	T2
Active rTMS	Mean	59.33	58.27	57.31
	SD	*10.14*	*9.73*	*10.93*
Sham rTMS	Mean	62.12	61.38	60.13
	SD	*14.19*	*14.37*	*14.31*
		PTA with HA – right side		
		T0	T1	T2
Active rTMS	Mean	58.08	58.08	57.12
	SD	*14.95*	*14.43*	*14.86*
Sham rTMS	Mean	55.00	53.94	54.90
	SD	*9.63*	*9.73*	*10.22*
		PTA – with HA – left side		
		T0	T1	T2
Active rTMS	Mean	50.58	50.67	50.10
	SD	*7.37*	*5.99*	*5.78*
Sham rTMS	Mean	48.94	47.88	48.46
	SD	*5.00*	*5.31*	*4.85*

The independent sample t-test showed no significant age difference between the Active and Sham groups, confirming that the study participants were age-matched ($p > .05$).

4. Discussion

In the present study, rTMS of the left auditory association cortex was utilized to enhance language comprehension in patients with a chronic SHL. This approach is currently unique, as no previous research has tackled this issue. The treatment program was found to be feasible, safe, devoid of adverse effects, and associated with relatively long-lasting beneficial effects. The results of this double-blind, parallel and age-matched groups, controlled study show that 5 days of real rTMS has a beneficial effect on the SRT and PTA performance in patients with presbycusis SHL. In the framework of a general improvement likely due to learning effects, significantly lower SRT and PTA were observed after the active treatment versus Sham. The findings suggest that the rTMS treatment could counteract the maladaptive effects of brain plasticity caused by deafness and significantly improve speech comprehension abilities and pure tone sounds reception skills in proficient HA users, particularly in a noisy environment.

Both primary and the auditory association cortices in the left hemisphere exhibit close connectivity with brain regions that govern receptive language abilities located in the superior temporal gyrus near the dorsal stream (Friederici, 2012). Damage to these cortical nodes or the white matter tracts that connect them can result in the development of a fluent aphasia syndrome, in which expressive language is typically preserved, while receptive speech ability is impaired (Friederici, 2017). In addition, damage to the superior temporal gyrus and of the middle temporal gyrus was found to reduce grammatical judgment (Wilson and Saygin, 2004). Aligned with recent research emphasizing the importance of specific temporal lobe regions in language reception ability, Versace and colleagues conducted a study on stroke patients with chronic fluent aphasia. They targeted the left superior temporal gyrus using an excitatory rTMS protocol, that resulted in a significant improvement in verbal comprehension ability at the end of the stimulation (Versace et al., 2020).

In SHL, the auditory association cortex is not damaged *per se*, but deafness has been shown to impoverish the functional connectivity of this area with brain regions of the auditory network and other large-scale networks (Bonna et al., 2021). This leads to difficulties in perceiving sounds and processing complex sentences, particularly in daily life where background noise is frequent and unpredictable and can mask target stimuli (Shepherd and Hardie, 2001). HA could improve sound reception performance, leading to a significant improvement in patients' daily lives, but speech perception deficits are still commonly reported by HA users, especially in a noisy environment. It is likely that such impairment could be due to maladaptive plasticity of the auditory cortex and related areas and to the deprivation or distortion of auditory inputs (Butler and Lomber, 2013; Bidelman et al., 2020).

In the present study, the significant reduction of SRT that emerged at T2 compared to T1 and to T0 in the Active group only is likely due to the real rTMS intervention. We speculated that the magnetic stimulation treatment might have favored mechanisms of long-term neural plasticity, restoring more physiological processing in the brain networks underlying speech perception. Indeed, it is known that the effect of rTMS treatment occurs in the whole network involving the cortical target and can last for a long time after the end of the treatment itself (Ridding and Rothwell, 2007; Jung et al., 2020).The neural correlates of the delayed rTMS-induced improvement might be revealed in a forthcoming dedicated neuroimaging investigation.

It is partly unclear why significant SRT change across evaluations was found in both groups when patients were tested wearing HA. One possible explanation is that speech perception performance with HA was already at a level that could not be further improved by rTMS and the reduction in SRT in both the active and sham groups might be due to the learning or placebo effects (Oken et al., 2008; Nuesse et al., 2019). For these reasons, results between assessments with HA must be interpreted with caution and with a broad perspective. Therefore, the significant result in the Active group without the HA is not only still satisfactory but probably more physiologically relevant. Furthermore, the improvement in speech perception in noise is not consistently associated with the adaptation of HA due to higher processing of complex auditory stimuli or to the possibility that the increased amplification and preprocessing of sounds by HA could lead to a variability of performance (Cubick et al., 2018). In a future study, changes in performance on audiological tests in patients wearing the same

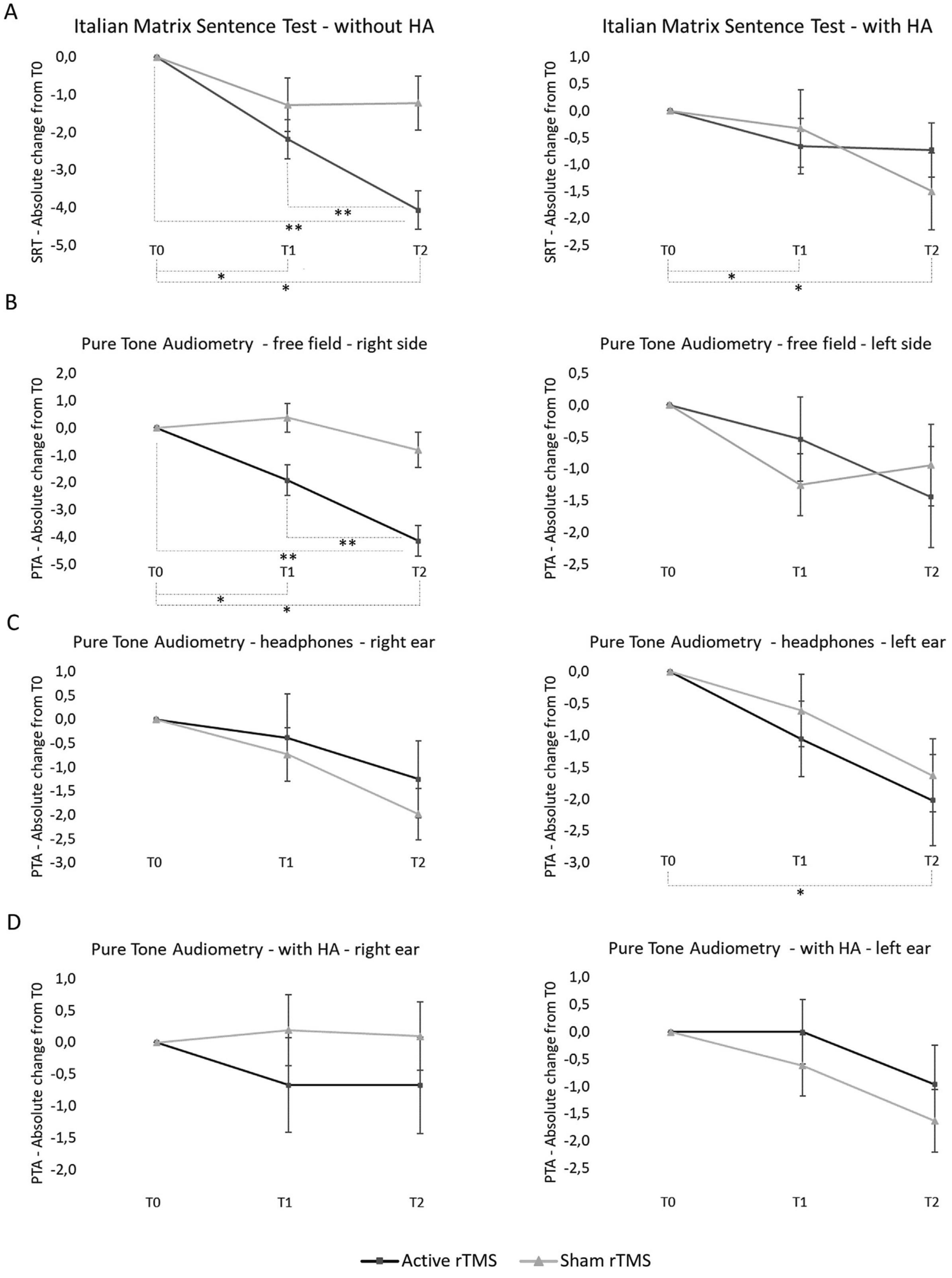

Fig. 2. Audiological assessment results. Legend and abbreviations: *: significant main effect of Timepoint factor; **: significant interaction between Timepoint and Group factors; SRT: speech reception threshold; PTA: pure tone average. **A:** in the Italian Matrix Sentence Test a significant main effect of Timepoint factor was found both in the evaluation without and with HA, with a reduction in SRT at T1 compared to T0 that was maintained at T2. In addition, a significant interaction between Timepoint and Group factors was also found in the analysis performed on the test without HA. Post hoc analysis revealed a lower SRT at T2 compared to T0 and at T2 compared to T1 only in the Active group. **B:** in Pure Tone Audiometry without HA in free field, a significant main effect of Timepoint factor was found with the tone directed to the right ear. This effect was found at T1 and T2 compared to T0. Moreover, a significant interaction between Timepoint and Group factors was also found, with higher performance at T2 compared to T0 and T1 only in the Active group. **C:** in Pure Tone Audiometry without HA using headphones, a main effect of Timepoint factor was found with an higher performance of both experimental groups. **D:** no effects were found in Pure Tone Audiometry with HA.

model of HA could be investigated, to obtain a more valid data in this evaluation condition and hopefully a less variability in results.

Performance on the Italian Matrix Sentence Test has an average SRT of −7.3 ± 0.2 dB in healthy subjects (Puglisi et al., 2015), and performance outside this threshold could indicate a deficit in test performance. In our study, the range of the SRT in patients without HA is from −0.3 to + 32.5 at T0. Therefore, an SRT below the cut-off value of −0.3 and within this range in a patient with SHL could indicate possible eligibility for the rTMS treatment.

A significant change in the PTA threshold was observed in the free field evaluation when pure tones were presented to the right ear of patients, but only in the Active group. This result was partly unexpected, because the peripheral auditory pathway dysfunction was already compensated by the correct use of the HA. This finding may be relevant for future rTMS treatment, as it suggests that the technique may have an effect on pure tone frequency reception, potentially offering new treatment options for deafness. Indeed, a decrease in pure tone audiometric thresholds was observed after TMS treatment in another study of patients with sudden deafness (Zhang and Ma, 2015). In our study, the stimulation triggers an area adjacent to the primary auditory cortex, which is recruited for processing pure tones, as shown in a previous study using the silent-fMRI technique (Yetkin et al., 2003). The reason why the enhancement effect was observed only when the tones were directed to the right ear and not to the left ear is unclear. In the case of sentence reception ability, brain activation occurs in the stimulated brain areas and it is consistent with the finding of a lower SRT after the treatment (Friederici, 2012), but in the case of pure tone reception, activation is different and involves more bilaterally homologous brain areas (Yetkin et al., 2003). In contrast, both experimental groups showed a significant improvement in PTA when pure tones were delivered to the left ear via headphones. Fig. 2 shows a clear trend toward improvement in the PTA that is present in all conditions of Pure Tone Audiometry testing conducted with or without hearing aids, likely due to the previously mentioned practice or placebo effect (Oken et al., 2008; Nuesse et al., 2019).

However, patients with chronic deafness seem to benefit from rTMS treatment especially in the areas of speech reception and comprehension. In fact, the most encouraging result of this study remains the reduction of SRT in noisy conditions, which may contribute to an improvement in the social life of patients with important implications on psychological well-being.

4.1. Limitations of the study and future research

This study represents the initial endeavor to enhance speech comprehension in SHL patients through a NIBS technique. It should be noted that the absence of robust empirical evidence could be seen as a limitation of the research. Additionally, the small sample size constitutes another limitation, although the sample is adequate for a proof-of-concept investigation. The Italian Matrix Sentence Test was used to gauge sentence recognition proficiency, although other speech assessments may be implemented to evaluate patients' ability to comprehend words and sentences. However, common speech tests have the disadvantage that timbre, pitch and loudness of the evaluator can be variable and poorly controllable, and this factor could lead to bias in the interpretation of results. Moreover, an evaluation over a longer period could have highlighted important aspects regarding the long-term improvement of TMS treatment. Network-level functional and connectivity changes were not examined in this study. EEG or fMRI performed before and after the treatment might help to fully understand the neural correlates underpinning the observed behavioral benefits.

The finding of an improvement in the speech perception in SHL patients might have important implications not only for the treatment of the hearing loss, but even for other neurological diseases. For example, patients with progressive cognitive decline usually report serious difficulties in understanding speech in a noisy environment in the first phase of the disease (Ralli et al., 2019). Future studies might investigate whether the improvement of early-stage deafness in Alzheimer Disease by rTMS could somewhat slow down the disease progression or induce some general cognitive benefits.

rTMS treatment was administered to a specific hub within the language network. However, investigations regarding the impact of stimulation carried out on alternative brain nodes, still involved in speech comprehension, should be conducted in future research. Primary auditory cortex stimulation may provide additional results on PTA and offer new therapeutic options beyond the use of HA. Furthermore, it is essential to consider employing various NIBS techniques, including transcranial electrical stimulation (tES), which uses low voltage current to target multiple hubs of the linguistic brain network responsible for receiving and processing verbal messages. Lastly, a speech therapy program might have a possible additional beneficial effect on the linguistic abilities of SHL patients (Denni-Krichel et al., 2011) and the possible effects of concurrent speech therapy combined with TMS should be investigated in a future study.

5. Conclusions

A 5-days rTMS treatment targeting the posterior superior part of the temporal gyrus, which is part of the auditory association cortex, produces a long-term reduction in SRT and PTA in SHL patients and improves their ability to hear a sentence in a background noise context.

Author Contributions

FN, CC MM and SR conceptualized and designed the study protocol. CC, AD and FV enrolled the participants. FN, SaR, CLS, AB and AC collected the data. FN and SR performed statistical analysis. SR, MM and ES oversaw study conduction. FN, SR, CC, MM edited the first draft. All authors critically reviewed the manuscript for content and approve the final version for publication.

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Conflicts of Interest

The authors declare no conflict of interest.

Financial disclosures

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