Research protocol

Roadmap for the use of non-invasive brain stimulation (NIBS) for tinnitus

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ABSTRACT | INTRODUCTION: The demand for effective interventions for tinnitus remains high, with low evidence in conventional therapeutic methods and non-invasive brain stimulation (NIBS). NIBS techniques are an important new alternative for the treatment of tinnitus, in different application modalities such as repetitive transcranial magnetic stimulation (rTMS) and transcranial electrical stimulation (tES). **OBJECTIVE:** The objective of this project is, therefore, to translate the available evidence into safe, personalized clinical practices that are effectively grounded in scientific data through the development of a roadmap for the use of NIBS in tinnitus. **METHODS AND MATERIAL:** Study protocol of a structured roadmap for NIBS use for tinnitus is proposed here based on systematic reviews with meta-analysis. The work team will proceed with that in a period of nine months of work to publish it.

KEYWORDS: Clinical Protocol. Tinnitus. Transcutaneous Electric Nerve Stimulation. Systematic Review.

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1. Introduction

The demand for effective interventions for tinnitus remains high, as it is a problematic symptom to treat and significantly compromises quality of life. It is estimated that between 10% and 25% of the population suffers from tinnitus, often accompanied by comorbidities such as anxiety and depression, and that conventional treatments usually do not provide adequate relief[1].

Given this scenario, non-invasive brain stimulation (NIBS) techniques have gained attention as promising alternatives, as they act to modulate neural circuits associated with the perception of tinnitus. The following modalities have been studied most extensively: repetitive transcranial magnetic stimulation (rTMS) and transcranial electrical stimulation (tES)[1,2].

Tinnitus Reduction System (TNS) is effective in reducing tinnitus symptoms in studies with specific parameters of intensity, frequency, and duration, with evidence still under construction, especially when combined with other interventions[3]. Soleimani et al.[4] found significant medium to large effects of clinical efficacy. However, for the most part, no large multicenter clinical trials of rTMS for tinnitus have been conducted.

In the theta burst modality, Chen et al.[5] demonstrated potential benefits in relation to tinnitus severity, both in a single session and in multiple sessions, and observed a more pronounced effect in tinnitus relief compared to high-frequency TMS.

Among the methods of electrical stimulation, transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS) are the most extensively studied, although with significant variability in protocols and clinical effects[2].

Meta-analyses have revealed that tDCS significantly reduces tinnitus intensity (SMD = –0.35) and discomfort (SMD = –0.50)[6]. Chen et al.[7] evaluated the responses of three clinical studies that used alpha-modulated tACS in the treatment of tinnitus, but no significant results were found. The combination of tDCS and tRNS demonstrated greater efficacy, suggesting a combined potential for reducing tinnitus severity and improving quality of life[5].

Additionally, transcranial auricular vagus nerve stimulation (taVNS) has emerged as a promising therapeutic approach for managing tinnitus. A recent meta-analysis[8] indicates that taVNS can reduce tinnitus-related disability symptoms with a moderate effect size, in addition to effects on perceived intensity and discomfort.

Although there is promising evidence for the use of NIBS in treating tinnitus, the wide variability in stimulation protocols, the scarcity of studies with robust samples, and the still inconsistent findings makes it challenging to consolidate these modalities in clinical practice. Therefore, there is consensus that structured guidelines and clinical roadmaps based on solid evidence are needed to guide decision-making and ensure the safety and efficacy of NIBS use in different contexts.

The roadmaps aim to: provide recommendations to guide the clinical use of NIBS in Brazil; ensure safe, effective, and evidence-based clinical practices; guide professionals and services, reducing variability in the application of protocols and providing ethics and safety; promote equity in access, avoiding a scenario in which only specialized centers in more developed regions benefit from these technologies; support the development of public policies and national regulations on the clinical use of these techniques; strengthen the integration between clinical, research, and healthcare practices, stimulating the training of qualified professionals and the production of scientific knowledge; foster national technological innovation, encouraging the development of protocols adapted to the Brazilian context; and promote open and collaborative science, favoring the sharing of data, results, and resources[9].

The objective of this project is, therefore, to translate the available evidence into safe, personalized clinical practices that are effectively grounded in scientific data through the development of a roadmap for the use of NIBS in tinnitus.

2. Material and methods

This study's design aims to facilitate evidence-based clinical decision-making, constructed, and presented using the roadmap method, based on non-invasive neuromodulation resources used for tinnitus treatment.

The roadmap will follow a structured, multi-stage process coordinated by the Scientific Committee of the Núcleo de Assistência e Pesquisa em Neuromodulação — NAPeN Network (Neuromodulation Assistance and Research Center) and executed by multidisciplinary working groups (WGs). The process will consist of three main stages: literature review, roadmap construction, and expert consensus.

2.1 Steps for developing the decision tree

2.1.1 Step 1: Literature review

To support clinical decision-making, studies with the highest levels of evidence will be sought, such as umbrella reviews and systematic reviews with meta-analyses. Based on these initial reviews, the most reliable clinical studies with the best available outcome results will be sought, as well as indications for application site, protocol parameters, and non-invasive neuromodulation techniques.

2.1.1.1 Step 1.1: Definition of search terms and strategy

The terms used in the searches were extracted from MeSH. Other free terms were also used in the searches, such as synonyms, acronyms, other related terms, or even unrepresented terms. Table 1 shows the terms extracted from MeSH and related free terms (keywords).

Table 1. MeSH descriptors and keywords that formed the basis for the search algorithms

MeSH	Keyword
Tinnitus	Tinnitus
AND	
Magnetic, transcranial stimulation	Repetitive magnetic transcranial stimulation rTMS TMS Non-invasive magnetic brain stimulation
	Theta Burst Stimulation Theta Burst Theta Burst Stimulation TBS
Transcranial Direct Current Stimulation	Transcranial Direct Current Stimulation tDCS Non-invasive brain electrical stimulation
Vagus Nerve Stimulation	Vagus Nerve Stimulation Trans Auricular Vagus Nerve Stimulation taVNS Vagus Nerve Neuromodulation
Transcranial Random Noise Stimulation	Transcranial Random Noise Stimulation tRNS
Transcranial Alternating Current Stimulation	Transcranial Alternating Current Stimulation TACS Non-sinusoidal tACS Amplitude-modulated tACS
AND	
Systematic Review	Systematic Review Umbrella Review Meta-Analysis Scoping Review

Source: the authors (2025).

Based on the choice of descriptors, search strategies were defined in a standardized manner to ensure the efficient retrieval of the best available evidence, as well as to facilitate standardization of updates in subsequent years. The formulation will follow the PICOT structure, using the components: P (Population), I (Intervention), C (Comparison), O (Outcome), and T (Time), which refers to the follow-up period or duration of the intervention until the outcome assessment. These components are connected by the Boolean operator 'AND' and grouped using the Boolean operator 'OR'.

Population: individuals of any age and gender complaining of non-pulsatile tinnitus.

Intervention: non-invasive electrical brain or peripheral stimulation resources.

Comparison: the results of the treated group will be compared with those of the placebo, untreated controls, or other combined resources.

Outcomes of interest: outcomes analyzed in systematic reviews will be considered in the analysis of this study, with special interest in PROMs (Patient Reported Outcome Measures), which include aspects such as:

- Physical and cognitive function;
- Mental health;
- Symptoms (pain, fatigue, etc.);
- Ability to return to work or previous activities;
- Quality of life.

We can cite examples such as:

- Reduction in the Tinnitus Handicap Inventory (THI) post-treatment ;
- Reduction in intensity, discomfort, and suffering on the Visual Analog Scale (VAS);
- Reduction in anxiety/depression scores related to tinnitus;
- Reduction on other scales such as the Tinnitus Handicap Questionnaire (THQ), Tinnitus Severity Index (TSI), etc.

Table 2 shows the search strategies used for the different modalities in the database, configured with the population, type of study, and neuromodulation modality investigated. After running the searches, the search time was limited to the last five years.

Table 2. Search strategies for PubMed

Search strategies for Medline (PubMed)
(((Tinnitus[Title]) AND (Systematic Review[Publication Type] OR Umbrella Review [Publication Type] OR (Scoping Review) [Publication Type] OR Meta-Analysis [Publication Type])) AND ((Repetitive magnetic transcranial stimulation) OR (rTMS) OR (TMS) OR (Non-invasive magnetic brain stimulation)))
(((Tinnitus[Title]) AND (Systematic Review[Publication Type] OR Umbrella Review [Publication Type] OR (Scoping Review) [Publication Type] OR Meta-Analysis [Publication Type])) AND ((Theta Burst) OR (Theta Burst Stimulation) OR (TBS)))
(((Tinnitus[Title]) AND (Systematic Review[Publication Type] OR Umbrella Review [Publication Type] OR (Scoping Review) [Publication Type] OR Meta-Analysis [Publication Type])) AND ((Transcranial Random Noise Stimulation) OR (TRN)))
(((Tinnitus[Title]) AND (Systematic Review[Publication Type] OR Umbrella Review [Publication Type] OR (Scoping Review) [Publication Type] OR Meta-Analysis [Publication Type])) AND (Transcranial Direct Current Stimulation) OR (tDCS) OR (Non-invasive brain electrical stimulation)))
(((Tinnitus[Title]) AND (Systematic Review[Publication Type] OR Umbrella Review [Publication Type] OR (Scoping Review) [Publication Type] OR Meta-Analysis [Publication Type])) AND ((Vagus Nerve Stimulation) OR (Trans Auricular Vagus Nerve Stimulation) OR (taVNS) OR (Vagus Nerve Neuromodulation)))
(((Tinnitus[Title]) AND (Systematic Review[Publication Type] OR Umbrella Review [Publication Type] OR (Scoping Review) [Publication Type] OR Meta-Analysis [Publication Type])) AND ((Transcranial Alternating Current Stimulation) OR (TACS) OR (non-sinusoidal tACS) OR (amplitude-modulated tACS)))

Source: the authors (2025).

2.1.1.2 Step 1.2: data search

After defining the search terms and strategies, two researchers will independently search for articles exclusively in the Medline database (via PubMed).

The objective will be to select from three to five systematic reviews with meta-analyses for each topic that meet the following criteria:

- Reviews published in the last five years, without language restrictions;
- Reviews that pass through the following steps: study selection, risk of bias analysis, and data extraction. The reviews will be performed by two independent authors;
- The use of appropriate statistical methods will be mandatory: use of standardized mean difference for the outcome measures including in the meta-analyses will be an inclusion criteria;
- Reviews must evaluated selected clinical trials using standardized tools for the quality evaluation, such as the Cochrane Risk of Bias Tool or PEDro — Assessment of Risk of Bias, for example;

- Reviews presenting effect size data on the use of neuromodulation on tinnitus-related symptoms. From each selected clinical trial, whether in a forest plot, table, or described in the text, but this analysis must be objectively presented and available with numerical outcomes;
- Articles from predatory journals will be excluded.

After searching and organizing the results, two authors will independently pre-select articles and filter them according to the above criteria by comparison and consensus.

Based on the selected studies, analyzed and significant clinical trials cited in the systematic reviews with meta-analyses will be selected and the present protocols will be extracted with their clinical effect. The possibility that they can be indicated and prescribed in clinical practice will also be discussed. The clinical trials selection will follow the following procedures:

- Randomized, sham-controlled, clinical trials;
- Clinical trials demonstrating scientific efficacy, and with their confidence interval in the forest plot not touching the null line;
- Clinical trials with largest effect size (avoiding the null line) and with the lowest sample heterogeneity (and the lowest confidence interval);
- Clinical trials reporting the larger samples for effect size (larger square on the forest plot);
- Articles from predatory journals will be excluded.

2.1.1.3 Step 1.3: extraction of clinical trials data

This step will be separated into two parts:

Collection of data from the reviews: from which the following will be extracted: outcomes, outcome measures, and type of stimulation from randomized clinical trials with the largest effect size for designing the significant effect protocol.

Collection of data from the randomized relevant clinical trials: from which the information on each protocol features, location of protocol using 10-20 EEG system, effect sizes of the outcome measures will be extracted.

2.1.2 Step 2. Construction of the infographic

Construction of the Infographic: the infographic aims to allow that the information collected will be visually organized and reflect the literature review into an objective minimalist and simple flowchart. This step aims to provide assessment and intervention protocols in a planned graphical manner, where the most relevant interventions options, analyzed with their effect sizes and identified in the literature were present. This will facilitate clinicians' decision-making in selecting treatment protocols with neuromodulatory techniques for tinnitus.

The most commonly used outcome measures will be extracted from the clinical trials, and along with the criteria for each intervention protocols, and respecting percentage improvement, will bring to the clinician the more actual evidence for each patient proposed intervention.

The percentage change between pre- and post-intervention measurements was calculated using the formula:

$$\Delta\% = (Mean_{post} - Mean_{pre} / Mean_{pre}) \times 100$$

where $Mean_{pre}$ and $Mean_{post}$ represent the mean values before and after the intervention, respectively, when the study presented the results only in graphs, we extracted the data using WebPlotDigitizer[10].

At this stage of constructing the infographic, a critical analysis of tinnitus evaluation instruments presented in clinical trials will be guided, along with search into the best evidence for the instruments for each purpose. The selected instruments for assessment will be considered if they are validated and adapted for the Brazilian population.

The evidence gathered in step 1 will be synthesized into a visual decision-making flowchart (infographic) for each technique (rTMS, tDCS, TBS, TaVNS, tRNS, and tACS separately). The roadmap will include:

Indications: outcomes with proven efficacy, linked to specific stimulation targets.

Prescription — stimulation targets: selection of cortical regions prioritized by effect size or frequency of use in literature. When meta-analyses include subgroup analyses by stimulation site, the site with the largest effect size will be selected. In the absence of meta-analyses with subgroups, the stimulation sites most frequently cited in the data extraction table will be prioritized for consideration.

Prescription — protocol parameters: ordered by effect size, starting with the protocol with the most robust evidence (Protocol 1) and including alternative protocols (Protocol 2, 3, etc.) for cases of unsatisfactory clinical response.

Expected results: effect size values and expected clinical changes for each protocol, based on the NIBS-treated group in the included RCTs.

Alternative protocols: evidence-based options, tested in other populations or on central nervous system (CNS) targets relevant to the same outcome, but whose efficacy has not yet been confirmed by meta-analyses.

Observations: additional considerations regarding the treatment phase (acute, subacute, chronic), safety, prognostic factors, and practical recommendations for clinical application.

Flowcharts will be designed to maximize clarity, clinical applicability, and consistency with the structure of the International Classification of Functioning, Disability, and Health (ICF).

2.1.3 Step 3. Round for specialists

This step will aim to evaluate the decision flowchart created by third-party experts who will be unbiased in the research step and in the development step. The experts will be invited to give their opinion using their knowledge and expertise on the decision tree. Their consideration identifying possible flaws or areas for improvement in the infographic will be discussed and in agreement guide any adjustments to the flowchart. This phase will enable these adjustments and will enhance the clinical evidence and applicability, with accuracy of the tree before its present to a clinical setting.

For the roadmap validation phase, the authors will select eight experts in NIBS and tinnitus. The eligibility criteria for the selection of experts will include: (1) clinical experience in the application of non-invasive neuromodulation for tinnitus; (2) active affiliation with a research institution or health service in Brazil; and (3) representation of different geographic regions to ensure greater applicability and diversity of perspectives.

After approximately four weeks of testing and evaluation, the WGs will conduct individual interviews with each expert, either via videoconference or in person. The purpose of these interviews will be to gather comprehensive feedback on the usability, design, and applicability of the roadmap, as well as to identify recommendations for adjustments. The WGs will use a standardized interview script, defined after the study protocol, to ensure consistency between interviews.

The questionnaire administered to experts will cover three main areas:

1. Applicability — Assess whether the roadmap is relevant to the neurological and psychiatric conditions described; whether the outcomes and outcome measures are clearly defined and aligned with best clinical practices; and whether the proposed neuromodulation protocols are appropriate, well represented, and contain all the information necessary (frequency, intensity, duration, and number of sessions) for clinical application.

2. Feasibility — Consider whether the application is feasible in the institution or in the specialist's practice context, considering available resources, costs, time required for implementation, and integration with existing care flows. Additionally, assess whether the roadmaps include all necessary information, such as safety, monitoring of adverse effects, inclusion/exclusion criteria, and recommendations for patient follow-up.

3. Design — Examine whether the flowchart is visually apparent, logically structured, and easy to understand; whether the use of colors, shapes, and arrows aids comprehension; whether captions and symbols are understandable; and whether the layout balances simplicity and detail, facilitating efficient monitoring and real-time decision-making. It will also be verified whether the design is standardized and consistent throughout the material, ensuring visual coherence and reducing ambiguities, considering the accessibility of the material for professionals with different levels of experience.

After data collection, the WGs will systematically review the feedback from experts to identify necessary adjustments to the roadmap. After incorporating these modifications, the final version of the roadmap

will be submitted for review and approval by the NAPeN Network Steering Committee (KMS, AFB, and KNS). Consensus will be defined in advance as at least 75% agreement among participants. This process will be repeated until consensus is reached, and the final validated version of the roadmap will be consolidated based on the experts' agreement.

2.1.4 Step 4. Presentation of results

The results of the research, analyses, and infographics will be presented to the scientific community at a specific annual event organized by the NAPEN Network and submitted for publication in a scientific journal.

2.1.5 Step 5. Publication and updating

The findings are expected to be updated annually (at most every two years), repeating the searches, selections, and analyses, and modifying the infographics with the new findings from the literature.

2.1.6 Step 6. Dissemination of knowledge

It is expected that free access to updated versions of the roadmaps will be maintained on the NAPEN network website for access, used in various clinical contexts, dissemination in academic, clinical, and human resources training settings, as well as in the general public.

3. Schedule

Table 3. Schedule of planned activities for the project

STEPS	SUB-STEPS	Months/year
STEP 1	*Step 1.1*	September 2025
	Step 1.2	October 2025
	Step 1.3	November 2025
STEP 2		December 2025
STEP 3		February 2026
STEP 4		May 2026
STEP 5		June 2026
STEP 6		July 2026

Source: the authors (2025).

Authors contributions

The authors declared that they have made substantial contributions to the work in terms of the conception or design of the research; the acquisition, analysis, or interpretation of data for the work; and the writing or critical review for relevant intellectual content. All authors approved the final version to be published and agreed to take public responsibility for all aspects of the study.

Competing interests

No financial, legal, or political conflicts involving third parties (government, private companies, and foundations, etc.) were declared for any aspect of the submitted work (including but not limited to grants and funding, advisory board participation, study design, manuscript preparation, statistical analysis, etc.).

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