European Journal of Pain

REVIEW ARTICLE

Evidence-Based Umbrella Review of Non-Invasive Neuromodulation in Chronic Neuropathic Pain

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Received: 27 August 2024 | **Revised:** 19 December 2024 | **Accepted:** 7 January 2025

Funding: A.F.B. acknowledges receiving a grant for scientific productivity from CNPq (Brazil). E.C.D. received a grant from FAPERJ (23/2021 and 26/2021) during the study development. T.S.L. received a postdoctoral grant from CAPES (process number: 88887.801519/2023-00). R.D.M. received a PhD grant from UFABC during the study development. M.M.A. received a MSc grant from UFABC and a capacitation grant from CAPES-Print (International Program of Internationalisation, CNPq (Brazil)-process: 88887.935462/2024-00) during the study development.

Keywords: chronic pain | neuropathic pain | non-invasive brain stimulation

ABSTRACT

Background and Objective: Non-invasive neuromodulation techniques (NIN), such as transcranial Direct Current Stimulation (tDCS) and repetitive Transcranial Magnetic Stimulation (rTMS), have been extensively researched for their potential to alleviate pain by reversing neuroplastic changes associated with neuropathic pain (NP), a prevalent and complex condition. However, treating NP remains challenging due to the numerous variables involved, such as different techniques, dosages and aetiologies. It is necessary to provide insights for clinicians and public healthcare managers to support clinical decision-making. This umbrella review aims to consolidate existing evidence on the effectiveness of various NIN in managing chronic NP.

Databases and Data Treatment: A systematic search was conducted in the PubMed/MEDLINE database, including meta-analyses of controlled trials comparing NIN techniques with sham interventions for NP treatment. The quality of included studies was assessed using the AMSTAR-2 tool and the GRADE system, with effect sizes adjusted to the standard mean difference (SMD).

Results: The review included 22 meta-analyses comprising 8151 participants from 214 controlled trials. The most investigated NIN techniques were tDCS and rTMS, with primary targets being the motor cortex and dorsolateral prefrontal cortex. The findings suggest that excitatory protocols, particularly high-frequency rTMS and anodal tDCS, are effective in reducing pain intensity in individuals with NP. However, the overall quality of evidence was rated low, primarily due to heterogeneity among studies and small sample sizes.

Conclusion: NIN techniques show promise in managing NP, with potential benefits in pain reduction. However, further high-quality research is needed to establish optimal protocols and long-term effects.

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Significance Statement: This paper consolidates the evidence regarding non-invasive neuromodulation for the treatment of neuropathic pain, including differentiating the most effective techniques based on the aetiology of pain, and provides clinicians with easy access to this critical information. It also highlights key aspects that require further research in the field of non-invasive neuromodulation and neuropathic pain.

1 | Introduction

Neuropathic pain is a prevalent and complex health condition that impacts 7%–10% of the global population, placing a considerable burden on individuals and healthcare systems alike (Cohen, Vase, and Hooten 2021). Non-invasive neuromodulation is widely researched and applied as a treatment approach to this population because of its pain-relieving effects (Xiong, Zheng, and Wang 2022). It holds the potential to reverse neuroplastic alterations associated with neuropathic pain, encompassing intracortical disinhibition, shifts in corticospinal excitability, blood flow and grey matter reduction within mesencephalic brain regions, as well as the deficits in the pain descending inhibition pathway (Naro et al. 2016).

There are several non-invasive neuromodulation techniques (NINs) used for neuropathic pain control with different action mechanisms (Baptista et al. 2023). Among these, non-invasive brain stimulation (NIBS) which includes transcranial Direct Current Stimulation (tDCS) and repetitive Transcranial Magnetic Stimulation (rTMS) are the most extensively investigated modalities (Xiong, Zheng, and Wang 2022). In the majority of neuropathic pain studies, stimulating the dorsolateral prefrontal cortex (DLPFC) and motor cortex (M1) through excitatory interventions, such as anodal tDCS or high-frequency rTMS, have the most robust efficacy for reducing pain intensity in chronic pain individuals (Hamid, Malik, and Hussain 2019). However, despite the existence of a substantial number of meta-analyses and guidelines addressing this subject (Baptista et al. 2019; Lefaucheur and Nguyen 2019), the establishment of the optimal practices for neuropathic pain patient care remains imperative. Additionally, other stimulation techniques, such as Transcranial Electrical Stimulation (Takeuchi 2023), Trans-spinal Electrical Stimulation (Rahman et al. 2022) and Peripheral Electrical Stimulation (Shao et al. 2023) and Trans-spinal Magnetic Stimulation (Hodaj et al. 2023), have been investigated, showing potential benefits in the treatment of chronic pain individuals (Lopes et al. 2023).

Clinical trials focusing on NIBS in the context of neuropathic pain have revealed a significant range of effect sizes, probably due to the intricate interplay of factors such as diverse aetiologies and origins of neuropathic pain, the multidimensional impact of pain and the heterogeneity of intervention parameters. Other important information for clinicians decision-making is about the efficacy of tDCS or rTMS stimulation on other brain targets, or the usage of different NIBS techniques, their limitations and future applications (Ciampi de Andrade and García-Larrea 2023).

To consolidate existing knowledge and evidence about the utilisation of NIBS for neuropathic pain management, the present umbrella review was performed. It includes a wide array of NIBS approaches and neuropathic pain conditions to aid clinicians and public healthcare managers in supporting their clinical decision-making. This umbrella review constitutes an integral facet of a larger series of analogous investigations conducted by the NAPEN Network (Núcleo de Assistência e Pesquisa em Neuromodulação; Shirahige et al. 2021; Table 1).

2 | Methods

2.1 | Study Design and Registration

The NAPEN Network is currently undertaking a series of umbrella reviews across various healthcare domains, including neurology, psychiatry, neurodevelopmental disorders and pain management. The protocol for these studies has been registered in PROSPERO (CRD42021239577) and published in SSRN (Shirahige et al. 2021), adhering to all recommendations outlined in the PRISMA statement of 2020 (Page et al. 2021).

This paper is part of the umbrella review focusing on the role of NIBS in pain management, specifically addressing individuals with neuropathic pain. Future umbrella review will delve into primary pain, musculoskeletal pain and visceral pain. This division of umbrella review using the ICD-11 IASP classification of pain (Treede et al. 2015) was deemed necessary to facilitate a more comprehensive analysis of the literature, given the abundance of meta-analyses related to NIBS and its application in pain management.

2.2 | Eligibility Criteria

This review included meta-analyses of controlled trials comparing NIBS techniques with sham interventions for the clinical treatment of any neuropathic pain condition. Eligible trials were randomised clinical trials (RCT) but only published in English language, since 2015, with adult participants. Studies with duplicate data, surrogate outcomes or those on animal research were excluded. Furthermore, if there was an update of a previous meta-analysis, only the most recent update was included in the analysis.

The NIBS techniques included were: 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; auricular, taVNS), high-definition transcranial direct current stimulation (HD-tDCS), rTMS, theta-burst rTMS (TBS) and cerebellar repetitive transcranial magnetic stimulation (crTMS). Eligibility criteria based on the PICOS strategy are summarised in Table 2.

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TABLE 1 | Abbreviation list.

Abbreviation	Definition
NIBS	Non-invasive brain stimulation
rTMS	Repetitive transcranial magnetic stimulation
TBS	Theta-burst rTMS
tDCS	Transcranial direct current stimulation
tACS	Transcranial alternating current stimulation
tVNS	Transcutaneous vagus nerve stimulation
tRNS	Transcranial random noise stimulation
tcDCS	Transcranial cerebellar direct current stimulation
tsDCS	Transcutaneous spinal direct current stimulation
HD-tDCS	High-definition transcranial direct current stimulation
crTMS	Cerebellar repetitive transcranial magnetic stimulation
CeNP	Central neuropathic pain
PeNP	Peripheral neuropathic pain
MS	Multiple sclerosis
PLP	Phantom limb pain
SCI	Spinal cord injury
BMS	Burning mouth syndrome
TBI	Traumatic brain injury
VAS	Visual analogue scale
M1	Motor cortex
DLFPC	Dorsolateral prefrontal cortex
PPC	Posterior parietal cortex
preM	Premotor area
PMC	Premotor cortex
S1	Primary somatosensory cortex
S2	Secondary somatosensory cortex
SMA	Supplementary motor area
RCT	Randomised clinical trials
AMSTAR-2	A measurement tool to assess systematic reviews

2.3 | Search Strategy

A systematic search was performed on the PubMed/MEDLINE electronic database from June 2021 to February 2024 by two independent researchers (RDM and IR). Keywords were based on the PICO strategy with Boolean terms 'OR' and 'AND'. Only a meta-analyses filter was used.

- *Population*: Pain, neuropathic pain, nociceptive pain, mixed pain, central sensitisation, migraine, headache, idiopathic orofacial pain, temporomandibular joint pain, muscle pain, joint pain, fibromyalgia, myofascial pain, low back pain, neck pain, sciatica, spinal cord pain, complex regional pain syndrome, multiple sclerosis (MS) pain, cancer pain, osteoarthritis, rheumatoid arthritis, inflammatory pain, central pain, post-herpetic pain, post-herpetic neuralgia, phantom limb pain (PLP), causalgia, whiplash pain, diabetes pain, trigeminal pain, polymyalgia.
- *Intervention*: Transcranial magnetic stimulation, repetitive transcranial magnetic stimulation, theta-burst stimulation, transcranial direct current stimulation, tACS, tRNS, cerebellar transcranial direct current stimulation, transcutaneous spinal cord stimulation, tVNS, electric brain stimulation, non-invasive brain stimulation, non-invasive brain stimulation; comparative: Sham.
- *Outcome*: Pain intensity, pain level.
    - The initial search strategy was intentionally broad to include various chronic pain conditions, as the original aim was to gather comprehensive evidence on NIBS. This explains the inclusion of keywords not specific to neuropathic pain. However, given the abundance of meta-analyses, we refined the scope of this review to focus exclusively on neuropathic pain, as explained earlier.

2.4 | Data Collection Process

The titles and abstracts of articles retrieved were screened by two independent authors (R.D.M. and I.R.). The full text of all potential studies was then screened by the same authors based on predefined inclusion and exclusion criteria. Only the neuropathic pain systematic reviews were selected for inclusion. Any discrepancies were resolved through consensus, and if this could not be reached, by a third independent author (A.F.B.).

Two independent reviewers (R.D.M. and I.R.) extracted data from the selected studies using a standardised extraction procedure. Extracted data included the name of the first author, name of the article, publication year and number of studies, parameters of NIBS intervention protocol, number of participants in each group (active and sham), outcome measures, number of sessions, adverse events, results, effect size and its related 95% (confidence interval). All data were double-checked to guarantee accuracy and consistency. Divergences were resolved by a third reviewer (A.F.B.).

2.5 | Data Items

The extracted data were imputed into the GRADE system tool (Grading of Recommendations, Assessment, Development and Evaluation Guideline Development Tool), available at https://www.gradepro.org. The extracted variables were: (1) the number of participants (active and control groups); (2) the number of responders (< 20% of pain intensity reduction is not clinically significant; 20%–30% is low, 30%–50% is moderate, and above 50%–80% is a high clinical effect); (3) the number of remitters

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TABLE 2 | Eligibility criteria for considering articles for the umbrella review.

Criteria	Inclusion	Exclusion
Population (P)	Population with NP of any type that has been treated with one of the NIN techniques	Animal studies
Intervention (I)	tDCS, rTMS, TBS, tACS, tRNS, tcDCS, crTMS, tsDCS, tVNS, tsDCS and HD-tDCS	Association of two or more active NIN techniques in the same intervention
Comparison (C)	Sham NIN	Comparison between two active NIN techniques (ex. rTMS vs. tDCS)
Outcome (O)	Pain intensity	Surrogate outcomes
Study design (S)	Systematic reviews with meta-analysis of clinical trials randomised or not; published in English	Meta-analysis published before 2015

Abbreviations: crTMS, cerebellar repetitive transcranial magnetic stimulation; HD-tDCS, high-definition transcranial direct current stimulation; NIBS, non-invasive brain stimulation; RCT, randomised 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.

(> 80% reduction in pain intensity); and (4) relative (odds ratio [OR], risk ratio or hazard ratio) or absolute effects. Two authors (R.D.M. and L.S.) were involved in the data extraction process, and one (A.F.B.) checked the extracted data independently.

2.6 | Effect Measure

All effect size measures (mean difference, odds ratio) were adjusted to the standard mean difference (SMD). For this, we plotted a new meta-analysis with the post-intervention data in mean and SD for each study included in the original meta-analysis and performed a new forest plot of SMD. When means and SDs were not provided, median values were considered to be equal to mean values, if data were normally distributed and interquartile ranges were divided by 1.35 to obtain the SD. If necessary, we also calculated the SD from confidence interval data informed in the studies as recommended by Chapter 7 of the Cochrane Handbook (Green and Higgins 2011). When the study only presented the results in graphs, we extracted the data using the WebPlotDigitizer, an extension tool from Google Chrome (available at https://apps.automeris.io/wpd/). All adjusted meta-analyses were analysed through the RevMan 5 software (Cochrane Information Management System). All tests were two-sided, and statistical significance was defined as $p = 0.05$. Homogeneity was evaluated by a heterogeneity test. Meta-analysis was considered homogeneous when the p value was greater than 0.05 and the heterogeneity index (I^2) was up to 30%. When heterogeneity was greater than 30%, a random effect model was used. When the heterogeneity index was less or equal to 30%, the fixed effect model was applied.

The primary outcome to assess relief symptoms for most of the neuropathic pain conditions was pain intensity measured mainly by visual analogue scale, numerical rating scale, visual numeric scale, verbal rating scales and brief pain inventory. Additional Likert pain scales were permissible, given the established validity of the scale. Secondary outcomes were also reviewed according to IMMPACT recommendations, and included the analysis of humour, quality of life, physical functioning and patient satisfaction, when presented in the included studies (Carey et al. 2020).

The studies were divided into central neuropathic pain (CeNP) and peripheral neuropathic pain (PeNP). As observed in prior studies, the outcomes were further categorised based on the timing of assessment, spanning short term (from immediately after the intervention to 1-week post-intervention), medium term (> 1 to 6 weeks post-intervention) and long term (≥ 6 weeks post-intervention). For figures comparing meta-analysis effect size, we used the data with the most recent assessment. Finally, all figures were created using the software Excel 365 for Windows.

2.7 | Risk of Bias Assessment

The quality of the studies was assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR-2, available online at https://amstar.ca/Amstar-2.php) according to the recommendations of Shea et al. (Shea et al. 2017). This tool uses a checklist of 16 domains to evaluate the quality of RCTs included in systematic reviews. Instead of generating a total score, AMSTAR-2 evaluates the quality of the included studies based on performance in critical and non-critical domains, which are assigned different weights in the rating rules. The certainty assessment criteria are described below.

2.8 | Certainty Assessment

The quality of each included meta-analysis was assessed considering critical items (2, 4, 7, 9, 11, 13 and 15) and non-critical flaws of the AMSTAR-2 by pairs (R.D.M. and I.R. or R.D.M. and F.H.). The meta-analyses were classified as 'high quality' (none 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) (Shea et al. 2017). Any discrepancies between authors were resolved by a fourth reviewer (AFB).

The analysis includes five main criteria: risk of bias, inconsistency, indirectness, imprecision and publication bias. We considered the AMSTAR 2 classification to rate the methodological quality of the included meta-analyses. Any discordance between

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reviewers was solved by consensus or by the third reviewer (A.F.B.). The GRADE tool provided a rating of high, moderate, low or very low quality for each outcome. High evidence means that future studies are unlikely to change the effect size estimate; moderate means that future RCTs may have an impact on the effect size estimate, low means that there is a high probability that future studies will change the effect size estimate, and critically low means that there is no certainty about the effect size estimate.

3 | Results

A total of 111 studies were screened. After applying the eligibility criteria, 20 meta-analyses and two network meta-analyses were included in this umbrella review (Che et al. 2021; Chung et al. 2024; Fregni et al. 2021; Gao et al. 2022; Gurdiel-Álvarez et al. 2024; Hadoush et al. 2022; Hsu et al. 2021; Jin et al. 2015; Kan et al. 2022; Li et al. 2021, 2022; Mehta et al. 2015; O'Connell et al. 2018; Pacheco-Barrios, Meng, and Fregni 2020; Saleh et al. 2022; Shen et al. 2020; Uygur-Kucukseymen et al. 2023; Wen et al. 2022; Wu et al. 2023; Jiang et al. 2022; Yu et al. 2020; Zhu et al. 2022). The network meta-analysis was addressed separately. The full text of one study could not be retrieved for complete reading, despite attempts to contact the authors via the provided email address (Gao et al. 2017). Details of the systematic review process are available in the flowchart diagram (Figure 1).

The included meta-analysis studies involved 8151 participants across 214 controlled trials. Of these studies, 13 addressed only CeNP, four specifically examined PeNP, and 10 conducted analyses that included both CeNP and PeNP conditions. The aetiologies contributing to neuropathic pain varied

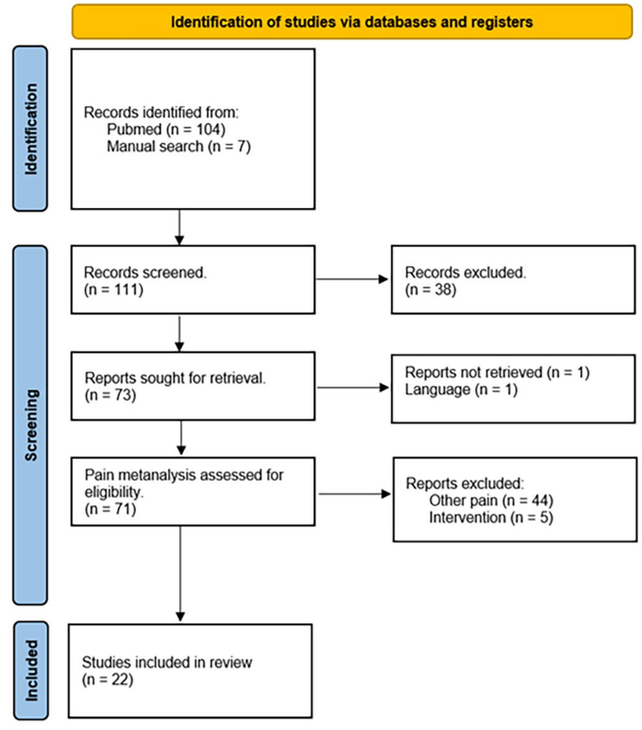

FIGURE 1 | Flowchart diagram.

widely and included conditions such as trigeminal neuralgia, diabetic neuropathy, brachial plexus injury, post-herpetic neuralgia, stroke, brainstem lesion, PLP, spinal cord injury (SCI), traumatic brain injury (TBI), burning mouth syndrome (BMS) and MS. Figures 2–4 (also Figures S1 and S2) present information on the study populations, NIBS modalities, follow-up durations, effect sizes, confidence intervals and methodological quality.

3.1 | Quality of Studies and Risk of Bias

The methodological quality of the studies ranged from 7 to 16 points on the AMSTAR-2 scale. The AMSTAR-2 scores for high-, moderate-, low- and critically low-quality meta-analyses were 35%, 15%, 20% and 30%, respectively. The main factors that lowered the AMSTAR rating were the lack of study registration, failure to investigate and/or discuss the risk of bias and heterogeneity observed in the review results. Additionally, hardly any study evaluated and reported the funding source of the clinical trials included in the reviews.

However, in the GRADE-Pro assessment, the majority of the studies demonstrate low or critically low levels of evidence, with only five analyses considered to have moderate evidence levels (Figures 2–4 and S1–S6). The primary factors contributing to the low GRADE scores are population and intervention heterogeneity, along with small sample sizes.

3.2 | Neuromodulation Modalities, Brain Targets and Dosage

The most widely employed NIBS modalities were rTMS and tDCS; and, in general, the primary targets were M1 and the left DLPFC, as anticipated. A substantial portion of the studies grouped trials with different therapeutic targets in the same analyses, but some studies managed to separate them. Additional brain targets explored for the management of neuropathic pain encompassed posterior parietal cortex (PPC), premotor area (preM), premotor cortex (PMC), insula, primary somatosensory cortex (S1), secondary somatosensory cortex (S2) and supplementary motor area (SMA). Among these, only PPC has been subjected to a separate meta-analysis assessing its efficacy (Pacheco-Barrios, Meng, and Fregni 2020), yet it does not appear to be a promising target.

In terms of the characteristics of stimulation, only excitatory protocols have demonstrated efficacy in reducing pain among individuals with neuropathic pain. Only two studies compared rTMS excitatory frequencies (5, 10 and 20 Hz), and the results do not allow conclusions on superiority between them, as they are heterogeneous between the studies (Figure 2). Neither of the analyses compared interventions regarding the number of pulses and intensity for rTMS nor duration and stimulus intensity of tDCS. In terms of the number of sessions, rTMS is effective in reducing pain intensity whether administered in single or multi-sessions, and this appears to be independent of the number of sessions used (Figure S3). However, there is no information available regarding how long the effects of stimulation last with different session quantities.

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Study	Modality	Target	Follow-up	SMD[95%IC]	n studies/ participants	I²; p-value	GRADE	AMSTAR-2	Serious Adverse Event
Yu-Rong Wen, 2022	atDCS	M1/ DLPFC	Short-Term	-0,84 [-1,34, -0,35]*	6/298	69.8%; 0.001	Low	15	acute mood swing
Gao Chengfei, 2022	atDCS	M1/ DLPFC	Short-Term	-0,56 [-0,71, -0,04]*	4/138	0.0% ;	Very Low	14	NR
Felipe Fregni, 2021	atDCS	M1	N.R.	-0,29 [-0,60, 0,02]	8/199	23.2% ; N.R	Very Low	10	No
O'Connell NE, 2018	atDCS	M1/ DLPFC	Short-Term	-0,26 [-0,53, 0,01]	9/174	40% ;0.056	Very Low	16	No
Yuanliang Zhu, 2022	HF rTMS	DLPFC	Short-Term	-0,86 [-2,55, 0,83]	3/67	88%; 0.32	Very Low	11	NR
Gao Chengfei, 2022	HF-rTMS	M1/ DLPFC	Short-Term	-0,95 [-1,85, -0,04]*	5/143	80.5%; NR	Very Low	14	NR
Gao Chengfei, 2022	LF-rTMS	M1/ DLPFC	Short-Term	-0,55 [-1,23, 0,13]	2/40	0.0% ; NR	Low	14	NR
Xue Jiang, 2022	HF rTMS (20Hz)	M1	Short-Term	-1,07 [-1,44, -0,70]*	6/221	38%; <0.001	Low	14	No
Xue Jiang, 2022	HF rTMS (10Hz)	DLPFC/ S1/ S2/ IPMC	Short-Term	-0,34 [-0,67, -0,01]*	5/244	33%; <0.04	Very Low		
Xue Jiang, 2022	HF rTMS (10Hz)	M1	Short-Term	-0,88 [-1,25, -0,51]*	17/772	82%; <0.0001	Moderate	14	No
Xue Jiang, 2022	HF rTMS (5Hz)	M1, S1, preM, SMA,	Short-Term	-0,42 [-0,68, -0,15]*	10/443	41%; 0.002	Low	14	No
Xue Jiang, 2022	LF rTMS	M1	Short-Term	0,27 [-0,20, 0,73]	4/192	57%;0.26	Very Low	14	No
Xianwei Che, 2021	HF-rTMS	DLPFC	Short-Term	-0,87 [-1,56, -0,18]*	4/118	NR ;0.01	Very Low	15	NR
O'Connell NE, 2018	HF-rTMS	M1, DLPFC, S1, PMA, SMA	Short-Term	-0,28 [-0,36, -0,20]*	17/432	86%; <0.00001	Very Low	16	No
O'Connell NE, 2018	LF-rTMS	M1	Short-Term	0,15 [-0,02, 0,32]	5/113	0.0%; 0.87	Very Low	16	No
Jin Y, 2015	HF rTMS (20Hz)	M1	N.R.	-0,80 [-1,26, -0,33]*	10/225	NR; 0.0008	Very Low	10	No
Jin Y, 2015	HF rTMS (10Hz)	M1	N.R.	-0,59 [-0,91, -0,27]*	14/266	NR; 0.0003	Very Low	10	No
Jin Y, 2015	HF rTMS (5Hz)	M1	N.R.	-1,37 [-2,31, -0,44]*	8/166	NR; 0.004	Very Low	10	No

Favours NIBS -2 0 2 Favours sham

FIGURE 2 | Overview of study characteristics and evidence in meta-analyses evaluating NIBS for pain control in both CeNP and PeNP with the most recent follow-up measure presented.

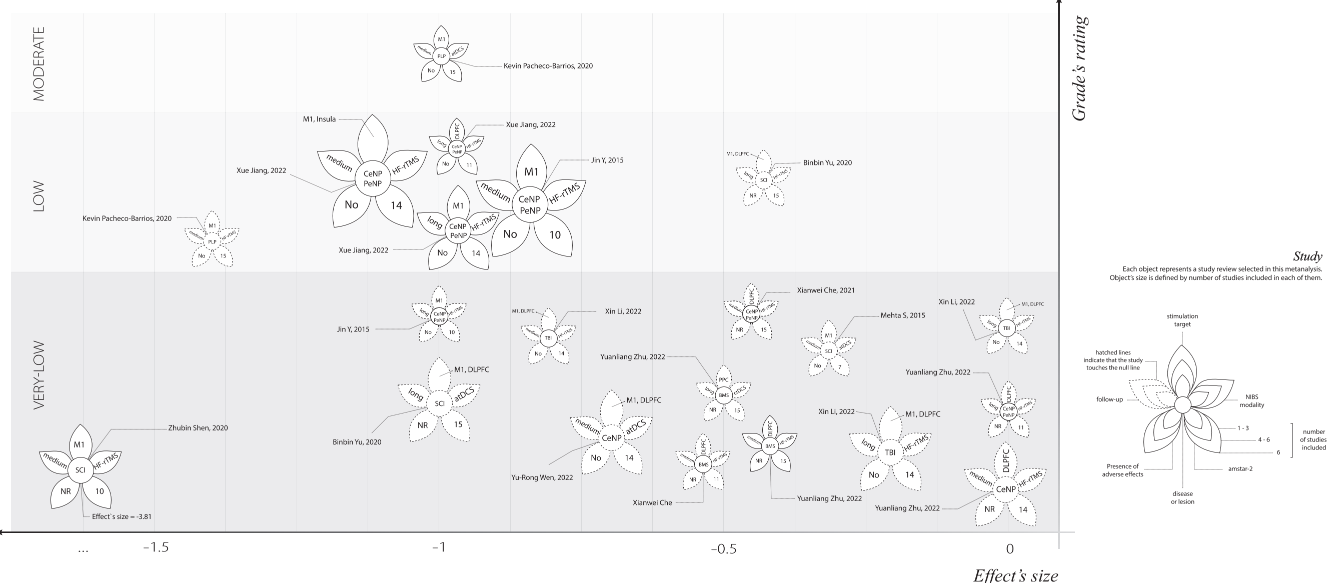

FIGURE 3 | Illustration summarising study attributes and findings from meta-analyses examining the efficacy of NIBS in managing CeNP with the most recent follow-up measure presented.

The only other NIBS modality was taVNS (Gao et al. 2022; Yu et al. 2020). Despite being included in two meta-analyses, it stems from a single clinical trial. It did not show superior results compared to sham in any outcome.

3.3 | Outcome Measures

In addition to the aforementioned pain scales, another scale found was the Defence and Veterans Pain Rating Scale, which is a valid and reliable instrument (Polomano et al. 2016). The majority of studies assessed the efficacy of NIBS in the short term, nine evaluated efficacy in the mid-term (Figure S4) and only five in the long term (Figure S5). Seven studies did not report or make clear the timing of the follow-up measurements (Fregni et al. 2021; Gurdiel-Álvarez et al. 2024; Hadoush et al. 2022; Hsu et al. 2021; Jin et al. 2015; Saleh et al. 2022; Uygur-Kucukseymen et al. 2023). Three studies presented data in MD and they were adjusted to the SMD (Li et al. 2022; Saleh et al. 2022; Zhu et al. 2022). No study measured or reported the number of responders or remitters.

Few studies assessed outcomes related to pain beyond pain intensity. NIBS efficacy in mood alterations, depression and anxiety was evaluated (Figure S6). Only one study reported superior efficacy of rTMS compared to sham in addressing mood comorbidities, specifically depression (Li et al. 2022). This study evaluated rTMS targeting the right, left or bilateral DLPFC in

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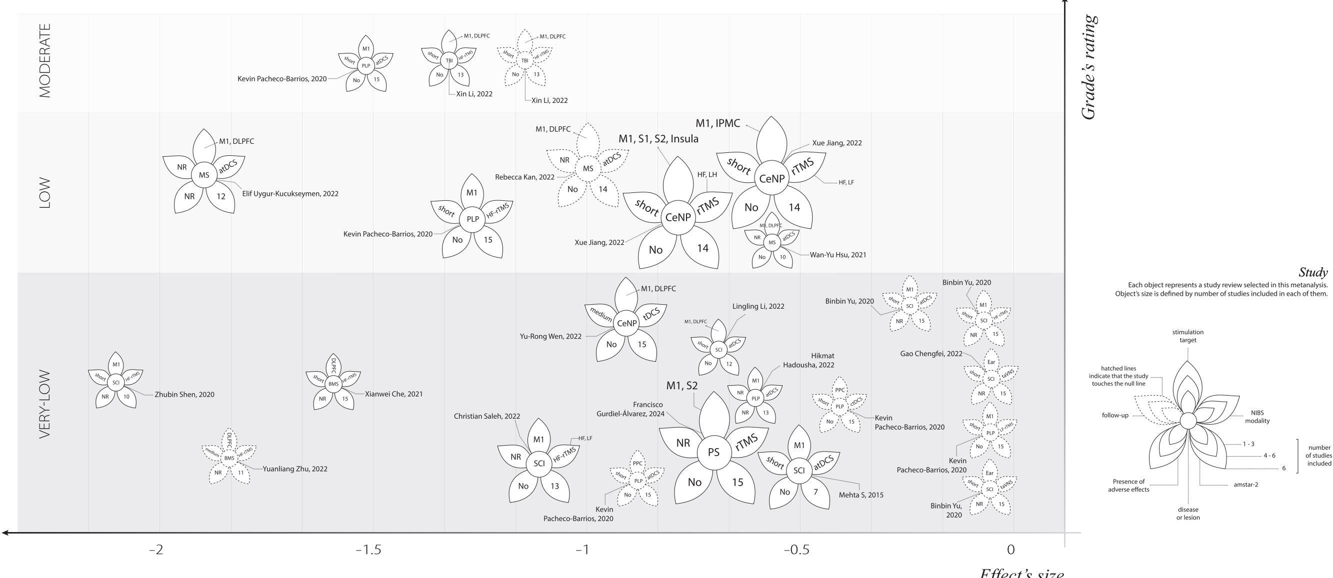

FIGURE 4 | Illustration summarising study attributes and findings from meta-analyses examining the efficacy of NIBS in managing PeNP with the most recent follow-up measure presented.

individuals with TBI, conducting sensitivity analyses using different scales, including the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HDRS) and Patient Health Questionnaire-9 (PHQ-9). However, it's worth noting that the efficacy of rTMS in depression was only observed when using the PHQ-9 scale. NIBS efficacy was measured for treating anxiety in neuropathic pain individuals, but it was not superior to sham for MS pain and it actually worsened the symptoms in SCI individuals (Uygur-Kucukseymen et al. 2023; Yu et al. 2020). None of the meta-analyses included secondary outcomes such as pain interference, quality of life, global impression of change or sleep.

3.4 | Network Meta-Analysis

A network meta-analysis assessed the efficacy of 'non-traditional' therapies for the treatment of PeNP caused by phantom limb pain (Chung et al. 2024). The study involved 12 trials and 783 participants. rTMS was the only efficacious included intervention for pain intensity when compared to the sham group, with MD of −2.90 and CI of −4.62 and −1.18. In addition, rTMS presented low adverse event rates. Other NIBS modalities investigated were tcDCS (MD: −1.00 [CI −3.13 to 1.13]) and peripheral nerve stimulation (MD −1.80 CI [−3.71 to 0.11]).

The other included network meta-analysis that assessed the efficacy of eight non-invasive therapies in treating post-stroke CeNP (Wu et al. 2023). It comprised 12 RCTs and 641 individuals. Both tDCS (MD: −1.84 [−2.39, −1.28] I^2: 67%, $p < 0.00001$) and rTMS (−1.33 [−1.67, −0.99] I^2: 0, $p < 0.00001$) were effective in reducing pain intensity when compared to a control intervention. Another NIBS modality investigated was continuous TBS and it was not superior to sham treatment (MD: −1.00 [−2.58, 0.58] $p = 0.21$).

4 | Discussion

This systematic umbrella review provides a comprehensive insight into the evidence regarding rTMS and tDCS interventions for managing individuals with neuropathic pain. The only other intervention studied was taVNS, which showed no superior effect compared to sham. The included population encompasses a wide range of CeNP and PeNP conditions, highlighting discernible differences in the effectiveness of NIBS modalities based on target, pain classification and aetiology. However, it is noteworthy that most studies grouped different aetiologies under the same analysis, which may affect the interpretation of the results. The quality of the studies included varied, with approximately 30% categorised as high methodological quality, 15% as moderate, and 55% as low and critically low quality according to the AMSTAR assessment. According to the GRADE system, the quality of evidence in most studies is rated as low or very low.

rTMS and tDCS stand out as the most commonly employed NIBS techniques in both clinical practice and research for treating a wide range of health conditions, not only in the context of chronic pain but also in mental health, neurology and developmental disorders (Baptista et al. 2019; Lefaucheur et al. 2014, 2017). This is likely due to the extensive research and understanding of their mechanisms of action, safety and applicability (Rossi et al. 2021; Rossini et al. 2015). Additionally, rTMS and tDCS are easily applicable techniques and are often conceptualised as having a dual purpose of increasing or decreasing excitability in a specific brain region, although this oversimplification can be misleading (Chung et al. 2016; Hosomi et al. 2013; Reed and Cohen Kadosh 2018). It is noteworthy that only excitatory stimulations were effective in reducing pain intensity (anodal tDCS and high-frequency rTMS).

taVNS emerged as the third most researched NIBS technique, albeit with only two meta-analyses encompassing the same

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clinical trial, which involved individuals with SCI. Neither of these studies demonstrated a significant reduction in pain intensity. taVNS is typically administered to the cervical region or the ear and is utilised to modulate autonomic activity (Colzato and Beste 2020). Despite being studied for a considerable time, there are few trials involving individuals with chronic pain. Furthermore, the extensive range of parameters examined probably complicates taVNS research and application (Yap et al. 2020).

NIBS treatment proved beneficial for both individuals with CeNP and PeNP. In the short-term most studies presented effect sizes ranging from moderate to large for excitatory interventions targeting M1 or DLPFC. The flexibility to utilise various techniques empowers therapists to tailor their approach according to their familiarity, cost, patient preferences and comorbidities. The recommendation to target M1 for treating individuals with neuropathic pain is well-established in the literature (Baptista et al. 2019; Fregni et al. 2021; Lefaucheur et al. 2020) and there is sufficient evidence to also consider the left DLPFC, besides, they have common mechanisms of analgesia (Moisset, de Andrade, and Bouhassira 2016). Evidence suggests that M1 stimulation may provide stronger analgesic effects than DLPFC, and rTMS has been found to be more effective than tDCS in reducing pain (Baptista et al. 2019; Fregni et al. 2021; Lefaucheur et al. 2020). However, this relationship is less clear in our study due to the heterogeneity of the studies included.

Meta-analyses that included other potential targets conducted analyses with multiple targets, with the exception of PPC, and showed small effect sizes or did not demonstrate efficacy in reducing pain intensity. Thus, it is not possible to evaluate the efficacy of these targets in pain management. More studies are needed using other targets for the treatment of neuropathic pain. Currently, the literature weakly recommends against the use of rTMS to stimulate the posterior insula or ACC for CeNP control, although this recommendation is based on a single study (Moisset et al. 2020). In contrast, there is one more recent study, this time focused on the control of PeNP, which demonstrates significant reductions in pain intensity with moderate to large effect sizes (Dongyang et al. 2021). Another target that requires further study is the secondary somatosensory cortex, as it also appears to be a promising target for pain management (Lindholm et al. 2015; Ojala et al. 2022).

Despite the clear reduction of pain intensity with NIBS treatment, a significant challenge in these studies is the inclusion of patients with various aetiologies of both PeNP and CeNP, making it difficult to provide a more specific protocol recommendation. Although certain pathophysiological mechanisms are shared between CeNP and PeNP (Jensen and Finnerup 2014), there is a growing inclination towards personalised treatment approaches (Baron et al. 2017; Bouhassira and Attal 2023). Clinical manifestations diverge, likely due to distinct alterations associated with each aetiology (Baron et al. 2017; Bouhassira and Attal 2023; Meacham et al. 2017). Analysing studies that separately assessed the effects of NIBS by aetiology, we found: positive outcomes from using excitatory stimulation of M1 for phantom limb pain, highlighting that atDCS demonstrates moderate quality evidence for pain control in the short and medium term; atDCS in M1 and DLPFC shows efficacy in MS pain; post-stroke individuals benefits from high-frequency rTMS in M1; TBI individuals benefit from DLPFC and M1 high-frequency rTMS, not immediately but after one-week post-intervention (moderate quality of evidence); BMS individuals likely benefits from high-frequency rTMS, but more studies are needed; however, for SCI individuals, there are conflicting reports regarding the use of tDCS and rTMS, with some showing superior results compared to sham while others do not.

A potential source of variation in the results is the treatment dosage. Almost no analysis was done considering tDCS intensity and treatment duration. While there is some data on the efficacy of frequency and number of sessions for rTMS treatment, we lack information about the number of pulses and trains. Our findings do not enable us to distinguish the efficacy between 5, 10 and 20 Hz, especially since some analyses focus on different areas. Although there is some indication in the literature that 10 Hz may produce better outcomes than 5 Hz, this difference was not apparent in our results, as the effect sizes were similar (Moisset et al. 2020). Regarding the number of sessions, we can affirm that treatment efficacy is observed from the first session, and this efficacy is maintained with additional sessions. Although there is no predictable pattern regarding the effect size with more sessions, it is known that NIBS has a cumulative clinical response (Bhattacharya et al. 2022). Also, none of the included studies analysed the number needed to treat. Another factor to consider is that the effect of NIBS becomes more long-lasting with an increased number of sessions (Khedr et al. 2005).

Another challenge in interpreting the findings is that many articles did not report or clarify the timing of the follow-up period from which the outcome measures were extracted from the original studies. This is important for a more robust understanding of what to expect from the treatment and how long its effects will last. Additionally, few studies have assessed the effects of NIBS on pain control in the medium term, with half of the studies demonstrating analgesic effects, and long term, with only one study showing treatment efficacy over 2 or more months. Despite the limited number of studies, the treatment's effectiveness appears to decline over longer follow-up periods. It's clear that studies assessing medium and long-term effects are necessary. However, this again raises questions regarding dosage and highlights the importance of investigating whether the maintenance phase of NIBS treatment is necessary to achieve longer analgesic effects and how we should conduct it (Lefaucheur and Nguyen 2019). In a study involving individuals with fibromyalgia, after five daily treatment sessions, a maintenance period was implemented in which the treatment frequency was gradually reduced from three sessions per week to one session per month, totalling 14 sessions overall. As a result, it was observed that even after 25 weeks, the individuals showed improvement in pain and other symptoms (Mhalla et al. 2011).

It is noteworthy that other symptoms accompanying neuropathic pain were not evaluated. Both positive and negative symptoms are present in neuropathic pain syndromes and can be assessed through physical examinations and specific scales (Hamdan, Galvez, and Katati 2024). Symptoms arising from perceptual alterations caused by hypoesthesia, hyperalgesia and allodynia are common in clinical practice and should be addressed. According to the IMMPACT recommendations, it is

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also important to gather information about physical functioning, participants' ratings of global improvement, quality of life, sleep quality and participants' disposition (Carey et al. 2020). Anxiety and depression were the only other outcome measures identified in the included meta-analyses. Based on our results, despite the extensive literature supporting the efficacy of NIBS in improving anxiety and depression (Lefaucheur et al. 2020; Sá et al. 2023), these findings were not consistently translated into the studies focusing on pain. Among the included studies, only one reported a modest improvement in depression, with the confidence interval nearly crossing the line of null effect, while another study noted a worsening in anxiety levels. This discrepancy may be related to the use of stimulation targets other than the DLPFC. However, even studies that exclusively targeted the DLPFC did not yield significant results, which might be attributed to suboptimal dosing protocols, as treatment protocols for depression typically involve longer treatment durations than those used for pain control (Nikolin et al. 2023).

Our umbrella review has several limitations, including the restriction of search to the PubMed database and the exclusive inclusion of meta-analyses in the English language. Also, we decided to calculate SMD based on MD, which may have increased the risk of bias. We prefer to use this analysis to summarise in a more standardised way the results of different meta-analyses. A significant limitation of the umbrella review design is that we could only synthesise the data and not analyse it in detail. Therefore, we advise caution in interpreting the results, as it was not possible to effectively dissect the efficacy of many meta-analyses that grouped various NIBS modalities, targets and populations. Future research should delve deeper into addressing this limitation and explore the effectiveness of NIBS in other types of NP not covered in our search (Table S1).

5 | Conclusion

The use of NIBS among people with CeNP and PeNP has been demonstrated to be efficacious for pain management, although data about its benefit in improving anxiety and depression in these individuals are lacking. The overall quality of evidence is predominantly classified as very low or low, indicating the need for new clinical trials characterised by larger cohorts, well-defined participant demographics and precise interventions. Substantial gaps in literature have been pinpointed, presenting opportunities to enhance clinical practice, and should be addressed in future studies. These encompass the exploration of novel therapeutic targets and NIBS modalities, examination of the influence of tDCS dosage, as well as the number of pulses and pulse trains in rTMS on the reduction of pain intensity. Moreover, there is a need to assess secondary mood outcomes systematically in future studies, scrutinise the efficacy of NIBS in addressing both positive and negative symptoms of neuropathic pain, evaluate its impact on quality of life and ascertain patient satisfaction levels.

Author Contributions

Conceptualisation was done by all authors. Data collection was conducted by Abrahão Fontes Baptista, Rafael Jardim Duarte-Moreira and Indira Enith Rodriguez-Prieto. Quality assessment was performed by Abrahão Fontes Baptista, Lívia Shirahige and Rafael Jardim Duarte-Moreira. The results were critically analysed by all authors. Rafael Jardim Duarte-Moreira played a leading role in preparing the manuscript, which was edited by Abrahão Fontes Baptista, Lívia Shirahige and Gabriel Taricani Kubota. Figures were created by Maércio Maia Alves and Lívia Shirahige. All authors contributed to the manuscript, approved the final version and agreed to be accountable for all aspects of the work.

Conflicts of Interest

The authors declare no conflicts of interest.

Use of Artificial Intelligence

The authors used ChatGPT to assist in correcting the English in the text, but the final version was thoroughly reviewed and approved by all authors.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

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