

Non-invasive brain stimulation for the treatment of neurological and psychiatric disorders and for improving physical performance: protocol of umbrella reviews

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ABSTRACT | BACKGROUND: With the increasing meta-analysis studies of noninvasive brain stimulation (NIBS) a major review has become a logical step to provide evidence to support decision-makers. **OBJECTIVE:** Umbrella reviews of the Working-Group of NAPeN Network (a Brazilian scientific network for NIBS development) will summarize the results of existing evidence in meta-analysis with focus on NIBS techniques applied for clinical settings, exercise and sports science. **METHODS AND MATERIALS:** Firstly, a screening was performed to identify meta-analysis in which NIBS were applied to neurological and psychiatric disorders and healthy subjects. A second literature search was conducted in the Pubmed using a PICO-question for each population and NIBS techniques found in the first search. Methodological quality and certainty of evidence will be evaluated using the AMSTAR 2 and GRADE framework, respectively. **PARTIAL RESULTS:** After the first search, we found meta-analyses including repetitive transcranial magnetic stimulation and transcranial direct current stimulation, applied in populations with neurological (cerebral palsy, chronic pain, dementia, epilepsy, essential tremor, multiple sclerosis, Parkinson's disease, tinnitus, tourette syndrome, and stroke) and psychiatric disorders (anxiety, attention-deficit hyperactivity, autism spectrum, obsessive-compulsive and post-traumatic stress disorders, schizophrenia, craving/addiction and depression), and in healthy subjects. A total of 118 meta-analyses will be included in the qualitative review. The results of evidence were identified in the outcomes of six umbrella reviews. **CONCLUSION:** Evidence of therapeutic and nontherapeutic use of NIBS techniques will support experts to produce consensus statements and assist professionals in making decisions of incorporating or not NIBS into clinical practice.

KEYWORDS: Transcranial magnetic stimulation. Transcranial direct current stimulation. Evidence-based medicine. Systematic review.

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Introduction

Non-invasive brain stimulation (NIBS) has been widely explored as a possible technical adjuvant for augmenting the efficacy of customarily used rehabilitative treatments of persons with neurological and psychiatric disorders¹⁻⁵, and for increasing the physical performance of healthy subjects and athletes.⁶⁻¹⁰ NIBS refers to a set of techniques that employs noninvasively electrical or magnetically-induced currents to modulate excitability of the specific brain areas and its networks.¹¹ By stimulating the cortical surface regularly over a period of time, NIBS modulates a mix of non-neuronal and neuronal cell populations^{12,13} and may activate, inhibit, or otherwise interfere with the local cortical activity, depending on the parameters of stimulation used.^{4,14} These effects are spread-out via structural and/or connectivity to other areas involved in the network corresponding to the stimulated area, with the aim of establishing optimal neural activity between their nodes.¹⁵

In recent decades, NIBS techniques have been used therapeutically to normalize aberrant patterns of cortical activity and ameliorate abnormal brain function for management of several neurological disorders including chronic pain^{16,17}, motor function, cognitive and communication impairments caused by stroke¹⁸⁻²², or neurodegenerative diseases²³⁻²⁵, or psychiatric disorders such as depression^{26,27}, anxiety disorders^{28,29}, obsessive-compulsive disorder^{30,31}, schizophrenia^{32,33}, and craving/addiction.^{34,35} In addition, some studies using NIBS have shown promise effects in improving motor performance in non-athletes^{9,36} and athletes.^{37,38}

NIBS techniques, mainly repetitive transcranial magnetic stimulation (rTMS), have been regulated for clinical use in many countries.^{5,39} In Brazil, since that some professional societies including the national medical (Conselho Federal de Medicina; only rTMS), physiotherapy councils (Conselho Federal de Fisioterapia e Terapia Ocupacional)^{5,39}, and recently, the speech therapy council (Conselho Federal de Fonoaudiologia), approved and regulated the clinical use, TMS and the transcranial direct current stimulation (tDCS) are routinely found in clinical practice.

Considering the massive literature on NIBS, it is a challenge for health professionals to make the best decision on the use of specific techniques in

their practice, which faces the necessity of practice guidelines. Consensus statements and guidelines are used to clarify and standardize practice, to assist professionals in making decisions and to provide a consistent approach across health policy.⁴⁰ The lack of guidelines may generate wide variation of practice among professionals, and result in inconsistencies in care and treatment.⁴¹

Ideally, the first step in developing a guideline is the overview of the existing evidence-based literature.⁴⁰ Therefore, through a series of umbrella reviews, we will present the results of the Working-Group on scientific evidence for the use of non-invasive brain stimulation within the NIBS Brazilian Guidelines Development group of the NAPeN Network (Núcleo de Assistência e Pesquisa em Neuromodulação - www.neuromodulation-net.com). The NAPeN is a scientific organization composed of professionals interested in the development of neuromodulation through an ecosystem of shared initiatives in teaching, research and assistance.

Umbrella reviews are qualitative meta-synthesis of systematic reviews or meta-analyses that aim to synthesize its findings and to investigate its bias.⁴² Therefore, they contribute to a higher contextual understanding of a specific question or topic. Not surprisingly, they have been considered the highest levels of evidence synthesis currently available.⁴³ There is some previous umbrella reviews regarding the use of NIBS to treat some psychiatric conditions, however they focused on the treatment of each disease, separately.⁴⁴⁻⁴⁶ The umbrella reviews of the NAPeN Network will summarize the evidence for the application of NIBS techniques to the treatment of some dysfunctions related to the neurological or psychiatric disorders and in improving motor performance in healthy people and athletes. Expanding the knowledge on the application of NIBS is a crucial step towards incorporating it into practice.

Methods

Study design and registration

The Working-Group on evidence to NIBS use of the NAPeN Network met regularly via video conference from May to September 2020 to discuss, define, and develop methods to conduct the umbrella reviews.

The Working-Group (35 members) consists of clinical scientists, experts in the field of brain stimulation and master's and doctoral students with experience in conducting systematic reviews. The results obtained by the Working-Group will be presented in a series of umbrella reviews. The protocol of umbrella reviews was registered in the International Prospective Register of Systematic Reviews (on February 25th, 2021).

Information Source and Search Strategy

Preliminary, searches of meta-analysis were conducted through an initial screening in the PubMed database to identify populations with neurological and psychiatric disorders which have been treated with one of the NIBS techniques: transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), transcranial cerebellar direct current stimulation (tcDCS), transcutaneous spinal direct current stimulation (tsDCS), transcutaneous vagus nerve stimulation (tVNS), high-definition transcranial direct current stimulation (HD-tDCS), repetitive transcranial magnetic stimulation (rTMS), theta burst stimulation (TBS), and cerebellar repetitive transcranial magnetic stimulation (crTMS). In addition, complementary searches were made to identify studies of physical performance in healthy subjects. We elaborated 20 PICO-based questions based on NIBS techniques and populations identified from this first search strategy (Table 1). After that, we searched the PubMed database using keywords corresponding to the PICOS design (Supplementary Material, S1). The timeframe of the search was from 8th February until 15th July 2020 and updated in September 2021. The search strategy for each PICO-question was formulated by a team of three researchers of Working-Group, in which at least one of them was expert in the subject under investigation.

Table 1. Pico-Question formulated after the first PUBMED database searching (to be continued)

Neurological conditions
In patients with CEREBRAL PALSY , how does noninvasive brain stimulation affect disease symptoms when compared to sham/no/other intervention approaches?
In patients with CHRONIC PAIN , how does noninvasive brain stimulation affect the symptoms when compared to sham/no/other intervention approaches?
In patients with DEMENTIA , how does noninvasive brain stimulation affect disease symptoms When compared to sham/no/other intervention approaches?
In patients with EPILEPSY , how does noninvasive brain stimulation affect disease symptoms When compared to sham/no/other intervention approaches?
In patients with ESSENTIAL TREMOR , how does noninvasive brain stimulation affect the symptoms When compared to sham/no/other intervention approaches?
In patients with MULTIPLE SCLEROSIS , how does noninvasive brain stimulation affect disease symptoms when compared to sham/no/other intervention approaches?
In patients with PARKINSON'S DISEASE , how does noninvasive brain stimulation affect disease symptoms when compared to sham/no/Other intervention approaches?
In patients with SPINAL CORD INJURY , how does noninvasive brain stimulation affect disease symptoms when compared to sham/no/other intervention approaches?
In patients with STROKE , how does noninvasive brain stimulation affect disease symptoms when compared to sham/no/other intervention approaches?
In patients with TINNITUS , how does noninvasive brain stimulation affect disease symptoms when compared to sham/no/other intervention approaches?
In patients with TOURETTE'S SYNDROME , how does noninvasive brain stimulation affect disease symptoms when compared to sham/no/other intervention approaches?
Psychiatric conditions
In patients with ANXIETY disorder, how does noninvasive brain stimulation affect the symptoms when compared to sham/no/other intervention approaches?
In patients with ATTENTION DEFICIT HYPERACTIVE DISORDER how does noninvasive brain stimulation affect the symptoms when compared to sham/no/other intervention approaches?

Table 1. Pico-Question formulated after the first PUBMED database searching (conclusion)

Psychiatric conditions
In patients with AUTISM SPECTRUM DISORDER , how does noninvasive brain stimulation affect the symptoms when compared to sham/no/other intervention approaches?
In patients with CRAVING , how does noninvasive brain stimulation affect the symptoms when compared to sham/no/other intervention approaches?
In patients with DEPRESSION , how does noninvasive brain stimulation affect the symptoms when compared to sham/no/other intervention approaches?
In patients with OBSESSIVE COMPULSIVE DISORDER , how does noninvasive brain stimulation affect the symptoms when compared to sham/no/other intervention approaches?
In patients with POST-TRAUMATIC STRESS DISORDER , how does noninvasive brain stimulation affect the symptoms when compared to sham/no/other intervention approaches?
In patients with SCHIZOPHRENIA , how does noninvasive brain stimulation affect the symptoms when compared to sham/no/other intervention approaches?
Motor performance
In ATHLETES or HEALTHY SUBJECTS , how does noninvasive brain stimulation may improve the motor performance when compared to sham/no/other intervention approaches?

Source: author's own elaboration (2022).

Study Selection and Data Extraction

For each PICO-question, the titles and abstracts of articles found will be screened by two reviewers independently. The full text of all potential reviews will be then screened by the same two reviewers based on predefined inclusion criteria. Any discrepancies between reviewers will be resolved through discussion or by consensus with a third independent reviewer (the expert of the team).

We will include systematic reviews with meta-analyses in English of controlled trials (CTs). Reviews of physiologic surrogate outcomes or animal studies will be excluded. Studies will be also excluded if comparison between two active NIBS techniques were made. Meta-analysis published before 2015 will be excluded and if it is an update of a previous meta-analysis, the most recent update will be selected. The eligibility criteria based on PICOS design are shown in Table 2.

Table 2. Eligibility Criteria for Considering Articles for the Umbrella Review

Criteria	Inclusion	Exclusion
Population (P)	Population with neurological and psychiatric disorders or healthy subjects which has been treated with one of the NIBS techniques	Animal studies
Intervention (I)	tDCS, rTMS, TBS, tACS, tRNS, tcDCS, crTMS, tsDCS, tvNS, and HD-tDCS	Association of two or more active NIBS techniques in the same intervention
Comparison (C)	Sham NIBS or no intervention associated or not with another approach of treatment (i.e., medication, physical therapy, occupational therapy, cognitive training, etc)	Comparison between two active NIBS techniques (ex. rTMS vs. tDCS)
Outcome (O)	Changes in the disease symptoms or changes in motor performance of healthy subjects.	Surrogate outcomes
Study design	Systematic reviews with meta-analysis of CT randomized or not; published in English	Meta-analysis without qualitative analysis Meta-analysis published before 2015

Legend: crTMS - cerebellar repetitive transcranial magnetic stimulation; CT - clinical trials; HD-tDCS - high-definition transcranial direct current stimulation; NIBS - non-invasive brain stimulation; RCT - randomized clinical trials; rTMS - repetitive transcranial magnetic stimulation; tACS - transcranial alternating current stimulation; TBS - theta burst stimulation; tcDCS - transcranial cerebellar direct current stimulation; tDCS - transcranial direct current stimulation; tRNS - transcranial random noise stimulation; tsDCS - transcutaneous spinal direct current stimulation; tvNS - transcutaneous vagus nerve stimulation.

Source: author's own elaboration (2022).

One of the two reviewers will extract data from the studies using a standardized extraction form including study characteristics (name of the first author, publication year and number of studies), type of NIBS and control intervention and number of participants in each group, outcome measures, protocol of stimulation, number of sessions, adverse events and results (effect size and its related 95%CI). The result of each plot of meta-analysis will be extracted separately. The other reviewer will check the form to ensure whether the extracted data are accurate and consistent.

Methodological Quality Assessment

The methodological quality of included meta-analysis will be assessed by the same two reviewers using the Assessment of Multiple Systematic Reviews 2 (AMSTAR 2) (available at <http://amstar.ca/Amstar-2.php>). The AMSTAR 2 was developed to rate the quality of systematic reviews and meta-analyses and includes 16 criteria referring to relevant methodological aspects of studies.

The quality of each included meta-analysis will be assessed considering critical (items 2, 4, 7, 9, 11, 13 and 15) and non-critical flaws of the AMSTAR 2. We will classify the meta-analysis as "high quality" (no or one non-critical weakness), "moderate quality" (more than one non-critical weakness), "low quality" (one critical flaw with or without non-critical weaknesses) and "critically low" (more than one critical flaw with or without non-critical weaknesses).⁴⁷ Any discrepancies between reviewers will be resolved by the third reviewer.

Evidence Quality Assessment

The two reviewers will assess the evidence quality for each outcome of meta-analysis using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The GRADE was developed to rate the quality of the best available evidence and develop health care recommendations.⁴⁸ The analysis includes five main criteria: risk of bias, inconsistency, indirectness, imprecision and publication bias.⁴⁹ We will consider the AMSTAR 2 classification to rate the methodological quality of included meta-analyses.

Any discordance between reviewers will be solved by consensus or by the third reviewer. The GRADE tool will provide a rating of high, moderate, low or very low quality and a weak or strong recommendation for each outcome.

Before the review starts, the working group members attended five training meetings via video conference, thus promoting consistency in conducting the review process among PICO-question teams. Finally, a Summary of Findings (SoF) table will be presented for each Outcome PICO, using the GRADEpro tool, available at <http://gradepr.org>. Outcomes considered important (rated 4-6) or critical (rated 7-9) for decision-making should be included in the evidence profile and SoF table.⁵⁰

Results

After the first search, we found only meta-analyses evaluating the effectiveness of two NIBS techniques, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). The studies investigated the effects of rTMS and tDCS in several population with neurological (cerebral palsy, chronic pain, dementia, epilepsy, essential tremor, multiple sclerosis, Parkinson's disease, tinnitus, tourette syndrome, and stroke) and psychiatric disorders (anxiety disorders, attention deficit hyperactivity disorder, autism spectrum disorder, craving/addiction, depression, obsessive-compulsive disorder, schizophrenia, and post-traumatic stress disorder).

After the PICO-question screening (second search), search strategies in PubMed yielded 1206 results, in total. After the removal of duplicates, 461 articles were identified but only 205 remained after reading titles and abstracts. Of these, 114 will be included in the qualitative analysis. Table 3 shows the flow diagram of study selection for each PICO-question.

Table 3. Flow diagram of study selection for the umbrella reviews

Population	Total screened	Excluded in screening due to:					Full-text Included	Eligibility		Total for the qualitative assessment		
		Duplicated	P	I	CO	S		Total	Full-text articles excluded		Reason (n)	
ADHD	63	29	1	1	0	3	1	58	5	1	recent update (1)	4
ASD	6	0	0	0	0	2	2	4	2	0	-	2
Anxiety	32	10	4	1	0	0	9	24	8	5	another language (1) recent update (4)	3
OCD	22	14	0	1	0	1	0	16	6	0	-	6
PTSD	17	9	1	2	0	0	2	14	3	1	NA (1)	2
Cerebral palsy	53	19	25	1	0	0	5	50	3	0	-	3
Craving	62	37	15	0	0	0	4	56	6	1	recent update (1)	5
Dementia	80	65	0	1	2	0	0	68	12	4	recent update (4)	8
Epilepsy	23	13	0	1	0	2	3	19	4	0	-	4
Essential tremor	35	5	18	0	0	2	9	34	1	1	Did not perform a separated analysis between NIBS techniques NA (1), another language (5), recent update (17)	0
Mood disorders	198	116	2	6	6	14	12	156	42	23	recent update (17)	19
Multiple sclerosis	24	21	0	0	0	0	2	23	1	0	-	1
Spinal cord injury	14	10	0	0	0	1	2	13	1	0	-	1
Parkinson's disease	105	68	8	6	0	0	8	90	15	7	recent update (7)	8
Pain	110	88	0	0	0	0	0	88	22	10	recent update (9), absence of a control group (1) another language (5), t	12
Schizophrenia	117	84	0	0	1	2	10	97	20	12	recent update (7) surrogate outcome (14), recent update (3), other reason (8)	8
Stroke	196	118	3	7	0	6	14	148	48	25	recent update (14), recent update (3), other reason (8)	23
Tinnitus	23	12	0	1	0	1	4	18	5	1	recent update (1)	4
Tourette's syndrome	26	4	16	0	0	1	4	25	1	0	-	1
Total	1206	745	93	28	9	35	91	1001	205	91	-	114

Legend: ADHD - attention deficit/hyperactivity disorder; ASD - autism spectrum disorder; n - number of studies; NA - not applicable; OCD - obsessive compulsive disorder; PTSD - Post-traumatic stress disorder; P – population; I – intervention; C – comparison; O – outcome; S – study design.

Source: author's own elaboration (2022).

The results of evidence on effectiveness of NIBS techniques will be present for outcomes in six umbrella reviews: 1) for the treatment of general functioning and disability of subjects with neurological disorders (stroke, Parkinson's disease, cerebral palsy and spinal cord injury), 2) for the treatment of non-motor symptoms of subjects with neurological disorders (stroke, Parkinson's disease, cerebral palsy and spinal cord injury, autism spectrum disorder, multiple sclerosis), 3) for the treatment of subjects with communication disorders (stroke and Parkinson's disease), 4) for the management of pain (neuropathic and nociceptive pain), 5) for the treatment of subjects with mental disorders (general anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder and panic disorder), and 6) for the physical performance of healthy subjects and athletes.

Discussion

There are numbers of meta-analyses evaluating the effectiveness of two of the most common NIBS techniques, rTMS and tDCS, for the treatment of persons with neurological and psychiatric disorders and for increasing the physical performance of healthy subjects and athletes. In parallel with scientific growth, rTMS and tDCS are also being increasingly used in clinical practice. Particularly in countries where NIBS techniques are commonly used in clinical settings, guideline development is crucial for ensuring high quality and safety patient care.

An umbrella review is a review published meta-analyses, which is viewed as one of the four next-generation meta-analyses, that aimed raise the bar and help shape a new generation of more reliable evidence synthesis.⁵¹ Recently, four umbrella reviews were published regarding the effects of non-invasive neuromodulation approaches for therapeutic use. Three investigated mental disorders^{44,52,53}, and one other, the improvement of cognitive outcomes in healthy and neuropsychiatric individuals.⁴⁵

Razza et al. aimed to investigate the use of NIBS in the control of depression⁴⁴ and another umbrella review summarized the use of invasive and non-invasive

brain stimulation techniques to treat general mental disorders.⁴⁶ Nonetheless, another anxiety disorders as panic disorders are not specifically investigated through an umbrella review. Xie and colleagues focused of rTMS therapies for the treatment of post-stroke patients.⁵² However, other clinically important outcomes for post-stroke patients as motor impairment, balance and pain⁵³ are not comprised in the analysis.

Farhat and colleagues evaluated the effects of prefrontal active vs sham tDCS on different domains of cognition among healthy and neuropsychiatric individuals.⁴⁵ However, the same outcome was still not explained in neurological disorders and the effects of magnetic stimulation were not investigated. As far as we know there is no other umbrella review regarding the use of non-invasive neuromodulation techniques for the treatment of other neurological disease and for the physical performance of healthy subjects and athletes.

We will perform rigorous PICO-driven research aimed to provide the best scientific evidence to support an initiative of NAPeN Network in developing a national guideline. In addition, our study will help health professionals to select an appropriate practice and in making decisions of incorporating or not NIBS techniques into clinical practice. This umbrella review will use data from secondary sources and will not involve interactions with study participants; it is thus exempt from ethical approval. The results of our umbrella reviews will be published in a peer-reviewed journal, and we believe that the result will benefit clinical practitioners, patients and policy-makers.

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Authors' contribution

Baptista AF, Sá KN, Tanaka C and Monte-Silva K created the idea that originated the work and elaborated the hypotheses. Shirahige L, Baptista AF, Sá KN, Baltar A, Marques D, Carneiro MS, Brito R, Brunoni A, Monte-Silva K and NAPeN Working Group structured and performed the methods. Shirahige L and Monte-Silva K drafted the manuscript. All authors reviewed the manuscript.

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Conflict of interest

Shirahige L, Baltar A, Marques D, Carneiro MS and Brito R work at a private non-invasive brain stimulation clinic. Baptista AF, Oda AL, Okano A, Brunoni A and Monte-Silva K are instructors at the non-invasive neuromodulation training program at São Paulo University (USP)/NAPeN. Sá KN and Tanaka C are coordinators of the non-invasive neuromodulation training program at São Paulo University (USP)/NAPeN. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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