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REVIEW

Analgesic Effect of Noninvasive Brain Stimulation for Neuropathic Pain Patients: A Systematic Review

Kun-Long Zhang · Hua Yuan · Fei-Fei Wu · Xue-Yin Pu · Bo-Zhi Liu · Ze Li · Kai-Feng Li · Hui Liu · Yi Yang · Ya-Yun Wang

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ABSTRACT

Introduction: The objective of this review is to systematically summarize the consensus on best practices for different NP conditions of the two most commonly utilized noninvasive brain stimulation (NIBS) technologies, repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS).

Methods: PubMed was searched according to the predetermined keywords and criteria. Only English language studies and studies published up to January 31, 2020 were taken into consideration. Meta-analyses, reviews, and systematic reviews were excluded first, and those related to animal studies or involving healthy volunteers were also excluded. Finally, 29 studies covering 826 NP patients were reviewed.

Results: The results from the 24 enrolled studies and 736 NP patients indicate that rTMS successfully relieved the pain symptoms of 715 (97.1%) NP patients. Also, five studies involving 95 NP patients (81.4%) also showed that tDCS successfully relieved NP. In the included studied, the M1 region plays a key role in the analgesic treatment of NIBS. The motor evoked potentials (MEPs), the 10–20 electroencephalography system (EEG 10/20 system), and neuro-navigation methods are used in clinical practice to locate therapeutic targets. Based on the results of the review, the stimulation parameters of rTMS that best induce an analgesic effect are a stimulation frequency of 10–20 Hz, a stimulation intensity of 80–120% of RMT, 1000–2000 pulses, and 5–10 sessions, and the most effective parameters of tDCS are a current intensity of 2 mA, a session duration of 20–30 min, and 5–10 sessions.

Conclusions: Our systematically reviewed the evidence for positive and negative responses to rTMS and tDCS for NP patient care and underscores the analgesic efficacy of NIBS in patients with NP. The treatment of NP should allow the design of optimal treatments for individual patients.

K.-L. Zhang · F.-F. Wu · X.-Y. Pu · B.-Z. Liu · Z. Li · K.-F. Li · H. Liu · Y. Yang · Y.-Y. Wang (✉)
Specific Lab for Mitochondrial Plasticity Underlying Nervous System Diseases, National Demonstration Center for Experimental Preclinical Medicine Education, Air Force Medical University, Xi'an 710032, China
e-mail: wangyy@fmmu.edu.cn

K.-L. Zhang · H. Yuan
Department of Rehabilitation Medicine, Xi-Jing Hospital, Air Force Medical University, Xi'an 710032, China

H. Liu · Y. Yang
Department of Human Anatomy, Yan-An University, Yan'an 716000, China

Y.-Y. Wang
State Key Laboratory of Military Stomatology, School of Stomatology, The Fourth Military Medical University, Xi'an, China

Keywords: Neuropathic pain; Noninvasive brain stimulation; Repetitive transcranial magnetic stimulation; Review; Transcranial direct current stimulation

Key Summary Points

Neuropathic pain (NP) in this review is categorized as typical NP (TNP) resulting from diabetes, stroke, spinal cord injury (SCI) and nerve lesions, and special NP (SNP), including facial NP (FaNP), cancer NP (CaNP), phantom limb NP (PhanNP), and other malformations.

Commonly used parameters of rTMS were a stimulation frequency of 10–20 Hz, a stimulation intensity of 80–120% of the resting motor threshold, 1000–2000 pulses, and 5–10 sessions.

The most common parameters of tDCS were a current intensity of 2 mA, a session duration of 20–30 min, and 5–10 sessions.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14105999.

INTRODUCTION

Neuropathic pain (NP) has been defined by the International Association for the Study of Pain as pain caused by a lesion or disease of the somatosensory system [1–3]. A treatment that addresses the dynamic neural system changes in NP is needed. Noninvasive brain stimulation (NIBS) is one such promising therapeutic technique [4].

NIBS is based on the interaction of electricity or magnetism with the body [5–8] (Fig. 1). Present NIBS techniques include the two most commonly utilized technologies, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) [9]. NIBS guidelines for the clinic are key for making patient care decisions in rehabilitation procedures, but no consensus of best practices for different NP conditions currently exists [10–16]. Therefore, we systematically reviewed the evidence for positive and negative responses to rTMS and tDCS for NP patient care.

METHODS

Literature Search Strategy

Studies published up to January 31, 2020 were taken into consideration for obtaining relevant literature findings. A PubMed search for articles published in and after 2010 with keywords "rTMS/tDCS AND neuropathic pain" identified 237 studies from different countries. The reference lists of articles that met the eligibility criteria were further screened to identify additional studies that may fall within the scope of this review.

Inclusion and Exclusion Criteria and Screening Process

Based on the abstracts of the studies, we first made an initial judgement on the 237 studies that might be of value, including only English language studies and excluding meta-analyses, reviews, and systematic reviews. For the remaining 162 studies, after reviewing the full text and excluding animal studies and studies of healthy volunteers, we made a final decision on which studies should be included in the review. In other words, studies eligible to be included in this review had to meet the following inclusion criteria: (1) only English language studies were included; (2) meta-analyses, reviews, and systematic reviews were excluded; (3) animal studies were excluded; (4) studies involving healthy volunteers were excluded.

Finally, 29 studies covering 826 NP patients were reviewed here. The summary on search strategy can be seen in Fig. 2. Through reading

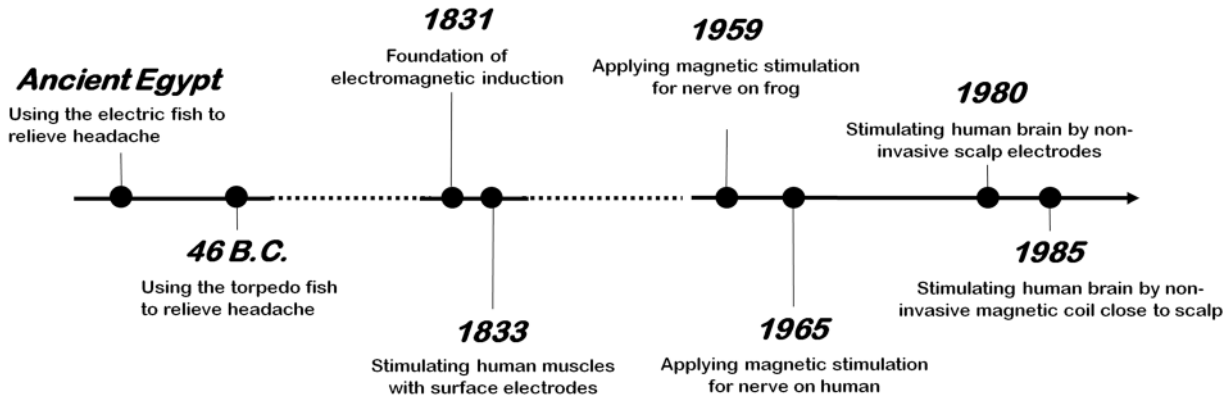

Fig. 1 Origin and development of NIBS. NIBS is based on the interaction of electricity or magnetism with the body. The historically important events related to brain electric or magnetic stimulation were indicated

the full text, we grasped the situation of NP patients in the 29 studies. In addition to counting the number of patients, we also made a statistical summary according to the treatment situation of NIBS, the targeted sites, and the different treatment parameters. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Written informed consent was obtained for the use of the two patients' photographs in this publication.

Data Synthesis

This study used aggregate data where possible, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [17].

Categories of NP in the Present Review

NP is classified as central or peripheral based on the anatomical location of the injury or disease [18]. Central NP is due to a lesion or disease of the spinal cord and/or brain, the most common causes of which include stroke and spinal cord injury. In the present review, nine types of NP have been studied. Among them, two types of NP belong to the central NP, including stroke and spinal cord injury, while seven types of NP belong to the peripheral NP, including diabetic neuropathy, nerve injury, facial pain, phantom limb pain, cancerous pain, malformation, and bladder pain syndrome. It should be noticed, however, that the most common cases of NP are the following four types including (1) stroke, (2) spinal cord injury, (3) nerve injury, and (4) diabetic neuropathy, which have been named as typical NP (TNP) in the manuscript. While the remaining types of NP have been named as special NP (SNP), including (1) facial pain, (2) phantom limb pain, (3) cancerous pain, and (4) others (malformation and bladder pain syndrome), because of the low incidences of such NP. The present classification could help the clinician deeply understand the analgesic effect of noninvasive brain stimulation for both typical and special NP.

In addition, according to the positive or negative effect of NIBS on NP in all reports, all NP patients can be divided into four categories: (1) rTMS-P, all NP patients with a positive analgesic effect from rTMS treatment; (2) rTMS-N, all NP patients with a negative analgesic effect from rTMS treatment; (3) tDCS-P, all NP patients with a positive analgesic effect from tDCS treatment; (4) tDCS-N, all NP patients with a negative analgesic effect from tDCS treatment.

The patients with NP have different symptoms such as paroxysmal pain, hyperalgesia, and allodynia. An increased sensation of pain in response to a normally painful stimulus is termed hyperalgesia, which can be assessed using painful thermal (cold or heat) or punctate (e.g., pinprick) stimuli whether patients have

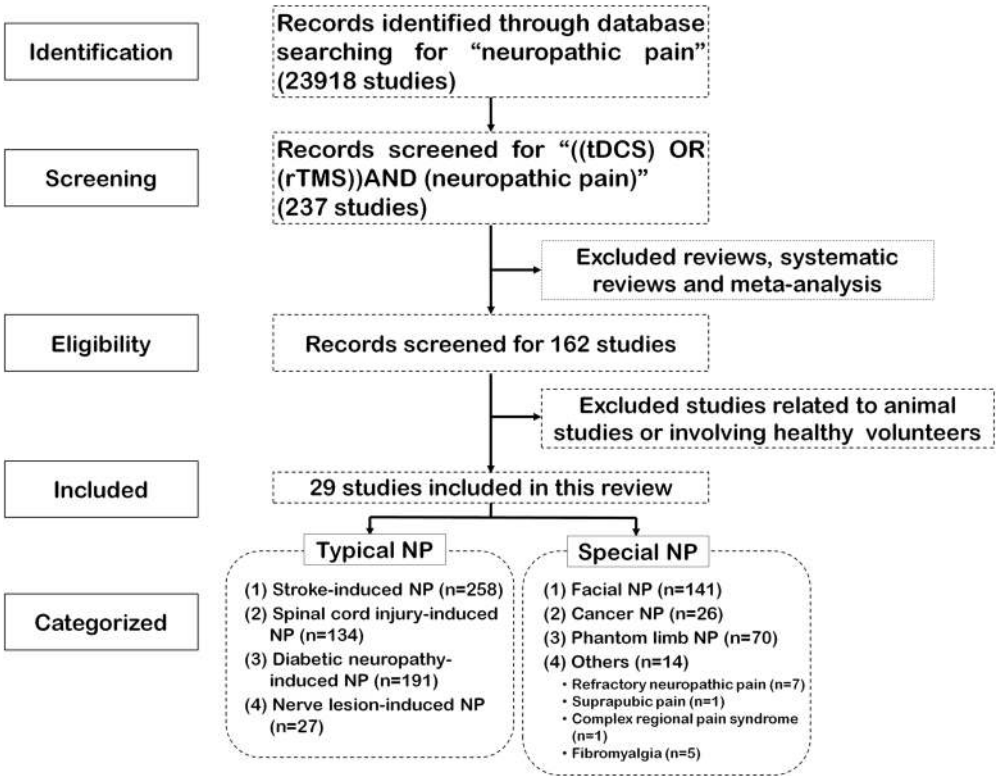

Fig. 2 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram. A PubMed search for articles published in and after 2010 with keywords "rTMS/tDCS AND neuropathic pain" identified 237 studies from different countries. Meta-analyses, reviews, and systematic reviews were excluded. Among the 162 filtered studies, those related to animal studies or involving healthy volunteers were excluded. Finally, 29 studies covering 826 NP patients were reviewed here. Instead of using the classic central and peripheral classifications, we classified the most common (large number of cases) types of NP as typical NP (TNP), including diabetic neuropathy, stroke, spinal cord injury (SCI), and nerve injury. The remaining clinically rare types are classified as special NP (SNP), such as facial pain, phantom limb pain, cancer pain, and other types of pain

improved hyperalgesia or allodynia after NIBS treatment [1]. The analgesic effects of rTMS or tDCS on NP patients are based on a total of eight kinds of NP screening tools including the Visual Analog Scale (VAS) [14, 19–32], Numeric Rating Scale (NRS) [33–41], Neuropathic Pain Questionnaire (NPQ) [30], Visual Numerical Scale (VNS) [42], Quantitative Sensory Testing (QST) [31], Verbal Descriptor Scale (VDS) [32] and McGill Pain Questionnaire/Short-Form McGill Pain Questionnaire (MPQ/SF-MPQ) [23, 30]. Pain relief is generally defined as an improvement of more than 20% in the pain score [1].

RESULTS

Analgesic Effect of NIBS on TNP and SNP

As shown in Table 1, the results from the 24 enrolled studies and 736 NP patients indicate that rTMS successfully relieved the pain symptoms of 715 (97.1%) NP patients. Only 21 NP patients (2.9%) did not experience pain relief, as reported by De Oliveira RA et al. [30]. Among 715 NP patients who experienced a significant analgesic effect of rTMS, 68.8% (n = 492) had TNP, while 31.2% (n = 223) had SNP.

As also outlined in Table 1, a total of six articles and 125 NP patients were involved in tDCS treatment. Among them, five studies

Table 1 Summary of the 29 manuscripts of analgesic effects by NIBS (both rTMS and tDCS) on NP patients

	Ref	NIBS Type	Stimulation Target	Total NP patients(n)	NP patients (n) TNP/SNP	TNP patients (n) Diabetic/Stroke/SCI /Nerve	SNP patients (n) FaNP/CaNP/PhanNP /others	Analgesic Effect
1.	Galhardonl R et al., **[36]**	rTMS	ACC / PSI	98	98 / 0	0 / 98 / 0 / 0	0 / 0 / 0 / 0	Pain relief by NRS
2.	Ander-Obadia N et al., **[37]**	rTMS	M1	32	20 / 12	0 / 12 / 5 / 3	12 / 0 / 0 / 0	Pain relief by NRS
3.	Benjamin P et al., **[19]**	rTMS	M1	12	9 / 3	0 / 7 / 2 / 0	0 / 0 / 1 / 2	40% Pain relief by VAS
4.	Nizard J et al., **[35]**	rTMS	DLPFC	1	0 / 1	0 / 0 / 0 / 0	0 / 0 / 0 / 1	Pain relief by NRS
5.	KOHúTOVá B et al., **[31]**	rTMS	M1	19	0 / 19	0 / 0 / 0 / 0	19 / 0 / 0 / 0	Pain relief by VAS/QST
6.	Shimizu T et al., **[20]**	rTMS	M1	18	18 / 0	1 / 12 / 5 / 0	0 / 0 / 0 / 0	Pain relief by VAS
7.	Ayache SS et al., **[26]**	rTMS	M1	66	50 / 16	0 / 17 / 11 / 22	16 / 0 / 0 / 0	Pain relief by VAS
8.	Malavera A et al., **[14]**	rTMS	M1	54	0 / 54	0 / 0 / 0 / 0	0 / 0 / 54 / 0	Pain relief by VAS
9.	Hodaj H et al., **[42]**	rTMS	M1	55	0 / 55	0 / 0 / 0 / 0	55 / 0 / 0 / 0	Pain relief by VNS
10.	Pommier B et al., **[21]**	rTMS	M1	40	40 / 0	0 / 0 / 0 / 40	0 / 0 / 0 / 0	41% pain relief by VAS
11.	Khedr EM et al., **[32]**	rTMS	M1	24	0 / 24	0 / 0 / 0 / 0	0 / 24 / 0 / 0	Pain relief by VDS / VAS
12.	Lindholm P et al., **[34]**	rTMS	S1 / M1 and S2	16	0 / 16	0 / 0 / 0 / 0	16 / 0 / 0 / 0	Pain relief by NRS
13.	Nizrad J et al., **[38]**	rTMS	M1	2	0 / 2	0 / 0 / 0 / 0	0 / 2 / 0 / 0	40% Pain relief by NRS
14.	Hosomi K et al., **[22]**	rTMS	M1	64	60 / 4	0 / 52 / 7 / 2	0 / 0 / 3 / 0	Modest pain relief by VAS
15.	Onesti E et al., **[28]**	rTMS	M1	25	25 / 0	25 / 0 / 0 / 0	0 / 0 / 0 / 0	Pain relief by VAS
16.	JETTé F et al., **[33]**	rTMS	M1	16	16 / 0	0 / 0 / 16 / 0	0 / 0 / 0 / 0	Pain relief by NRS
17.	Lefaucheur JP et al., **[23]**	rTMS	M1	14	11 / 3	0 / 8 / 0 / 3	3 / 0 / 0 / 0	41% pain relief by VAS and 31% SF-MPQ
18.	Lefaucheur JP et al., **[24]**	rTMS	M1	59	44 / 15	0 / 20 / 12 / 12	15 / 0 / 0 / 0	Pain relief by VAS
19.	Sampson SM et al., **[29]**	rTMS	DLPFC	9	2 / 7	0 / 0 / 1 / 1	0 / 0 / 2 / 5	50% Pain relief by VAS
20.	Di Rollo A et al., **[45]**	rTMS	M1	1	0 / 1	0 / 0 / 0 / 0	0 / 0 / 1 / 0	25% Pain relief by VAS
21.	Lefaucheur JP et al., **[27]**	rTMS	M1	32	32 / 0	0 / 10 / 6 / 16	0 / 0 / 0 / 0	Pain relief by VAS
22.	Picarelli H et al., **[25]**	rTMS	M1	23	23 / 0	0 / 0 / 0 / 23	0 / 0 / 0 / 0	50.9% Pain relief by VAS
23.	De Oliveira RA et al., **[30]**	rTMS	PMC / DLPFC	21	21 / 0	0 / 21 / 0 / 0	0 / 0 / 0 / 0	No pain relief by VAS / MPQ / NPQ
24.	Attal N et al., **[39]**	rTMS / tDCS	M1	35	35 / 0	0 / 0 / 0 / 35	0 / 0 / 0 / 0	rTMS & DCS: Pain relief by NRS
25.	Houde F et al., **[44]**	tDCS	M1	1	0 / 1	0 / 0 / 0 / 0	0 / 0 / 0 / 1	Pain relief by VAS
26.	Bolognini N et al., **[16]**	tDCS	M1	8	0 / 8	0 / 0 / 0 / 0	0 / 0 / 8 / 0	Pain relief by VAS
27.	Soler MD et al., **[40]**	tDCS	M1	39	39 / 0	0 / 0 / 39 / 0	0 / 0 / 0 / 0	Pain relief by NRS
28.	Antal A et al., **[43]**	tDCS	M1	12	1 / 11	0 / 1 / 0 / 0	5 / 0 / 1 / 5	Pain relief by VAS
29.	Jensen MP et al., **[41]**	tDCS	M1	30	30 / 0	0 / 0 / 30 / 0	0 / 0 / 0 / 0	No pain relief by NRS

Studies of rTMS treatment are labeled yellow, studies of tDCS treatment are labeled green, and studies of ineffective treatment are labeled gray

rTMS repetitive transcranial magnetic stimulation, *tDCS* transcranial direct current stimulation, *ACC* anterior cingulate cortex, *PSI* posterior superior insula, *M1* primary motor cortex, *DLPFC* dorsolateral prefrontal cortex, *PMC* premotor cortex, *S1* primary somatosensory cortex, *S2* secondary somatosensory cortex

involving 95 NP patients (76.0%) also showed that tDCS successfully relieved NP [39, 40, 43, 44]. Thirty NP patients (24.0%) did not experience pain relief, as reported by Jensen MP et al. [41]. Among 95 NP patients who experienced a significant analgesic effect of tDCS, 81 had TNP (85.3%) and 14 had SNP (14.7%).

TNP

As shown in Fig. 3, among 575 patients with TNP, 505 received rTMS treatment for TNP induced by stroke (50.9%, $n = 257$), nerve trunk or root legions (30.9%, $n = 156$), SCI (12.9%, $n = 65$), and diabetic neuropathy (5.3%, $n = 27$). Furthermore, among the 575 patients with TNP, 105 patients received tDCS treatment, including TNP induced by SCI (65.7%, $n = 69$), lesions of the nerve trunks or roots (33.3%, $n = 35$), and stroke (1.0%, $n = 1$). There were no patients with TNP induced by diabetic neuropathy ($n = 0$).

Stroke-Induced TNP

Stroke-induced NP occurs in 2–8% of stroke survivors, with a prevalence of up to 18% in patients with somatosensory deficits and about half of the lesions affect solely the spinothalamic pathway, which may severely impair their quality of life [19, 36, 46]. Among NIBS-treated patients with stroke-induced TNP ($n = 258$) (Fig. 3), most were rTMS-P (91.5%, $n = 236$), and only one patient was tDCS-P (3.9%, $n = 1$). Unfortunately, 21 patients were rTMS-N (8.1%). However, no reports described cases of tDCS-N

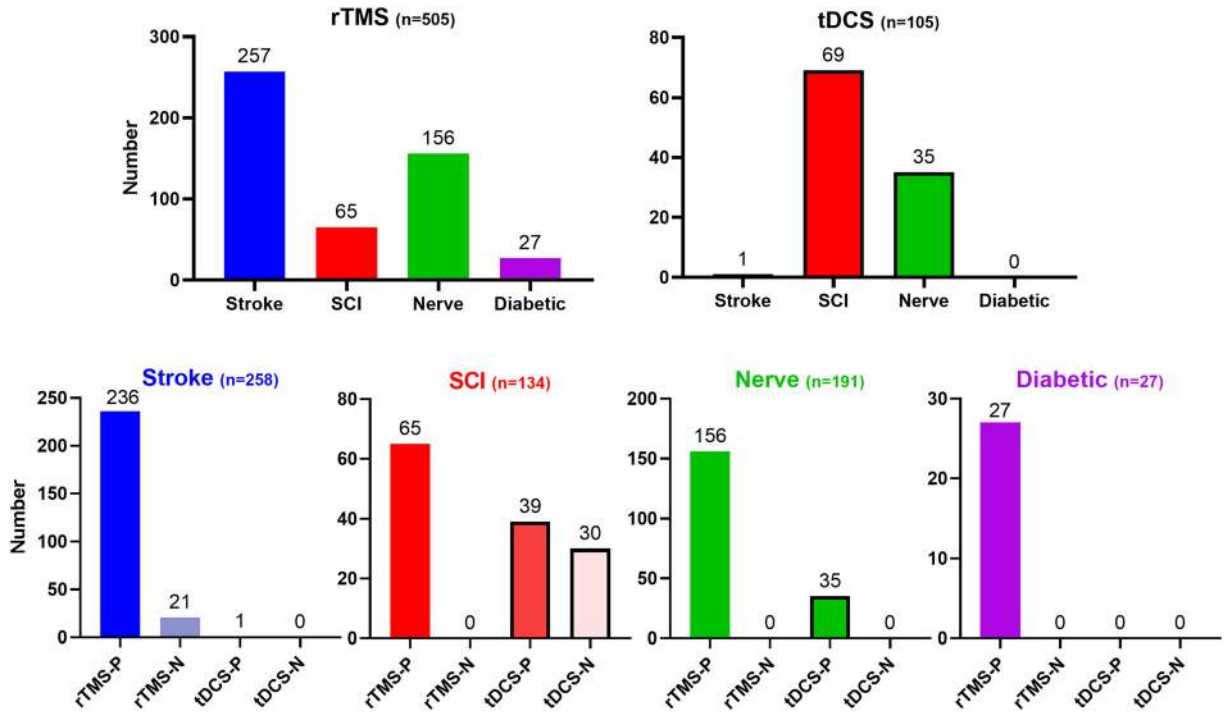

Fig. 3 Effect of NIBS on different subtypes of TNP. The figure shows the therapeutic effect of NIBS on four subtypes of typical NP (TNP) (above): (1) stroke (*blue*), (2) spinal cord injury (SCI) (*red*), (3) nerve trunk or root lesions (*green*), and (4) diabetes (*purple*). In the same subtype of data (below), the *dark color* represents the positive treatment results and the *light color* represents the negative treatment results. All NP patients can be divided into four categories: (1) rTMS-P, all NP patients with a positive analgesic effect from rTMS treatment; (2) rTMS-N, all NP patients with a negative analgesic effect from rTMS treatment; (3) tDCS-P, all NP patients with a positive analgesic effect from tDCS treatment; and (4) tDCS-N, all NP patients with a negative analgesic effect from tDCS treatment

($n = 0$). This result may imply that rTMS is effective in refractory and drug-resistant post-stroke NP, although this conclusion deserves confirmation in larger replication studies.

SCI-Induced TNP

SCI-induced NP ranks among the most debilitating complications of traumatic SCI, affecting > 80% of patients within 5 years after trauma and leading to NP in up to 59% of individuals [36]. Among the NIBS-treated patients with TNP induced by SCI ($n = 134$) (Fig. 3), half were rTMS-P (48.5%, $n = 65$), and nearly one-third were tDCS-P (29.1%, $n = 39$). Unfortunately, 30 were tDCS-N (22.4%). No reports described cases of rTMS-N ($n = 0$). This result may imply that rTMS is a reliable treatment for SCI-induced NP. However, the application of tDCS treatment for SCI-induced TNP patients may need much more careful assessment.

Diabetic Neuropathy-Induced TNP

Diabetic NP is the most common peripheral neuropathy globally, and its principal pathology involves distal autonomic and sensory dysfunction, predominantly affecting the patient's feet, estimated to affect approximately 30% of people with diabetes [47]. Among NIBS-treated diabetic TNP patients ($n = 27$) (Fig. 3), all of them were rTMS-P (100%). There were no cases of rTMS-N ($n = 0$), tDCS-P ($n = 0$), or tDCS-N ($n = 0$). This result, however, does not indicate that rTMS is most suitable for this type of NP because of the limited number of clinical trials. We can only advocate caution when we encounter this kind of complicated pain condition.

Nerve Lesion-Induced TNP

Lesions of the nerve can affect peripheral nerves, plexus trunks, or spinal nerve roots, causing paralysis, paresthesia, and pain [21, 48]. Among NIBS-treated patients with TNP induced by lesions of the nerve trunks or roots ($n = 191$) (Fig. 3), most of them were rTMS-P (81.7%, $n = 156$), and some were tDCS-P (18.3%, $n = 35$). There were no cases of either rTMS-N ($n = 0$) or tDCS-N ($n = 0$). This result could imply that NIBS is effective for damaged nerve-induced NP, which would be of benefit to NIBS supporters and victims of drug-resistant NP.

SNP

As shown in Fig. 4, among 251 patients with SNP, 92.0% ($n = 231$) received rTMS treatment, and only 8.0% ($n = 20$) received tDCS treatment. Among the 231 rTMS-treated SNP patients (Fig. 4), 58.9% ($n = 136$) had FaNP, 11.3% ($n = 26$) had CaNP, 26.4% ($n = 61$) had PhanNP, and others (3.4%, $n = 8$). Among the 20 tDCS-treated SNP patients, 25.0% ($n = 5$) had FaNP, 45.0% ($n = 9$) had PhanNP, others (30.0%, $n = 6$) and none ($n = 0$) had CaNP.

FaNP

NIBS has not been frequently studied in patients with FaNP until now. As shown in Fig. 4, in total, among the 141 FaNP patients, most were rTMS-P (96.5%, $n = 136$), and some were tDCS-P (3.5%, $n = 5$). There were no cases of either rTMS-N ($n = 0$) or tDCS-N ($n = 0$). Previous literature data concerning 86 patients with FaNP [31, 37, 42] indicate that motor cortex rTMS provides transient and modest subjective pain relief. Hodaj et al. [42] have reported that that in 55 patients (cluster headache, $n = 19$; trigeminal NP, $n = 21$; atypical facial pain, $n = 15$), three pain measures (intensities of permanent pain and paroxysmal pain and daily number of painful attacks) were significantly decreased. Therefore, this result could imply that NIBS is suitable for FaNP patients in the clinic.

CaNP

CaNP may arise from nerve compression or direct infiltration by a growing tumor or secondarily from changes in the neuronal media resulting from cancer and is difficult to control [32]. As shown in Fig. 4, among the 26 CaNP patients, all were rTMS-P (100%). There were no cases of rTMS-N ($n = 0$), tDCS-P ($n = 0$), or tDCS-N ($n = 0$). Therefore, the present results indicate the potential efficacy of rTMS for CaNP patients.

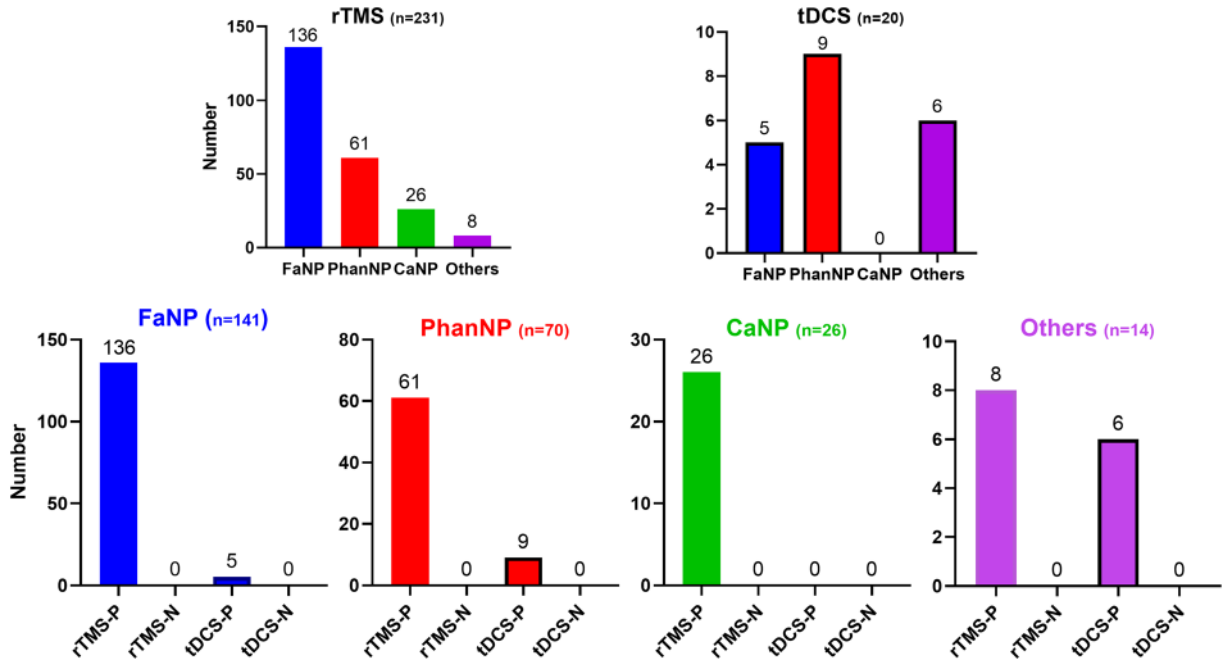

Fig. 4 Effect of NIBS on different subtypes of SNP. The figure shows the therapeutic effect of NIBS on four subtypes of special NP (SNP) (above): (1)facial NP (FaNP) (*blue*), (2) phantom limb NP (PhanNP) (*red*), (3) cancer NP (CaNP) (green), and (4) other conditions (purple), such as malformation, and bladder pain syndrome. In the same subtype of data (below), the *dark color* represents the positive treatment results and the *light color* represents the negative treatment results. All NP patients can be divided into four categories: (1) rTMS-P, all NP patients with a positive analgesic effect from rTMS treatment; (2) rTMS-N, all NP patients with a negative analgesic effect from rTMS treatment; (3) tDCS-P, all NP patients with a positive analgesic effect from tDCS treatment; and (4) tDCS-N, all NP patients with a negative analgesic effect from tDCS treatment

PhanNP

PhanNP is very common after limb amputation and difficult to treat, usually responding poorly to conventional pain treatments [45]. As shown in Fig. 4, among the 70 PhanNP patients, most were rTMS-P (87.1%, $n = 61$), and 12.% were tDCS-P ($n = 9$). There were no cases of rTMS-N ($n = 0$) or tDCS-N ($n = 0$). Nevertheless, the positive analgesic effects of NIBS deserve further research in a large number of populations experiencing NP in an amputated limb.

Other SNPs

Other conditions, such as complex regional pain syndrome (CRPS) [44], fibromyalgia, or polyneuropathy [41], can also cause NP. Among NIBS-treated patients with TNP induced by other sources ($n = 14$) (Fig. 4), most of them were rTMS-P (57.1%, $n = 8$), and some were tDCS-P (42.9%, $n = 6$). There are no cases of either rTMS-N ($n = 0$) or tDCS-N ($n = 0$). This result could reflect the fact that rTMS could not relieve pain effectively in some clinical trials, and tDCS could be attempted and potentially effective.

Analgesic Target and Localization of rTMS

As shown in Table 1 and Fig. 3, among the 484 TNP patients with rTMS-P, 79.4% ($n = 384$) of the rTMS treatments targeted M1, 10.1% ($n = 49$) targeted the anterior cingulate cortex (ACC), 10.1% ($n = 49$) targeted the posterior superior insula (PSI), and 0.4% ($n = 2$) targeted the dorsolateral prefrontal cortex (DLPFC).

As shown in Table 1 and Fig. 4, among the 231 SNP patients with rTMS-P, almost all (96.5%, $n = 223$) were administered rTMS that

targeted M1, and only 3.5% ($n = 8$) received rTMS that targeted the DLPFC. There are no reports on SNP patients with a positive response to rTMS targeting other brain regions. This may suggest that for NP patients with FaNP, CaNP, or PhanNP, M1-targeted rTMS should be the first choice.

As mentioned above, 79.4% of effective analgesia targeted M1 (Table 1), which means that the M1 region plays a key role in the analgesic treatment of NIBS. Therefore, it is crucial to accurately localize the M1 region during treatment. Currently, motor evoked potentials (MEPs), the 10–20 electroencephalography system (EEG 10/20 system) and neuro-navigation methods are used in clinical practice to locate M1 targets.

MEP-Based Method

Nineteen of 30 selected studies used the MEP-based method to target M1. The optimal stimulation site, the motor hot spot, could be determined according to visual detection of muscle twitches with this method [22] (Fig. 5a). The resting motor threshold (RMT) is defined as the minimum stimulator intensity needed to evoke at least one visible muscle twitch in the extensor hallucis brevis muscle while maintaining a relaxed position [20, 22, 24, 25, 32, 33, 37, 42]. The DLPFC/PMC location can also be defined with respect to M1 (5 cm anterior to M1) [29, 30, 49, 50] (Fig. 5a). MEP recordings are simple and maneuverable and are by far the most widely used method to locate M1 in clinical rTMS treatment.

EEG 10/20 System Method

The EEG 10/20 system is the standard electrode placement system developed by the International Brain Mapping Society [51]. It is characterized by the arrangement of electrodes with respect to the size and shape of the skull. Electrodes are appropriately distributed in the main part of the skull in the standard position (Fig. 5b). Marker points with the same name can be considered to correspond to roughly the same anatomical regions of the brains of different subjects. In the literature, the stimulating electrode is typically placed over C3 or C4 (in the EEG 10/20 system) to target M1 contralateral to the painful side [16, 39–41, 52]. This method is simple and convenient and is also widely used in clinical practice.

Neuro-Navigation Method

A $1 \times 1 \times 1$ mm^3 3D T1-weighted MRI for frameless stereotaxic neuro-navigation can be used to define the target of magnetic stimulation, for example, the subdivision of M1 representing the hand [53, 54] (Fig. 5c). Of the articles we reviewed, six studies reported the use of a neuro-navigation technique that can detect hypermetabolic or hyperactive cortical regions by positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) [19, 21, 23, 26, 34, 36]. This method should allow better reproducibility and accuracy regarding the identification of the stimulation site and potentially increased efficacy [12].

Stimulation Parameters of Analgesic rTMS

rTMS paradigms are mainly defined with four stimulation parameters: stimulation frequency, stimulation intensity, number of pulses, and number of sessions (Table 2).

Stimulation Frequency

Stimulation frequency is the most crucial parameter for rTMS therapeutic applications [12]. rTMS typically falls into two categories: high-frequency rTMS (HF rTMS), with a frequency between 5 and 20 Hz, and low-frequency rTMS (LF rTMS), with a frequency at 1 Hz or less. HF rTMS is commonly considered excitatory, whereas LF rTMS is considered inhibitory [55–58]. Among the 24 rTMS studies, HF rTMS was used in 21 (87.5%), and LF rTMS was used in three (12.5%). Among the 21 HF rTMS studies, 5—10 Hz stimulation was used in 17 studies (81.0%), and 20 Hz stimulation was used in four studies (19.0%).

Stimulation Intensity

To indicate treatment dosage, the RMT is determined at the initial treatment session, and treatment intensity is titrated from 80 to 120% of the RMT depending upon patient tolerance

[59]. Among the 24 rTMS studies, 11 selected 90% of the RMT, eight selected 80% of the RMT, and five selected at least 100% of the RMT as the final intensity.

Pulse Number

According to the different number of pulses, TMS is usually divided into single-pulse TMS (sTMS), paired-pulse TMS (pTMS), and rTMS [60–62]. rTMS is mostly used for analgesia [12]. Of the 24 rTMS studies in this review, 18 studies (75%) used between 1000 and 2000 pulses. Three studies (12.5%) used 500–600 pulses, and three studies (12.5%) used 2500–3000 pulses.

Session Number

Although the duration of the effects of a single rTMS is short-lasting, longer-lasting subsequent effects can be achieved by using longer periods of stimulation or multiple rTMS sessions [63]. Researchers tend to use more than a single rTMS session, since the most robust analgesic effects were found to occur 2–4 days after an rTMS session, and the analgesic effect remained for a fortnight after the last treatment, but this beneficial effect generally lasted less than 1 month [12, 26].

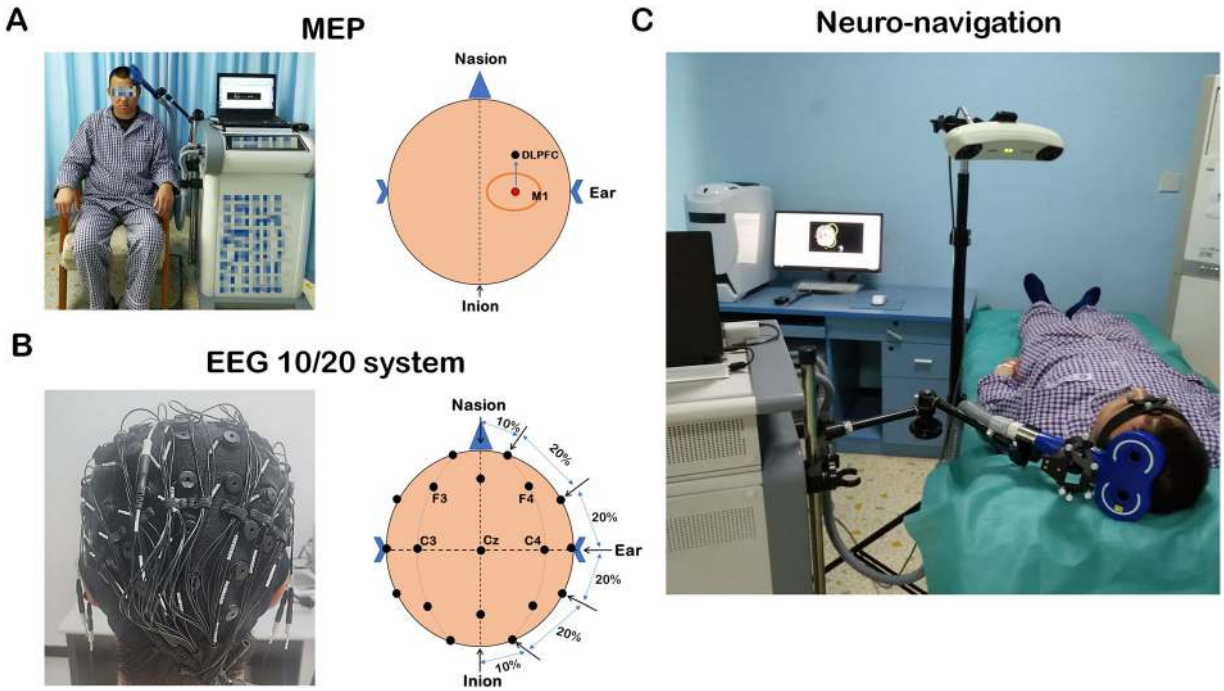

Fig. 5 Common methods for targeting brain regions in NIBS. **a** MEP-based method was used to target M1 of the patient (*left*). In detail, the coil is placed over the contralateral hemisphere in the area corresponding to the M1, and the optimal stimulation site is found by moving the coil over the scalp to the site that evokes the largest MEP amplitude in the resting state of target muscle (the *orange circle* represents the M1 area of the brain, and the *red spot* represents the optimal stimulation site), and then along the central axis direction forward 5 cm is considered DLPFC region (*the black spot*) (*right*). **b** Picture of electrode cap on patient's head, in which the electrodes are properly distributed in the main part of the skull in a standard position (*left*). Schematic diagram of standard electrode placement for EEG 10/20 system (*right*). The position of the C3/C4 electrode is assumed to correspond to the M1 region, while the DLPFC region is targeted by placing the stimulating electrode on the scalp at F3/F4. Cz = vertex. **c** Schematic diagram of using neuro-navigation to target brain regions. The patient lies on the bed in a relaxed posture, and neuro-navigation is used to define the target of magnetic stimulation which is the M1 in its subdivision representing the hand

Table 2 Summary of the parameters of rTMS on NP patients

	Ref	rTMS Parameters			
		Stimulation Frequency (Hz)	Stimulation Intensity (% RMT)	Pulse Number (n)	Session Number (n)
1.	Galhardonl R et al., 2019 **[36]**	10	90	1500	5
2.	Ander-Obadia N et al., 2018 **[37]**	10	90	2000	2
3.	Benjamin P et al., 2018 **[19]**	20	80	1600	4
4.	Nizard J et al., 2018 **[35]**	1	110	1200	6
5.	KOHúTOVá B et al., 2017 **[31]**	5	80	600	1
6.	Shimizu T et al., 2017 **[20]**	5	90	500	5
7.	Ayache SS et al., 2016 **[26]**	10	90	3000	3
8.	Malavera A et al., 2016 **[14]**	10	90	1200	10
9.	Hodaj H et al., 2015 **[42]**	10	80	2000	7
10.	Pommier B et al., 2015 **[21]**	20	80	1600	4
11.	Khedr EM et al., 2015 **[32]**	20	80	2000	10
12.	Lindholm P et al., 2015 **[34]**	10	90	1000	5
13.	Nizrad J et al., 2015 **[38]**	10	80	2000	5
14.	Hosomi K et al., 2013 **[22]**	5	90	1500	10
15.	Onesti E et al., 2013 **[28]**	20	100	1500	5
16.	JETTé F et al., 2013 **[33]**	10	90	2000	1
17.	Lefaucheur JP et al., 2012 **[23]**	10	90	2000	3
18.	Lefaucheur JP et al., 2011 **[24]**	10	90	2000	2
19.	Sampson SM et al., 2011 **[29]**	1	110	1600	15
20.	Di Rollo A et al., 2011 **[45]**	1	80	600	10
21.	Lefaucheur JP et al., 2010 **[27]**	10	90	2000	2
22.	Picarelli H et al., 2010 **[25]**	10	100	2500	10
23.	De Oliveira RA et al., 2014 **[30]**	10	120	1250	10
24.	Attal N et al., 2016 **[39]**	10	80	3000	3

Study of ineffective treatment is labeled gray
rTMS repetitive transcranial magnetic stimulation, *RMT* resting motor threshold

Stimulation Parameters of Analgesic tDCS

The design of a tDCS protocol particularly requires establishing three parameters: current intensity, session duration, and number of sessions (Table 3).

Current Intensity

The stimulation form of tDCS includes anode tDCS (atDCS) and cathode tDCS (ctDCS). When a positively charged electrode (anode) is placed on the surface of the skull, a portion of the current is thought to enter the brain and polarize the neurons close to the electrode, thereby increasing neuronal firing. Conversely, a negatively charged electrode (cathode) decreases the excitability of the cortex and induces hyperpolarization of the neurons [64, 65]. The tDCS used in the studies summarized in the present review achieved an analgesic effect when the current intensity was 1 or 2 mA (Table 3).

Session Duration

Session duration is the total amount of time the patient spends in treatment [39, 66]. The tDCS used in the present review could achieve

Table 3 Summary of the parameters of tDCS on NP patients

Ref	tDCS Parameters		
	Current Intensity (mA)	Session Duration (min)	Session Number (n)
1. Attal N et al., 2016 **[39]**	2	30	3
2. Houde F et al., 2020 **[44]**	2	25	5
3. Bolognini N et al., 2013 **[16]**	2	15	5
4. Soler MD et al., 2010 **[40]**	2	20	10
5. Antal A et al., 2010 **[43]**	1	20	5
6. Jensen MP et al., 2013 **[41]**	2	20	1

Study of ineffective treatment is labeled gray
tDCS transcranial direct current stimulation

analgesic effects when the session duration was 20–30 min (Table 3).

Session Number

Session repetition timing may reflect the non-linear relationship between tDCS settings and the biological effects produced [13, 67]. The tDCS used in the present review achieved an analgesic effect over 5–10 sessions (Table 3).

Potential Analgesic Mechanisms of NIBS

Unfortunately, the mechanism underlying the analgesic treatment effect of NIBS is unclear. The following three hypotheses have been described in the literature in this review.

Wide Brain Regulation Beyond M1

Bearing the anatomical evidence of structural and functional connections in mind, the widespread impact of neuromodulation of M1 stimulation to treat NP can be explained [64, 68, 69]. In fact, the effects of rTMS are not only exerted in the area of stimulation, but also spread over the associated cortical, subcortical, and spinal structures. In addition, rTMS on the M1 can modulate the activity of cortical and subcortical regions such as the contralateral M1, thalamus, ACC, somatosensory cortex, insula, and cerebellum. Notably, M1-rTMS consistently interferes with activity in brain areas associated with painful emotions, including the ACC and insula, explaining the effects of M1 stimulation on the emotional aspect of pain [25, 70].

Similar to rTMS, the analgesic effects of tDCS may be due to the modulation of the distal neural structures of NP, including sensory-discriminative, cognitive, or emotional aspects of NP [71]. Imaging studies have shown that tDCS additionally affects structures involved in affective, cognitive, and emotional aspects of pain, such as the cingulate and orbitofrontal cortices [72, 73].

Activation of the Endogenous Opioid System

However, the mechanisms of NIBS must be multiple and complex, related to the regulation of neural excitability and synaptic plasticity, and involve various neurotransmitter systems, such as endogenous opioids, glutamate, gamma-aminobutyric acid (GABA), and/or dopamine [74, 75]. rTMS of the DLPFC can also cause endogenous opioidergic pain relief when combined with opioid activity [59]. Studies suggest that tDCS in combination with medication-assisted treatment could be an effective strategy in reducing cravings for opioid use [13, 52, 76].

Promotion of GABA Release

Cortical inhibition is the neurophysiological process by which GABA-inhibited interneurons selectively attenuate the activity of cortical pyramidal neurons, and impairment of this cortical inhibition is a mechanism associated with NP [63, 77, 78]. HF rTMS produces excitatory effects, and is thought to enhance synapse

plasticity by inducing long-term potentiation (LTP). In contrast, LF rTMS generates inhibitory effects, presumably through long-term depression (LTD) [23, 79, 80]. rTMS may induce multiple alterations related to LTD and LTP [63]. Magnetic resonance spectroscopy (MRS) studies have shown that atDCS reduces local concentrations of the inhibitory neurotransmitter GABA, whereas ctDCS reduces excitatory glutamate levels [81–83].

DISCUSSION

NP resulting from lesions or diseases of the nervous system represents an important medical challenge. Our systematic review highlights the analgesic effects of NIBS in patients with NP. It is important to note that NIBS is a noninvasive neuromodulation technique that, although generally well tolerated, warrants special safety considerations for side effects in patient populations, such as local burning, tinnitus, headache, disturbance of grafts, and even induction of seizures. Therefore, the aim of this paper is to summarize the analgesic effects of NIBS on different NPs in order to reduce the occurrence of adverse effects.

In this manuscript, instead of using the classic central and peripheral classifications, we classified the most common (large number of cases) types of NP as typical NP (TNP), including diabetic neuropathy, stroke, spinal cord injury, and nerve injury. The remaining clinically rare types are classified as special NP (SNP), such as facial pain, phantom limb pain, cancer pain, and other types of pain. We hope that this new classification will provide additional benefit in terms of understanding and treating NP. This systematic review reveals that, in general, the optimal therapeutic parameters for rTMS/tDCS and the treatment of NP should allow the design of optimal treatments for individual patients.

Based on the results of the review, the stimulation parameters of rTMS that best induce an analgesic effect are a stimulation frequency of 10—20 Hz, a stimulation intensity of 80–120% of RMT, 1000–2000 pulses, and 5–10 sessions, and the most effective parameters of tDCS are a current intensity of 2 mA, a session duration of 20–30 min, and 5–10 sessions.

A limitation of this review is that when we summarized the analgesic effect of NIBS, we focused on NP and further divided NP into TNP and SNP. However, we did not involve other types of pain, so it is inevitable that there are some omissions in the summary of the parameters of the analgesic treatment effects of NIBS.

The placebo effect of NIBS can be studied by two means: firstly, the clinicians have positioned an active coil over an area distant from the targeted stimulation area; alternatively, the coil positioned as the targeted stimulation area has been adjusted to an angle of 45° or 90° relative to the scalp has from the tangential style [1]. In the present review, 15 reports from a total of 24 rTMS reports as well as four reports from total six tDCS reports have provided the observations and analysis of the placebo effect. In 15 rTMS studies, four have reported that pain scores did not change significantly by sham rTMS, which has indicated the lack of placebo effect of rTMS [24, 26, 28, 37]. In four tDCS studies, two have reported that pain scores did not change significantly by sham treatment, which has indicated the lack of placebo effect of tDCS [16, 40]. Furthermore, all other 11 rTMS reports and two tDCS reports have shown that the pain scores of the subjects could be significantly reduced by active rTMS or tDCS, but not by sham rTMS or sham tDCS.

There are few data related to the long-term benefit of tDCS as a useful tool to alleviate neuropathic pain. Dalla Volta et al. have observed that 3 months after the last tDCS stimulation, the patients with drug-resistant migrainous could still obtain a reduction of 50% of pain scores [84]. However, some reports have shown that there is no long-term analgesic effect of tDCS on chronic migraine [85] or lung cancer pain [86], while the long-term effect of rTMS on pain relief has been shown in a 6-month study of rTMS treatment in patients with facial pain [42] or with nerve injury induced NP [35]. We have also noticed that the active rTMS could significantly reduce pain intensity with the time course of 25 weeks [79] or even 2.8 years [21].

Given that the scientific evidence is still limited, there is a need for multicenter coordination, more randomized controlled studies and the integration of big data to deepen the current understanding of the analgesic mechanisms of rTMS and tDCS.

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