frontiers | Research Topics

Combining a non-invasive transcranial stimulation technique with another therapeutic approach: Mechanisms of action, therapeutic interest and tolerance

Edited by
Jean Paul Buu Cuong Nguyen, Julien Nizard, Helena Knotkova, Simone Rossi and Jean-Pascal Lefaucheur

Published in
Frontiers in Neurology

ISSN 1664-8714
ISBN 978-2-8325-5187-5
DOI 10.3389/978-2-8325-5187-5

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Combining a non-invasive transcranial stimulation technique with another therapeutic approach: Mechanisms of action, therapeutic interest and tolerance

Topic editors

Jean Paul Buu Cuong Nguyen — Centre Hospitalier Universitaire (CHU) de Nantes, France

Julien Nizard — Université de Nantes, France

Helena Knotkova — MJHS Institute for Innovation in Palliative Care, United States

Simone Rossi — University of Siena, Italy

Jean-Pascal Lefaucheur — Hôpitaux Universitaires Henri Mondor, France

Citation

Nguyen, J. P. B. C., Nizard, J., Knotkova, H., Rossi, S., Lefaucheur, J.-P., eds. (2024). *Combining a non-invasive transcranial stimulation technique with another therapeutic approach: Mechanisms of action, therapeutic interest and tolerance*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5187-5

Table of contents

frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 16 July 2024
DOI 10.3389/fneur.2024.1440696

OPEN ACCESS

EDITED AND REVIEWED BY
Thomas Platz,
University of Greifswald, Germany

*CORRESPONDENCE
Jean-Pascal Lefaucheur
✉ jean-pascal.lefaucheur@hmn.aphp.fr

RECEIVED 29 May 2024
ACCEPTED 28 June 2024
PUBLISHED 16 July 2024

CITATION
Lefaucheur J-P, Nguyen J-P, Knotkova H, Rossi S and Nizard J (2024) Editorial: Combining a non-invasive transcranial stimulation technique with another therapeutic approach: mechanisms of action, therapeutic interest and tolerance.
Front. Neurol. 15:1440696.
doi: 10.3389/fneur.2024.1440696

Editorial: Combining a non-invasive transcranial stimulation technique with another therapeutic approach: mechanisms of action, therapeutic interest and tolerance

Jean-Pascal Lefaucheur[1,2]*, Jean-Paul Nguyen[3], Helena Knotkova[4,5], Simone Rossi[6,7] and Julien Nizard[7,8]

[1]UR 4391, Excitabilité Nerveuse et Thérapeutique, Université Paris-Est Créteil, Créteil, France, [2]Unité de Neurophysiologie Clinique, Hôpital Henri Mondor, Assistance Publique - Hôpitaux de Paris (AP-HP), Créteil, France, [3]Unité de stimulation transcrânienne, clinique Bretéché, groupe Elsan, Nantes, France, [4]MJHS Institute for Innovation in Palliative Care, New York, NY, United States, [5]Department of Family and Social Medicine, Albert Einstein College of Medicine, Bronx, NY, United States, [6]Siena Brain Investigation and Neuromodulation Lab (Si-BIN Lab), Department of Medicine, Surgery and Neuroscience, Neurology and Clinical Neurophysiology Section, University of Siena, Siena, Italy, [7]Service Douleur, Soins palliatifs et de Support, Hôpital Laennec, Centre Hospitalier Universitaire de Nantes, Nantes, France, [8]UMR 1229, Médecine Régénératrice et Squelette, INSERM, Université de Nantes Université, Nantes, France

KEYWORDS

repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), transauricular vagus nerve stimulation (taVNS), non-invasive neuromodulation techniques, combined strategy

Editorial on the Research Topic
Combining a non-invasive transcranial stimulation technique with another therapeutic approach: mechanisms of action, therapeutic interest and tolerance

Numerous publications have attested to the therapeutic efficacy of non-invasive neuromodulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and low-intensity transcranial electrical stimulation (tES), but also peripheral magnetic (pMS) or electrical (pES) stimulation techniques, particularly applied to certain cranial nerves, such as transauricular vagus nerve stimulation (taVNS) or occipital nerve stimulation (ONS). These nerves can also be stimulated invasively (iVNS, iONS) using surgically implanted electrodes and pulse generators. These methods have been used in the treatment of various neurological conditions, such as chronic pain, cognitive disorders, poststroke rehabilitation, or movement disorders. In these different domains, evidence suggests that therapeutic efficacy could be improved by combining neuromodulation techniques with other types of non-pharmacological approaches, such as motor or cognitive tasks or training. In this Research Topic collection, we gathered together nine publications

evaluating such a combined strategy in different clinical contexts. They concerned the treatment of various pain conditions (Wandrey et al., Agostinho et al.), even associated with cognitive impairment (Caloc'h et al.), a pure cognitive disorder (Horczak et al.), disorder of consciousness (Zhuang et al.), motor stroke rehabilitation (Wang et al., Qi et al.), dystonia (Bleton et al.), or motor, language, or cognitive enhancement before brain surgery (Boccuni et al.). Concerning the type of neuromodulation technique, publications have addressed the value of tDCS (Wandrey et al., Agostinho et al., Horczak et al., Bleton et al.), tDCS or rTMS (Boccuni et al.), tDCS and taVNS (Zhuang et al.), taVNS or iVNS (Wang et al.), rTMS and iONS (Caloc'h et al.), and tES, rTMS, pES, or pMS (Qi et al.). Complementary techniques were cognitive training (Caloc'h et al.), mirror therapy or behavioral interventions (Agostinho et al., Horczak et al., Qi et al., Boccuni et al.), motor training or rehabilitation (Wang et al., Bleton et al.), local anesthetic infiltrations (Wandrey et al.), or just a combination of two neuromodulation techniques (Zhuang et al.).

First, Wandrey et al. show in a randomized sham-controlled trial that anodal or cathodal tDCS delivered to the primary motor cortex (M1) did not significantly enhance pain alleviation provided by subsequent local anesthetic infiltrations (primarily targeting the sphenopalatine ganglion) compared to sham tDCS in patients with either trigeminal neuralgia or persistent idiopathic facial pain. However, due to a high dropout rate, only a few patients completed the study (six, three, and four patients for anodal, cathodal, and sham tDCS, respectively), which therefore remains inconclusive and warrants further investigation in larger series.

Second, Agostinho et al. review the literature on the value of combining tDCS with other non-pharmacological approaches in the field of pain. These authors specifically highlight their own experience with combining anodal tDCS of M1 and mirror therapy to treat phantom limb pain. They showed that applying this therapeutic strategy at an early stage from the onset of symptoms produced impressive pain relief with long-lasting after-effects. In this perspective article, the authors recommend applying such an intervention at the acute stage of a painful disease, or as early as possible to limit maladaptive plasticity and prevent the chronification of a pain syndrome.

Third, Caloc'h et al. address a clinical condition combining pain and cognitive impairment, secondary to traumatic brain injury. In the reported case, the patient was first treated with bilaterally iONS to relieve chronic refractory headaches (8 years after the head trauma). Two years later, he was treated with a 6-week protocol combining rTMS delivered to multiple cortical sites and cognitive training (CogT) targeting memory, language, and visuospatial functions. Pain relief and cognitive improvement were observed after iONS but the multisite rTMS-CogT protocol provided additional significant improvement on apathy, depression, and anxiety.

Fourth, Horczak et al. show in a parallel randomized sham-controlled study involving 17 participants that active anodal tDCS of the left dorsolateral prefrontal cortex performed prior to sessions of cognitive behavioral therapy (attention task) did not provide significant additional improvement over sham stimulation in treating rumination linked to negative mood. Again, a too small sample size possibly prevented statistical differences between active and sham tDCS-combined protocols from being achieved.

Fifth, Zhuang et al. describe a protocol for a randomized sham-controlled study of the combination of tDCS and taVNS to treat disorders of consciousness. The goal of such a strategy is to enhance bottom-up thalamo-cortical connections using bilateral taVNS and simultaneously increase top-down cortico-cortical connections using high-definition tDCS (HD-tDCS) centered on Pz with four return electrodes placed at Cz, P3, P4, and POz to target the precuneus and the posterior parietal cortex. All patients will undergo a 4-week treatment and will be evaluated on clinical aspects and electroencephalogram (EEG) microstates.

Sixth, Wang et al. report a systematic review of the literature (with meta-analysis) on the efficacy of taVNS or iVNS combined with motor training in the rehabilitation of poststroke upper limb motor dysfunction. Ten trials with 335 patients were included in the meta-analysis. Regarding upper extremity motor function, based on Fugl-Meyer assessment scores, VNS combined with other treatment options had immediate and long-term (1–3 months) beneficial effects compared to that of the control treatment. Subgroup analyses showed that taVNS may be superior to iVNS, that a stimulation frequency set at 20 Hz may be superior to higher frequencies, and that VNS combined with integrated treatment may be superior to VNS combined with upper extremity training alone. Beyond motor improvement, VNS may improve activities of daily living and depression, but perhaps not the overall quality of life. The mechanisms underlying the effects of VNS on motor recovery in stroke patients remain unclear, potentially related to a non-specific modulation of cortical network excitability, which is able to facilitate functional recovery specifically related to the task performed in combination.

Seventh, Qi et al. review the literature on the potential benefits of combining various non-invasive stimulation techniques (tES, rTMS, pES, pMS) with action observation training in poststroke rehabilitation. Furthermore, they discussed how tES or rTMS over the contralesional hemisphere or the lesioned hemisphere combined with pES or pMS of the paretic limbs during motor observation followed by action execution have super-additive effects to potentiate the effect of conventional rehabilitation strategies.

Eight, Bleton et al. report a case series of five patients with cervical dystonia poorly controlled by botulinum toxin injections and treated by repeated daily sessions of anodal tDCS of the cerebellum combined with oriented motor training, specifically developed to treat this clinical condition. The combined strategy produced a more striking and prolonged improvement in dystonia and dystonia-related pain than the application of cerebellar tDCS alone.

Ninth, Boccuni et al. describe a study protocol to assess the value of 10–20 sessions (one or two sessions each weekday, 30-min duration) of "inhibitory" non-invasive brain stimulation (NIBS) protocol (either low-frequency rTMS or mostly cathodal tDCS) coupled with intensive motor, language, or cognitive training session (30-min duration) in a series of patients with brain tumor before the surgical removal. The objective of this protocol is to reduce the activation of the brain regions concerned by the surgery by locally applying inhibitory neuromodulation

and to concomitantly promote neuroplasticity and increase the activation of alternative brain pathways by intensive training with specifically adapted tasks. Thus, the goal of this strategy called "neuromodulation-induced cortical prehabilitation" (NICP) is to reduce the functional relevance of cortical areas by applying inhibitory NIBS and then to facilitate their resection with reduced risks of neurological sequelae. The post-surgical assessment will be based on clinical outcomes (motor function, balance, cognitive and language performance, quality of life), as well as on functional neuroimaging and navigated TMS mapping.

This Research Topic collection clearly shows that the non-invasive neuromodulation procedures (tDCS, rTMS, taVNS) that can be used in combination with other nonpharmacological approaches are extremely varied, as are the potential therapeutic indications for these combinations. These publications, although innovative, have significant limitations. There were only two randomized sham-controlled studies and both report negative results of a tDCS protocol (Wandrey et al., Horczak et al.). This may be explained by a small total sample size (13–17 patients), further divided into parallel groups. Another possible explanation is the fact that the complementary therapeutic intervention (local anesthetic infiltration or cognitive behavioral therapy) led to a "ceiling" effect which did not allow to highlight an additional effect of tDCS. In contrast beneficial effects of NIBS procedures (rTMS or tDCS) were reported in two other studies (Caloc'h et al., Bleton et al.), but based on open-labeled single or few case reports. The other articles are points of view, literature reviews or meta-analyses (Agostinho et al., Wang et al., Qi et al.) or study protocol description (Zhuang et al., Boccuni et al.).

In terms of neuromodulation techniques to be used in a combined strategy, there is a preference for tES or taVNS, which can be applied more easily than rTMS, including at home. Invasive procedures, such as iVNS and iONS, were also addressed in the present studies and should not be neglected to promote long-term benefits in clinical practice. An additional interesting point is also the timing of the intervention, an early application being particularly promising as suggested by Agostinho et al..

The efficacy of non-invasive neuromodulation techniques could be increased in the future by additional improvements, such as a better definition of indications, the personalization of targeting (including new targets), or the optimization of maintenance protocols. The simplification of procedures, the portability of the devices, and their lower costs will also contribute to their diffusion among patients.

Such combined protocols in any case present a good safety profile, but they need to be better standardized and better evaluated, as the available scientific data still remains largely insufficient. The publications of this Research Topic collection do not yet make it possible the establishment of good practice recommendations regarding any of these combined therapeutic approaches. This of course underlines the importance of new controlled studies on larger sample sizes to confirm the potential benefits of such treatment combinations in the different indications described in this Research Topic, but also very probably in many others which will emerge in the near future.

Author contributions

J-PL: Writing – original draft, Writing – review & editing. J-PN: Writing – review & editing. HK: Writing – review & editing. SR: Writing – review & editing. JN: Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

frontiers | Frontiers in Neurology

TYPE Perspective
PUBLISHED 30 January 2023
DOI 10.3389/fneur.2023.1115370

OPEN ACCESS

EDITED BY
Simone Rossi,
University of Siena, Italy

REVIEWED BY
Jean-Pascal Lefaucheur,
Univ Paris-Est Créteil, AP-HP, France

*CORRESPONDENCE
Roi Treister
✉ rtreister@univ.haifa.ac.il

SPECIALTY SECTION
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

RECEIVED 03 December 2022
ACCEPTED 11 January 2023
PUBLISHED 30 January 2023

CITATION
Agostinho M, Weissman Fogel I and Treister R (2023) Time since onset might be of essence: A recommendation to assess the effects of combination of non-pharmacological neuromodulatory approaches at early stage since symptoms onset.
Front. Neurol. 14:1115370.
doi: 10.3389/fneur.2023.1115370

Time since onset might be of essence: A recommendation to assess the effects of combination of non-pharmacological neuromodulatory approaches at early stage since symptoms onset

Mariana Agostinho[1,2], Irit Weissman Fogel[3] and Roi Treister[1]*

[1]The Cheryl Spencer Department of Nursing, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa, Israel, [2]Centre for Interdisciplinary Health Research, CIIS, Institute of Health Sciences, Universidade Católica Portuguesa, Lisbon, Portugal, [3]Physical Therapy Department, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa, Israel

In the past decade researchers began to assess the potential beneficial effects of non-invasive brain stimulation (NIBS) combined with a behavioral task as a treatment approach for various medical conditions. Transcranial direct current stimulation (tDCS) applied to the motor cortex combined with another treatment approach has been assessed as analgesic treatment in neuropathic and non-neuropathic pain conditions, and was found to exert only modest pain relief. Our group results show that combined tDCS and mirror therapy dramatically reduced acute phantom limb pain intensity with long-lasting effects, potentially preventing pain chronification. A review of the scientific literature indicates that our approach differs from that of others: We applied the intervention at the acute stage of the disease, whereas other studies applied the intervention in patients whose disease had already been established. We suggest that the timing of administration of the combined intervention is critical. Unlike in patients with chronic painful condition, in which the maladaptive plasticity associated with pain chronification and chronicity is well-consolidated, early treatment at the acute pain stage may be more successful in counterbalancing the not-yet consolidated maladaptive plasticity. We encourage the research community to test our hypothesis, both in the treatment of pain, and beyond.

KEYWORDS

neuromodulation, non-invasive brain stimulation, combined therapy, analgesic therapy, mirror therapy

1. Introduction

1.1. Transcranial direct current stimulation (tDCS) for the treatment of pain

Although the use of electrical currents for medical treatment has been documented historically (1–3), technological developments in recent decades have enabled the use of electrical-based non-invasive brain stimulation techniques, such as transcranial magnetic stimulation and transcranial direct current stimulation (tDCS), to alleviate various symptoms, such as depression and pain. This perspective article focuses on the combination of tDCS plus an additional non-pharmacological neuromodulatory treatment aimed at relieving pain.

tDCS is believed to exert its effects by modulating the resting membrane potential of a neuron and thereby changing the threshold for generating action potentials (4). Anodal motor cortex stimulation is a common montage often tested for the treatment of pain. The analgesic effect of anodal tDCS of the motor cortex was proposed to originate from local and connectional effects in remote cortical and subcortical areas through enhanced neuronal excitability. Current evidence suggests that M1 stimulation modulates thalamic and somatosensory activity by descending corticothalamic pathways, brain areas of the fronto-striatal circuit, limbic brain areas, and the periaqueductal gray [i.e., (4–6)].

1.2. Combining tDCS with other non-pharmacological neuromodulatory approaches

Although the past 20 years have seen much research on the effects of tDCS on both the brain and pain (7), the accumulated results of the early investigations highlighted only modest and short-term analgesic effects. More recently, researchers hypothesized that combining tDCS with another neuromodulatory treatment could enhance analgesic effects (7–11).

To address this hypothesis, researchers began to explore the analgesic effects of such combined treatments in various pain indications, including phantom limb pain (12–14), neuropathic pain (15–23), complex regional pain syndrome (24, 25), fibromyalgia (26–33), headache (34), chronic musculoskeletal pain (35), chronic low-back pain (36–40), knee osteoarthritis pain (41–45), temporomandibular disorders (46), burning mouth syndrome (47), chronic visceral pain (48), neurogenic pain (49), myofascial pain (50, 51), tendinopathy (52), and radiculopathy (53) (Table 1).

The other neuromodulatory approaches that were combined with the tDCS could be grouped into 4 categories: The first category includes mirror therapy (12–15), visual illusion (16–18, 22) and motor graded imagery (24). These three interventions are sharing similar characteristic—in all these behavioral tasks the participants receive (or imagine) visual input (with, or without additional sensory-motor input) that is assumed to counterbalance the maladaptive plasticity associated with the painful condition. The second category of neuromodulatory approaches includes different exercises (20, 26, 27, 33, 36, 41, 46, 47, 51, 52, 54), in which participants were requested to use a treadmill to perform aerobic exercise or to produce a series of movements specifically intended to increase mobilization, strength and endurance of a painful limb. The therapeutic effects of these exercises are assumed to be produced *via* modulation of several systems, such as enhancement of corticothalamic excitability, and motor and attentional areas, increase in activity of the descending pain modulatory system and release of dopaminergic and endogenous opioids (58–60). The third category of neuromodulatory approaches comprised of other physical therapy interventions, included the use of transcutaneous electrical nerve stimulation, intramuscular electrical stimulation, mobilization through physical therapy, among other similar techniques, (25, 28, 34, 35, 37–39, 43, 45, 48–50, 53, 55, 56). These approaches assumed to activate descending pain inhibition systems and promote the release of endogenous opioid mechanisms (45, 61–63). The fourth category includes cognitive/behavioral interventions, in which participants perform cognitive tasks such as attentional, memory, executive functioning tasks, mindfulness-meditation, or breathing interventions which are also related to attention processes, processes that are commonly impaired in chronic pain patients (21, 29, 30, 32, 40, 42, 47, 57). These tasks target brain regions such as dorsolateral prefrontal cortex and limbic brain areas, that process cognitive and emotional demands of painful stimuli and exerts a role in modulating pain perception and related emotions (64–70). Summary of all neuromodulatory interventions that were assessed in conjunction with tDCS for the treatment of pain are summarized in Table 1.

TABLE 1 Painful indications and the neuromodulatory approaches used in combination with transcranial direct current stimulation (tDCS).

Painful indications	Neuromodulatory approaches
• Phantom limb (12–14) • Neuropathic pain due to traumatic brachial plexus injury (15) • Spinal cord injury (16–22) • Complex regional pain syndrome (24, 25) • Fibromyalgia (26–33) • Chronic musculoskeletal pain (35) • Chronic low-back pain (36–40) • Knee osteoarthritis pain (41–45) • Temporomandibular disorders (46) • Chronic visceral pain (48) • Neurogenic pain (49) • Myofascial pain (50, 51) • Tendinopathy (52) • Radiculopathy (53) • Burning mouth syndrome (47) • Headache/migraine (34)	• Mirror therapy (12–15) • Visual illusion (16–18, 22) • Motor graded imagery (24) • Exercise (20, 26, 27, 33, 36, 41, 46, 47, 51, 52, 54) • Physical therapy (25, 28, 34, 35, 37–39, 43, 45, 48–50, 53, 55, 56) • Cognitive and behavioral interventions (21, 29, 30, 32, 40, 42, 47, 57)

1.3. Combined treatment at early stage of the painful condition

In a paper published by our group (12), we compared the effects of mirror therapy stand alone or with either real or sham tDCS on phantom limb pain. The study included 30 lower limb amputees who had been amputated up to 8 weeks previously and who were in the acute phase of phantom pain. Participants were randomized into 1 of the 3 groups (mirror therapy, mirror therapy + sham tDCS, mirror therapy + real tDCS) receiving 10 sessions (5 per week). They were assessed at baseline, at the end of the intervention, and 1 and 3 months thereafter, with the change in pain intensity between baseline and 1 month following the end of treatment predefined as the primary end-point.

The analgesic effects seen in our study were overwhelming (Figure 1). 3 months after the end of the treatment, the combined-treatment group experienced a robust analgesic effect, with mean pain reduction of 5.4 ± 2.6 points (on a 0–10 scale), and in percentage of change, about an 80% reduction), significantly more than the other 2 study arms. The analgesic effects were so large that it virtually eliminated the development of chronic phantom pain, with 90 and 80% of participants reporting pain

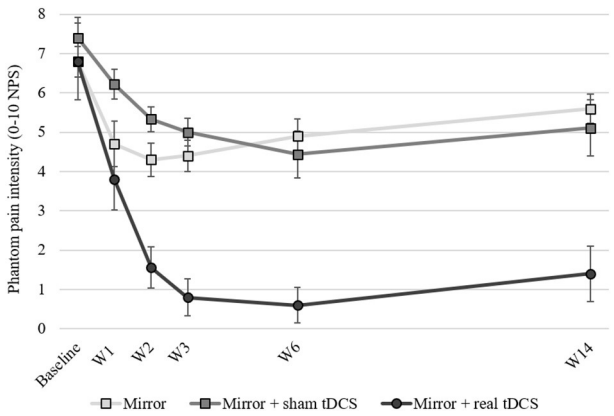


FIGURE 1
Phantom pain intensity at baseline, across treatment weeks and up to 3 months following the end of treatment. W1, during 1st week of treatment; W2, during 2nd week of treatment; W3, 1st week following end of treatment; W6, 1-month following the end of treatment; W14, 3-months following the end of treatment. tDCS, transcranial direct current stimulation; NPS, numerical pain scale. Error bars represent the Standard Error of the Mean (SEM).

of ≤2/10 at 1 and 3 months after the end of treatment, respectively. The analgesic effects in the two control arms were, in line with the literature, only modest, leaving the participants with significant phantom pain (>5/10) 3 months after the end of treatment.

2. Hypothesis

While most methodological aspects of our study were identical or similar to all the other studies that tested the effects of tDCS combined with other neuromodulatory therapy, there was one clear distinction: our study was the only one in which the patients were at the acute stage of pain. Hence, the unprecedented huge analgesic effects seen in our study might be attributed to this characteristic—the short time between the onset of the phantom limb pain and the administration of the therapy. All the other studies included chronic pain patients—that is, those who had been experiencing pain for a long time, sometimes even years or decades.

To gain more insight on our hypothesis, we searched the literature for all relevant studies that used similar treatment approaches, including mirror therapy, visual illusion, and motor graded imagery combined with tDCS. We summarized the relevant studies results in Table 2. To support a fair comparison, only studies in which 10 treatment sessions (or more) were administrated were included in the table. The indications included in the table consist of phantom pain, spinal cord injury, neuropathic pain due to traumatic brachial plexus injury, and complex regional pain syndrome. While our study included only participants who were amputated <8 weeks previously, all the other studies included only patients with chronic pain. Treatment characteristics were similar: All the studies except ours used anodal motor cortex stimulation at 2 mA. Our study used 1.5 mA in an attempt to support blinding. To compare the clinical effects of adding tDCS to the other therapy, we gathered the means (and standard deviations) of pain scores before (at baseline) and after each study arm. Whenever possible (not all studies included the two relevant study arms), we calculated the analgesic effects in terms of standardized effect sizes (Cohen's d), as follows: the change in pain in the combined treatment (real tDCS plus real other intervention) minus the change in pain in the sham tDCS plus real other intervention, divided by their pooled standard deviation.

In our study, at 1 month following the end of treatment, the analgesic effects were approximately twice as great as those found in the other studies. On the 0–10 scale, phantom pain intensity was reduced by an average of 6.2 points. Our study also showed much larger standardized effect size than did the other studies, except Soler et al. (17), which demonstrated similar effect size. Although Soler et al. (17) found modest average reductions in pain in the combined-treatment arm (−2.2 points on the 0–10 scale), they observed no change at all in the control arm. The lack of any pain reduction in the control produces a huge calculated effect size. In contrast, in our study, the reductions in pain in the 2 control arms were, as expected, in the magnitude of 2 and 3 points on the 0–10 scale in the mirror therapy alone and in the mirror therapy plus sham tDCS, respectively.

3. Discussion

To conclude, the data summarized in Table 2 support further investigation of our hypothesis. The analgesic effects of non-invasive brain stimulation combined with other neuromodulator treatments seem to be much stronger when the interventions are administrated at an early phase of the condition. Given that the comparison derived from Table 2 is descriptive rather than statistical, the results of this preliminary investigation should be regarded as a hypothesis generator. At the early onset of the painful condition—the acute stage—the abnormal neuroplasticity that is associated with the development of a chronic pain condition might not yet have been consolidated. By enrolling patients as early as possible after their pain develops, we might be at a favorable window of opportunity to counterbalance the abnormal neuroplasticity.

The rationale for our hypothesis assumes that after a longer period of pain, the abnormal neuroplasticity that is seen in various painful indications is already consolidated (71, 72) and might be resistant to changes. In contrast, at the acute phase, the central neuroplastic changes have not yet consolidated and are more easily reversed or even prevented. The importance of conducting neuroplasticity-related treatments soon after an injury is well-accepted in the rehabilitation arena, such as in treating post-stroke movement disorders (73). Interestingly, already 20 years ago, McCabe et al. (74) found that the analgesic effects of mirror therapy in complex regional pain syndrome are better when administrated at an early stage (<8 weeks after onset of pain) than when administered later (1 year or more) (74).

TABLE 2 Comparison of the analgesic effects among similar studies of tDCS combined with other therapies for pain.

Study	Authors	Pain indication	Time since onset	Study arms (*N*)	Number of treatment sessions	Baseline pain intensity (mean ± SD)	Pain intensity 1 month following end of treatment (mean ± SD)	Change in pain following treatment (mean ± SD)	Effect size (Cohen's d)
1	Segal et al. (12)	Phantom pain after unilateral lower limb amputation	<8 weeks	Mirror therapy (10)	10	6.80 ± 1.23	4.90 ± 1.37	−1.9 ± 1.30	
				Sham tDCS and Mirror therapy (10)	10	7.40 ± 1.65	4.44 ± 1.88	−2.96 ± 1.77	1.58
				Real tDCS and mirror therapy (9)	10	6.80 ± 2.94	0.60 ± 1.35	−6.2 ± 2.29	
2	Gunduz et al. (13)	Phantom pain after unilateral lower limb amputation	≥3 months	Sham tDCS and sham mirror therapy (27)	10 sham tDCS plus 20 sham mirror therapy sessions; first 10 sessions were combined	5.90 ± 1.57	3.31 ± 2.57	−2.59 ± 2.13	
				Real tDCS and sham mirror therapy (28)	10 real tDCS plus 20 sham mirror therapy sessions; first 10 sessions were combined	6.29 ± 1.67	2.93 ± 2.65	−3.36 ± 2.21	
				Sham tDCS and mirror therapy (28)	10 sham tDCS plus 20 real mirror therapy sessions; first 10 sessions were combined	6.03 ± 1.75	4.25 ± 2.55	−1.78 ± 2.19	0.47
				Real tDCS and mirror therapy (29)	10 real tDCS plus 20 real mirror therapy sessions; first 10 sessions were combined	6.12 ± 1.88	3.27 ± 2.80	−2.85 ± 2.38	
3	Ferreira et al. (15)[a]	Neuropathic pain following traumatic brachial plexus injury	≥3 months	Sham tDCS and mirror therapy (8)	12	No available data	No available data	No available data	
				Real tDCS and mirror therapy (8)	12	No available data	No available data	No available data	
4	Soler et al. (17)	Neuropathic pain following spinal cord injury	≥6 months	Sham tDCS and control illusion (10)	10	7.1 ± 1.5	6.4 ± 1.9	−0.7 ± 1.71	
				Real tDCS and control illusion (10)	10	6.3 ± 2.0	6.1 ± 2.5	−0.2 ± 2.26	
				Sham tDCS and visual illusion (9)	10	7.2 ± 1.6	7.2 ± 1.5	0 ± 1.55	1.54
				Real tDCS and visual illusion (10)	10	7.5 ± 1.2	5.3 ± 1.4	−2.2 ± 1.30	

(Continued)

10.3389/fneur.2023.1115370

TABLE 2 (Continued)

Study	Authors	Pain indication	Time since onset	Study arms (*N*)	Number of treatment sessions	Baseline pain intensity (mean ± SD)	Pain intensity 1 month following end of treatment (mean ± SD)	Change in pain following treatment (mean ± SD)	Effect size (Cohen's d)
5	Soler et al. (16)[a,b]	Neuropathic pain following spinal cord injury	≥6 months	Control (no intervention) (65)	No treatment	31% ± 14	31% ± 14	0% ± 14	
				Real tDCS and visual illusion (65)	10	34% ± 16	25% ± 16	−9% ± 16	
6	Kumru et al. (18)[a]	Healthy subjects (14)		Real tDCS and visual illusion (14)	10	No available data	No available data	No available data	
		No neuropathic pain following spinal cord injury (20)		Real tDCS and visual illusion (20)	10	No available data	No available data	No available data	
		Neuropathic pain following spinal cord injury (18)	≥3 months	Real tDCS and visual illusion (20)	10	7.8 ± 0.9	4.9 ± 2.0	−2.9 ± 1.55	
7	López-Carballo et al. (22)[a,b]	Neuropathic pain following spinal cord injury (23)	≥3 months	Real tDCS and visual illusion with gestural control	10	14.4 ± 6.5	10.5 ± 7.3	−3.9 ± 6.9	
8	Lagueux et al. (24)	Complex regional pain syndrome	>3 months	Sham tDCS and graded motor imagery (11)	14 combined sessions: 10 sessions during first 2 weeks, then maintenance therapy for 4 more weeks	6.09 ± 1.51	4.91 ± 2.17	−1.18 ± 1.87	0.018
				Real tDCS and graded motor imagery (11)	14 combined sessions: 10 sessions during first 2 weeks, then maintenance therapy for 4 more weeks	5.95 ± 2.21	4.73 ± 2.69	−1.22 ± 2.46	

Only studies that performed ≥10 sessions were included in the table to allow a fair comparison.

All studies used the same tDCS montage, with the following considerations: in case of phantom pain, the anode was placed over the motor cortex contralateral to the amputated limb, and the cathode over the supraorbital area ipsilateral to the amputated limb. In neuropathic pain indications and complex regional pain syndrome, the anode was placed on the motor cortex contralateral to the painful side for patients with asymmetric pain and at the dominant hemisphere for patients with symmetric pain.

All the studies used a combination of tDCS and another non-pharmacological neuromodulatory approach. In all studies, the tDCS intensity was set to 2mA, except for Segal et al. (12), which used 1.5 mA. In all the studies, the tDCS duration was 20 min, except in Ferreira et al. (15), which used 30 min per session. The duration of the non-pharmacological neuromodulatory approaches ranged from 12 to 20 min, except for Ferreira et al. (15), which used 30 minutes per session. All studies conducted the combined therapy 5 times per week for 2 weeks, except Ferreira et al. (15), which conducted the therapy 3 times per week.

Change in pain was calculated as baseline pain minus pain 1 month after the end-of-treatment time-point, except in Gunduz et al. (13), Ferreira et al. (15), and Soler et al. (16), in which posttreatment pain intensity was measured at the end of treatment (and not 1 month later) because follow-up data at 1 month were unavailable. In these studies, effect size estimation is based on the pain intensity at the end of treatment. In López-Carballo et al. (22), change in pain was calculated with posttreatment data collected 15 days after end of treatment.

The effect size was calculated as the mean change in pain in real tDCS combined with a real neuromodulatory approach versus the mean change in the sham tDCS combined with a real neuromodulatory approach, divided by the pooled standard deviation, using the following formula $d = \frac{|M1-M2|}{\sqrt{(SD1^2+SD2^2)/2}}$. Hence, it provided an estimate to the effect of adding tDCS on top of the other neuromodulatory approach.

[a] Effect sizes were not calculated for the following reasons: In Soler et al. (16), Kumru et al. (18), and López-Carballo et al. (22), because one of two of study arms of interest was not included in the study design; in Ferreira et al. (15) the results were reported as medians of the McGill Pain Questionnaire, and because the means and standard deviations no were reported, the SES calculation was not possible.

[b] Soler et al. (16) and López-Carballo et al. (22) used the neuropathic pain symptoms inventory (NPSI). In Soler et al. (16), pain intensity was measured with NPSI as percentage of change.

10.3389/fneur.2023.1115370

Given the currently inadequate treatments for phantom limb pain and other chronic painful conditions, the healthcare field urgently needs therapeutic interventions to prevent chronicity. A clearer understanding of how maladaptive plasticity is related to the development of chronic pain and how neuromodulation interference at the acute stage can prevent it will pave the way toward a new era of pain treatment: clinical adoption of neuromodulation targeting dysfunctional networks. We encourage the relevant research community to test our hypothesis and to assess the benefits of combined neuromodulatory approaches at earlier time-points of symptoms duration, whenever possible, both in the field of pain and beyond.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MA performed the literature search and contributed to writing and reviewing the manuscript. IW and RT conceptualization, writing, reviewing, and editing. All authors contributed to the article and approved the submitted version.

Acknowledgments

We thank Patricia Boyd for assisting with manuscript reviewing and editing.

Conflict of interest

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.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Cambiaghi M, Sconocchia S. Scribonius Largus (probably before 1CE–after 48CE). *J Neurol.* (2018) 265:2466–8. doi: 10.1007/s00415-018-8739-5

2. Sarmiento CI, San-Juan D, Prasath VBS. Letter to the editor: brief history of transcranial direct current stimulation (tDCS): from electric fishes to microcontrollers. *Psychol Med.* (2016) 46:3259–61. doi: 10.1017/S0033291716001926

3. Althaus J. *A Treatise on Medical Electricity*. Longman: London (1873).

4. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol.* (2017) 128:56–92. doi: 10.1016/j.clinph.2016.10.08

5. Dasilva AF, Mendonca ME, Zaghi S, Lopes M, Dossantos MF, Spierings EL, et al. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. *Headache.* (2012) 52:1283–95. doi: 10.1111/j.1526-4610.2012.02141.x

6. Polanía R, Nitsche MA, Paulus W. Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. *Hum Brain Mapp.* (2011) 32:1236–49. doi: 10.1002/hbm.21104

7. Pinto CB, Teixeira Costa B, Duarte D, Fregni F. Transcranial direct current stimulation as a therapeutic tool for chronic pain. *J ECT.* (2018) 34:e36–50. doi: 10.1097/YCT.0000000000000518

8. Massetti T, Crocetta TB, Silva TD da, Trevizan IL, Arab C, Caromano FA, et al. Application and outcomes of therapy combining transcranial direct current stimulation and virtual reality: a systematic review. *Disabil Rehabil Assist Technol.* (2016) 12:551–9. doi: 10.1080/17483107.2016.1230152

9. Cardenas-Rojas A, Pacheco-Barrios K, Giannoni-Luza S, Rivera-Torrejon O, Fregni F. Noninvasive brain stimulation combined with exercise in chronic pain: a systematic review and meta-analysis. *Expert Rev Neurother.* (2020) 20:401–12. doi: 10.1080/14737175.2020.1738927

10. Damercheli S, Ramne M, Ortiz-Catalan M. transcranial direct current stimulation (tDCS) for the treatment and investigation of Phantom Limb Pain (PLP). *Psychoradiology.* (2022) 2:23–31. doi: 10.1093/psyrad/kkac004

11. Nascimento RM do, Cavalcanti RL, Souza CG, Chaves G, Macedo LB. Transcranial direct current stimulation combined with peripheral stimulation in chronic pain: a systematic review and meta-analysis. *Expert Rev Med Devices.* (2022) 3:9623. doi: 10.1080/17434440.2022.2039623

12. Segal N, Pud D, Amir H, Ratmansky M, Kuperman P, Honigman L, et al. Additive analgesic effect of transcranial direct current stimulation together with mirror therapy for the treatment of phantom pain. *Pain Med.* (2021) 22:255–65. doi: 10.1093/pm/pnaa388

13. Gunduz ME, Pacheco-Barrios K, Bonin Pinto C, Duarte D, Vélez FGS, Gianlorenco ACL, et al. Effects of combined and alone transcranial motor cortex stimulation and mirror therapy in phantom limb pain: a randomized factorial trial. *Neurorehabil Neural Repair.* (2021) 35:704–16. doi: 10.1177/15459683211017509

14. Teixeira PEP, Pacheco-Barrios K, Gunduz ME, Gianlorenço AC, Castelo-Branco L, Fregni F. Understanding intracortical excitability in phantom limb pain: a multivariate analysis from a multicenter randomized clinical trial. *Neurophysiol Clin.* (2021) 51:161–73. doi: 10.1016/j.neucli.2020.12.006

15. Ferreira CM, de Carvalho CD, Gomes R, Bonifácio de. Assis ED, Andrade SM. Transcranial direct current stimulation and mirror therapy for neuropathic pain after brachial plexus avulsion: a randomized, double-blind, controlled pilot study. *Front Neurol.* (2020) 11:568261. doi: 10.3389/fneur.2020.568261

16. Soler D, Moriña D, Kumru H, Vidal J, Navarro X. Transcranial direct current stimulation and visual illusion effect according to sensory phenotypes in patients with spinal cord injury and neuropathic pain. *J Pain.* (2021) 22:86–96. doi: 10.1016/j.jpain.2020.06.004

17. Soler MD, Kumru H, Pelayo R, Vidal J, Tormos JM, Fregni F, et al. Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. *Brain.* (2010) 133:2565–77. doi: 10.1093/brain/awq184

18. Kumru H, Soler D, Vidal J, Navarro X, Tormos JM, Pascual-Leone A, et al. The effects of transcranial direct current stimulation with visual illusion in neuropathic pain due to spinal cord injury: an evoked potentials and quantitative thermal testing study. *Eur J Pain.* (2013) 17:55–66. doi: 10.1002/j.1532-2149.2012.00167.x

19. Roosink M, Robitaille N, Jackson PL, Bouyer LJ, Mercier C. Interactive virtual feedback improves gait motor imagery after spinal cord injury: An exploratory study. *Restor Neurol Neurosci.* (2016) 34:227–35. doi: 10.3233/RNN-150563

20. Yeh NC, Yang YR, Huang SF, Ku PH, Wang RY. Effects of transcranial direct current stimulation followed by exercise on neuropathic pain in chronic spinal cord injury: a double-blinded randomized controlled pilot trial. *Spinal Cord.* (2021) 59:684–92. doi: 10.1038/s41393-020-00560-x

21. Li S, Stampas A, Frontera J, Davis M. Combined transcranial direct current stimulation and breathing-controlled electrical stimulation for management of neuropathic pain after spinal cord injury. *J Rehabil Med.* (2018) 50:814–20. doi: 10.2340/16501977-2379

22. Lopez-Carballo J, Rodriguez N, Soler D, Opisso E, Sbert M. Gestural interaction and visual illusion for lower limbs' neuropathic pain treatment. *IEEE Trans Neural Syst Rehabil Eng.* (2018) 26:2217–25. doi: 10.1109/TNSRE.2018.2873593

23. McCallion E, Robinson CSH, Clark VP, Witkiewitz K. Efficacy of transcranial direct current stimulation-enhanced mindfulness-based program for chronic pain: a single-blind randomized sham controlled pilot study. *Mindfulness.* (2020) 11:895–904. doi: 10.1007/s12671-020-01323-8

24. Lagueux E, Bernier M, Bourgault P, Whittingstall K, Mercier C, Léonard G, et al. The effectiveness of transcranial direct current stimulation as an add-on modality to graded motor imagery for treatment of complex regional pain syndrome: a randomized proof of concept study. *Clin J Pain.* (2018) 34:145–54. doi: 10.1097/AJP.0000000000000522

25. Houde F, Harvey MP, Labrecque PFT, Lamarche F, Lefebvre A, Guillaume L. Combining transcranial direct current stimulation and transcutaneous electrical nerve stimulation to relieve persistent pain in a patient suffering from complex regional pain syndrome: a case report. *J Pain Res.* (2020) 13:467–73. doi: 10.2147/JPR.S226616

26. Mendonca ME, Simis M, Grecco LC, Battistella LR, Baptista AF, Fregni F. Transcranial direct current stimulation combined with aerobic exercise to optimize analgesic responses in fibromyalgia: a randomized placebo-controlled clinical trial. *Front Hum Neurosci.* (2016) 10:68. doi: 10.3389/fnhum.2016.00068

27. Desbiens S, Girardin-Rondeau M, Guyot-Messier L, Lamoureux D, Paris L, da Silva RA, et al. Effect of transcranial direct stimulation combined with a functional task on fibromyalgia pain: a case study. *Neurophysiol Clin.* (2020) 50:134–7. doi: 10.1016/j.neucli.2020.02.006

28. Yoo H. bin, Ost J, Joos W, van Havenbergh T, de Ridder D, Vanneste S. Adding prefrontal transcranial direct current stimulation before occipital nerve stimulation in fibromyalgia. *Clin J Pain.* (2018) 34:421–7. doi: 10.1097/AJP.0000000000000552

29. Gardoki-Souto I, Martín de la Torre O, Hogg B, Redolar-Ripoll D, Valiente-Gómez A, Martínez Sadurní L, et al. Augmentation of EMDR with multifocal transcranial current stimulation (MtCS) in the treatment of fibromyalgia: study protocol of a double-blind randomized controlled exploratory and pragmatic trial. *Trials.* (2021) 22:5042. doi: 10.1186/s13063-021-05042-w

30. Santos VS dos S dos, Zortea M, Alves RL, Naziazeno CC dos S, Saldanha JS, Carvalho S da CR de, et al. Cognitive effects of transcranial direct current stimulation combined with working memory training in fibromyalgia: a randomized clinical trial. *Sci Rep.* (2018) 8:1–11. doi: 10.1038/s41598-018-30127-z

31. Ramasawmy P, Khalid S, Petzke F, Antal A. Pain reduction in fibromyalgia syndrome through pairing transcranial direct current stimulation and mindfulness meditation: a randomized, double-blinded, sham-controlled pilot clinical trial. *Front Med.* (2022) 9:908133. doi: 10.3389/fmed.2022.908133

32. Riberto M, Alfieri F, Pacheco K, Leite V, Kaihami H, Fregni F, et al. Efficacy of transcranial direct current stimulation coupled with a multidisciplinary rehabilitation program for the treatment of fibromyalgia. *Open Rheumatol J.* (2011) 5:45–50. doi: 10.2174/1874312901105010045

33. Arroyo-Fernández R, Avendaño-Coy J, Velasco-Velasco R, Palomo-Carrión R, Bravo-Esteban E, Ferri-Morales A. Effectiveness of transcranial direct current stimulation combined with exercising in people with fibromyalgia: a randomized sham-controlled clinical trial. *Arch Phys Med Rehabil.* (2022) 103:1524–32. doi: 10.1016/j.apmr.2022.02.020

34. Alhassani G, Treleaven J, Schabrun SSM. Combined transcranial and trans-spinal direct current stimulation in chronic headache: a feasibility and safety trial for a novel intervention. *Hong Kong Physiother J.* (2017) 37:1–9. doi: 10.1016/j.hkpj.2016.11.001

35. Kim S, Salazar Fajardo JC, Seo E, Gao C, Kim R, Yoon BC. Effects of transcranial direct current stimulation on physical and mental health in older adults with chronic musculoskeletal pain: a randomized controlled trial. *Eur Geriatr Med.* (2022) 13:959–66. doi: 10.1007/s41999-022-00626-4

36. Straudi S, Buja S, Baroni A, Pavarelli C, Pranovi G, Fregni F, et al. The effects of transcranial direct current stimulation (tDCS) combined with group exercise treatment in subjects with chronic low back pain: A pilot randomized control trial. *Clin Rehabil.* (2018) 32:1348–56. doi: 10.1177/0269215518777881

37. Schabrun SM, Jones E, Elgueta Cancino EL, Hodges PW. Targeting chronic recurrent low back pain from the top-down and the bottom-up: a combined transcranial direct current stimulation and peripheral electrical stimulation intervention. *Brain Stimul.* (2014) 7:451–9. doi: 10.1016/j.brs.2014.01.058

38. Hazime FA, Baptista AF, de Freitas DG, Monteiro RL, Maretto RL, Hasue RH, et al. Treating low back pain with combined cerebral and peripheral electrical stimulation: a randomized, double-blind, factorial clinical trial. *Eur J Pain.* (2017) 21:1132–43. doi: 10.1002/ejp.1037

39. Schabrun SM, Burns E, Thapa T, Hodges P. The response of the primary motor cortex to neuromodulation is altered in chronic low back pain: a preliminary study. *Pain Med.* (2018) 19:1227–36. doi: 10.1093/pm/pnx168

40. Luedtke K, Rushton A, Wright C, Jürgens T, Polzer A, Mueller G, et al. Effectiveness of transcranial direct current stimulation preceding cognitive behavioral management for chronic low back pain: Sham controlled double blinded randomized controlled trial. *BMJ.* (2015) 350:1640. doi: 10.1136/bmj.h1640

41. Chang WJ, Bennell KL, Hodges PW, Hinman RS, Young CL, Buscemi V, et al. Addition of transcranial direct current stimulation to quadriceps strengthening exercise in knee osteoarthritis: a pilot randomized controlled trial. *PLoS ONE.* (2017) 12:e0180328. doi: 10.1371/journal.pone.0180328

42. Ahn H, Zhong C, Miao H, Chaoul A, Park L, Yen IH, et al. Efficacy of combining home-based transcranial direct current stimulation with mindfulness-based meditation for pain in older adults with knee osteoarthritis: a randomized controlled pilot study. *J Clin Neurosci.* (2019) 70:140–5. doi: 10.1016/j.jocn.2019.08.047

43. Li X, Yu W, Li H, Wang B, Xu J. Prospective, single-center comparison of transcranial direct current stimulation plus electro acupuncture and standard analgesia in patients after total knee arthroplasty: effect on rehabilitation and functional recovery. *Med Sci Monit.* (2021) 27:e930363. doi: 10.12659/MSM.930363

44. Pollonini L, Montero-Hernandez S, Park L, Miao H, Mathis K, Ahn H. Functional near-infrared spectroscopy to assess central pain responses in a nonpharmacologic treatment trial of osteoarthritis. *J Neuroimaging.* (2020) 30:808–14. doi: 10.1111/jon.12782

45. da Graca-Tarragó M, Lech M, Angoleri LDM, Santos DS, Deitos A, Brietzke AP, et al. Intramuscular electrical stimulus potentiates motor cortex modulation effects on pain and descending inhibitory systems in knee osteoarthritis: a randomized, factorial, sham-controlled study. *J Pain Res.* (2019) 12:209–21. doi: 10.2147/JPR.S181019

46. Oliveira LB, Lopes TS, Soares C, Maluf R, Goes BT, Sá KN, et al. Transcranial direct current stimulation and exercises for treatment of chronic temporomandibular disorders: a blind randomised-controlled trial. *J Oral Rehabil.* (2015) 42:723–32. doi: 10.1111/joor.12300

47. Sánchez-Cuesta FJ, González-Zamorano Y, Arroyo-Ferrer A, Avellanal M, Fernández-Carnero J, Romero JP. Transcranial direct current stimulation (tDCS) combined with therapeutic exercise and cognitive rehabilitation to treat a case of burning mouth syndrome (BMS) related pain. *Appl Sci.* (2021) 11:11538. doi: 10.3390/app112311538

48. Thibaut A, Russo C, Hurtado-Puerto AM, Morales-Quezada JL, Deitos A, Petrozza JC, et al. Effects of transcranial direct current stimulation, transcranial pulsed current stimulation, and their combination on brain oscillations in patients with chronic visceral pain: a pilot crossover randomized controlled study. *Front Neurol.* (2017) 8:576. doi: 10.3389/fneur.2017.00576

49. Boggio PS, Amancio EJ, Correa CF, Cecilio S, Valasek C, Bajwa Z, et al. Transcranial DC stimulation coupled with TENS for the treatment of chronic pain: a preliminary study. *Clin J Pain.* (2009) 25:691–5. doi: 10.1097/AJP.0b013e3181af1414

50. Choi YH, Jung SJ, Lee CH, Lee SU. Additional effects of transcranial direct-current stimulation and trigger-point injection for treatment of myofascial pain syndrome: a pilot study with randomized, single-blinded trial. *J Altern Complement Med.* (2014) 20:698–704. doi: 10.1089/acm.2013.0243

51. Sakrajai P, Janyacharoen T, Jensen MP, Sawanyawisuth K, Auvichayapat N, Tunkamnerdthai O, et al. Pain reduction in myofascial pain syndrome by anodal transcranial direct current stimulation combined with standard treatment: a randomized controlled study. *Clin J Pain.* (2014) 30:1076–83. doi: 10.1097/AJP.0000000000000069

52. Belley AF, Mercier C, Bastien M, Léonard G, Gaudreault N, Roy JS. Anodal transcranial direct-current stimulation to enhance rehabilitation in individuals with rotator cuff tendinopathy: a triple-blind randomized controlled trial. *J Orthop Sports Phys Ther.* (2018) 48:541–51. doi: 10.2519/jospt.2018.7871

53. Chen Z, Zhang W, Yu Y, Tan T. A retrospective comparative cohort study of the effects of neural mobilization (NM) alone and NM combined with transcranial direct current stimulation in patients with cervical radiculopathy. *Ann Palliat Med.* (2022) 11:2961–7. doi: 10.21037/apm-22-746

54. Borovskis J, Cavaleri R, Blackstock F, Summers SJ. Transcranial direct current stimulation accelerates the onset of exercise-induced hypoalgesia: a randomized controlled study. *J Pain.* (2021) 22:263–74. doi: 10.1016/j.jpain.2020.08.004

55. Jafarzadeh A, Ehsani F, Yosephi MH, Zoghi M, Jaberzadeh S. Concurrent postural training and M1 anodal transcranial direct current stimulation improve postural impairment in patients with chronic low back pain. *J Clin Neurosci.* (2019) 68:224–34. doi: 10.1016/j.jocn.2019.07.017

56. Rahimi F, Nejati V, Nassadj G, Ziaei B, Mohammadi HK. The effect of transcranial direct stimulation as an add-on treatment to conventional physical therapy on pain intensity and functional ability in individuals with knee osteoarthritis: a randomized controlled trial. *Neurophysiol Clin.* (2021) 51:507–16. doi: 10.1016/j.neucli.2021.06.002

57. Powers A, Madan A, Hilbert M, Reeves ST, George M, Nash MR, et al. Effects of Combining a brief cognitive intervention with transcranial direct current stimulation on pain tolerance: a randomized controlled pilot study. *Pain Med.* (2018) 19:677–85. doi: 10.1093/pm/pnx098

58. Neva JL, Brown KE, Mang CS, Francisco BA, Boyd LA. An acute bout of exercise modulates both intracortical and interhemispheric excitability. *Eur J Neurosci.* (2017) 45:1343–55. doi: 10.1111/ejn.13569

59. Tajerian M, David Clark J. Nonpharmacological interventions in targeting pain-related brain plasticity. *Neural Plast.* (2017) 2017:8573. doi: 10.1155/2017/2038573

60. Wakaizumi K, Kondo T, Hamada Y, Narita M, Kawabe R, Narita H, et al. Involvement of mesolimbic dopaminergic network in neuropathic pain relief by treadmill exercise: a study for specific neural control with Gi-DREADD in mice. *Mol Pain.* (2016) 12:1567. doi: 10.1177/1744806916681567

61. Leonard G, Goffaux P, Marchand S. Deciphering the role of endogenous opioids in high-frequency TENS using low and high doses of naloxone. *Pain.* (2010) 151:215–9. doi: 10.1016/j.pain.2010.07.012

62. Choi JC, Kim J, Kang E, Lee JM, Cha J, Kim YJ, et al. Brain mechanisms of pain relief by transcutaneous electrical nerve stimulation: a functional magnetic resonance imaging study. *Eur J Pain.* (2016) 20:92–105. doi: 10.1002/ejp.696

63. Schabrun SM, Chipchase LS. Priming the brain to learn: the future of therapy? *Man Ther.* (2012) 17:184–6. doi: 10.1016/j.math.2011.12.001

64. Seminowicz DA, Shpaner M, Keaser ML, Krauthamer GM, Mantegna J, Dumas JA, et al. Cognitive-behavioral therapy increases prefrontal cortex gray matter in patients with chronic pain. *J Pain.* (2013) 14:1573–84. doi: 10.1016/j.jpain.2013.07.020

65. McCracken LM, Turk DC. Behavioral and cognitive-behavioral treatment for chronic pain: outcome, predictors of outcome, and treatment process. *Spine.* (2002) 27:2564–73. doi: 10.1097/00007632-200211150-00033

66. Pardos-Gascón EM, Narambuena L, Leal-Costa C, van-der Hofstadt-Román CJ. Differential efficacy between cognitive-behavioral therapy and mindfulness-based therapies for chronic pain: systematic review. *Int J Clin Health Psychol.* (2021) 21:100197. doi: 10.1016/j.ijchp.2020.08.001

67. Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci.* (2013) 14:502. doi: 10.1038/nrn3516

68. Zeidan F, Emerson NM, Farris SR, Ray JN, Jung Y, McHaffie JG, et al. Mindfulness meditation-based pain relief employs different neural mechanisms than placebo and sham mindfulness meditation-induced analgesia. *J Neurosci.* (2015) 35:15307–25. doi: 10.1523/JNEUROSCI.2542-15.2015

69. Ong WY, Stohler CS, Herr DR. Role of the prefrontal cortex in pain processing. *Mol Neurobiol.* (2019) 56:1137. doi: 10.1007/s12035-018-1130-9

70. Haase L, Thom NJ, Shukla A, Davenport PW, Simmons AN, Stanley EA, et al. Mindfulness-based training attenuates insula response to an aversive interoceptive challenge. *Soc Cogn Affect Neurosci.* (2016) 11:182. doi: 10.1093/scan/nsu042

71. Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumers N, et al. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature.* (1995) 375:482–4. doi: 10.1038/375482a0

72. Ramachandran VS, Rogers-Ramachandran D, Stewart M, Pons TP. Perceptual correlates of massive cortical reorganization. *Science.* (1992) 258:1159–60. doi: 10.1126/science.1439826

73. Krakauer J, Carmichael T. *Broken Movement The Neurobiology of Motor Recovery after Stroke*. Cambridge, MA: MIT Press (2017).

74. McCabe CS, Haigh RC, Ring EFJ, Halligan PW, Wall PD, Blake DR, et al. controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1). *Rheumatology.* (2003) 42:97–101. doi: 10.1093/rheumatology/keg041

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 01 March 2023
DOI 10.3389/fneur.2023.1069434

OPEN ACCESS

EDITED BY
Julien Nizard,
Université de Nantes, France

REVIEWED BY
Xiechuan Weng,
Chinese Academy of Medical Sciences and Peking Union Medical College, China
Marcos Fabio DosSantos,
Federal University of Rio de Janeiro, Brazil

*CORRESPONDENCE
Jan D. Wandrey
✉ jan.wandrey@charite.de

SPECIALTY SECTION
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

RECEIVED 13 October 2022
ACCEPTED 07 February 2023
PUBLISHED 01 March 2023

CITATION
Wandrey JD, Kastelik J, Fritzsche T, Denke C, Schäfer M and Tafelski S (2023) Supplementing transcranial direct current stimulation to local infiltration series for refractory neuropathic craniocephalic pain: A randomized controlled pilot trial. *Front. Neurol.* 14:1069434. doi: 10.3389/fneur.2023.1069434

Supplementing transcranial direct current stimulation to local infiltration series for refractory neuropathic craniocephalic pain: A randomized controlled pilot trial

Jan D. Wandrey*, Joanna Kastelik, Thomas Fritzsche, Claudia Denke, Michael Schäfer and Sascha Tafelski

Department of Anesthesiology and Intensive Care Medicine, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

Background: Some patients with neuralgia of cranial nerves with otherwise therapy-refractory pain respond to invasive therapy with local anesthetics. Unfortunately, pain regularly relapses despite multimodal pain management. Transcranial direct current stimulation (tDCS) may prolong pain response due to neuro-modulatory effects.

Methods: This controlled clinical pilot trial randomized patients to receive anodal, cathodal or sham-tDCS stimulation prior to local anesthetic infiltration. Pain attenuation, quality-of-life and side effects were assessed and compared with historic controls to estimate effects of tDCS stimulation setting.

Results: Altogether, 17 patients were randomized into three groups with different stimulation protocols. Relative reduction of pain intensity in per protocol treated patients were median 73%, 50% and 69% in anodal, cathodal and sham group, respectively ($p = 0.726$). Compared with a historic control group, a lower rate of responders with 50% reduction of pain intensity indicates probable placebo effects (OR 3.41 stimulation vs. non-stimulation setting, NNT 3.63). 76.9% ($n = 10$) of tDCS patients reported mild side-effects. Of all initially included 17 patients, 23.5% ($n = 4$) withdrew their study participation with highest proportion in the cathodal group ($n = 3$). A sample size calculation for a confirmatory trial revealed 120 patients using conservative estimations.

Discussion: This pilot trial does not support series of anodal tDCS as neuro-modulatory treatment to enhance pain alleviation of local anesthetic infiltration series. Notably, results may indicate placebo effects of tDCS settings. Feasibility of studies in this population was limited due to relevant drop-out rates. Anodal tDCS warrants further confirmation as neuro-modulatory pain treatment option.

KEYWORDS

tDCS, chronic pain, neuropathic pain, craniocephalic pain, infiltration series

1. Introduction

Pain in the head-neck area can be debilitating for patients (1). Chronic neuropathic pain in particular can be a relevant factor contributing to global burden of disease (2, 3). First line treatment for patients with neuropathic pain includes medications such as gabapentinoids, duloxetine and tricyclic antidepressants together with adjunctive therapies such as physical and psychological therapy (4–6). Management of these patients can be challenging, and sometimes pain remains refractory to non-invasive treatment (7). In selected patients, interventional procedures provide alternative treatment options (4, 8). Although under debate, infiltration series with ganglionic and nerve blocks are commonly used by pain physicians (9). Results from our previous retrospective study indicate relevant beneficial effects of these infiltration series in multimodal therapy concepts: in a cohort of 83 patients with chronic neuropathic pain in the head-neck area refractory to standard treatment, a reduction of pain intensity on the numeric rating scale (NRS, 0-10) was achieved by mean 3.2 points (SD 3.3, $p < 0.001$) (10). Furthermore, about half of the included patients achieved clinically relevant improvement in NRS scores with a reduction of pain intensity by 30–50%. In this study, we used infiltrations at sphenopalatine ganglion (SPG), superior cervical ganglion and stellate ganglion, peripheral nerve blocks at occipital nerve and trigeminal nerve as described in the literature (10–12).

Recent fMRI studies support the use of infiltration series, since they change resting state functional activity in domains relevant for pain. Single infiltrations seem to facilitate small network changes (13) which may relate to relatively small clinical effects provided by single interventions (14). For longer lasting effects, repetitions of infiltrations were advocated (13, 15). In contrast, there are only few reported long-term effects on pain (10, 16). This could be due to maladaptive structural plasticity and neuronal reorganization (17). Hence, central modulation of this reorganization in addition to the peripheral infiltration series, is required.

Non-invasive brain stimulation is an emerging field in clinical research (18, 19). Though exact neurobiological mechanisms are still unclear, results from *in vitro* and *in vivo* studies suggest long term central changes of repetitive transcranial direct current stimulation (tDCS) mediated by metaplasticity rather than long-term potentiation or depression as discussed earlier in the literature (20). This metaplasticity includes changes in cellular mechanisms [e.g., effects of tDCS on excitatory synaptic efficacy (21)], neurotransmission [e.g., motor cortex excitability (22)] and effects on the neuroinflammatory system [e.g., anodal tDCS induced stimulation of neural stem cell migration and cathodal tDCS induced stimulation of neuroinflammatory response (23)] (20). The use of tDCS may be an option for pain disorders (18), oro-facial pain disorders in particular (24). Treatment with tDCS reorganizes neuronal representation of pain (25) and modulates maladaptive plasticity (18, 26). A recent study suggests changes in maladaptive corticomotor excitability by tDCS and thus leading to anti-nociceptive effects (27). A different approach discusses that the effects on pain by non-invasive brain stimulation are mediated by top-down modulation and restoration of defective endogenous inhibitory pain pathways (28).

tDCS has been used in studies in a variety of conditions focussing on pain, neurological and psychiatric diseases (29). A higher evidence level of recommendation in favor of treatment with tDCS was found for depression, craving and fibromyalgia (29).

Depending on polarity, tDCS either enhances (anodal tDCS) or reduces (cathodal tDCS) motor cortical excitability measured in motor-evoked potentials (MEP) (22, 30). Though anodal stimulation seems more promising, evidence suggests efficacy in pain treatment for both anodal (31, 32) and cathodal (33) tDCS above the M1 area.

Not only the direction of the current but also the electrode montage is critical in tDCS (34). In pain processing, a large network of different pain processing sites is activated and called the pain neuromatrix (32, 33, 35, 36). The superficial parts of the pain neuromatrix include the primary sensory cortex (S1), primary motor cortex (M1), and dorsolateral prefrontal cortex (DLPFC), making them the most common montage settings of tDCS in the literature (30). Compared to anodal tDCS of S1 and DLPFC, M1 stimulation seems to be the best spot to enhance brain excitability (32). Thus, anodal M1 stimulation is the most used and most promising stimulation side (30).

Since it appears to be safe, the use of tDCS additional to other treatment is common (37). For instance, a recent meta-analysis showed moderate to large effects of combined intervention of exercise with anodal tDCS on motor cortex compared to sham and exercise in chronic pain (38). Both, infiltration techniques (13) and tDCS (25, 39) seem to change resting state functional connectivity. Synergistic interactions in neuronal networks are a potential target by tDCS and infiltration series (18). To date, there is no data on a combination of these two interventions on pain intensity.

Therefore, this pilot study was performed to investigate trial feasibility, individual course of pain and pain relief, associated symptoms and side effects of tDCS and subsequent local infiltration series in patients with refractory cranial neuropathic pain syndromes.

2. Materials and methods

This prospective study was conducted in chronic pain patients at the pain outpatient center of the Charité-Universitätsmedizin Berlin, Campus Virchow Klinikum. The department provides clinical care for chronic pain patients and is run by a team of pain specialists, behavioral psychologists and trained pain nurses. All patients treated in the department from June 2016 to March 2019 were screened for eligibility. For inclusion, a clinical diagnosis of a condition according to the ICHD3 [chapter *13. Painful lesions of the cranial nerves and other facial pain*, e.g., trigeminal-neuralgia, post-herpetic trigeminal neuralgia, persistent idiopathic facial pain (PIFP)] was mandatory (40). Furthermore, only patients receiving local infiltration series for treatment of these cranial conditions were included. Infiltration series were performed based on judgement of attending physician and following standardized infiltration protocol (11, 41). Infiltration techniques used in this study are reported in detail in a previous study (10).

Exclusion criteria were patients under the age of 18, current reported pregnancy, accommodation in an institution due to an official or judicial order, patients participating in another trial

during this study and patients with contraindications for tDCS (e.g., epilepsy, metal implants in stimulation area and implanted defibrillators). Patients fulfilling inclusion criteria were offered to participate in the study to receive additional tDCS application before each local infiltration. Eligible patients were asked for written informed consent. All infiltration series were performed as part of a multi-modal therapy concept following current recommendations (42, 43). This study uses some of the methods of our previous study and thus the methods description partly reproduces their wording (10). This study was approved by the Charité ethics committee (EA1/031/16) and followed the rule of the declaration of Helsinki in its updated 2013 version (44). Moreover, the study was registered (ClinicalTrials: NCT02747758) and applied the CONSORT checklist (45).

2.1. Study design

Patients were planned to receive 10 consecutive sessions of the infiltration and stimulation series with 48–72 h between each session following recommendations for long-lasting after-effects (30, 46–48). Before each session, the attending physician decided in a context-sensitive approach if a continuation of infiltration and thus stimulation series was indicated. If applicable, first tDCS (anodal/cathodal/sham, depending on study group) and afterwards local infiltration was performed. After completion of series, patients were followed-up for 6 months.

2.2. Outcome parameter

The primary outcome parameter was relative pain intensity reduction after completion of therapy series (typically after 2 weeks of treatment) measured in NRS score as a numeric value between 0 and 10. The secondary outcome parameter include absolute and relative pain reduction measured in NRS score after completion of tDCS stimulation vs. initial NRS score measured before stimulation and time until patients need additional regional-anaesthesiological interventions. The number of required regional-anaesthesiological interventions to achieve sufficient pain reduction and the analysis of adverse reaction (skin redness, headache, concentration, other) were other secondary outcome parameter.

We further evaluated patients' conditions, the used blockade technique, the response rate and the effect of sole tDCS stimulation. In addition to that, analyses of side-effects, drop-outs, self-assessment and a *post-hoc* sample size calculation was conducted.

2.3. Assessment of pain

For pain assessment, two assessment tools were used: the pain assessment protocol for infiltration series and the German Pain Questionnaire [daily report form, version 2007 (49)]. The assessment protocol was the basis of the evaluation of the primary outcome parameter and contained the NRS on an 11-point Likert scale (0–10) for static (at rest) and dynamic (maximum pain in stress) pain before and after tDCS. The German Pain Questionnaire was used both during stimulation and infiltration series and for the Follow-Up. Its core questions are derived from the grading of chronic pain status (50). They consist of four questions on a 11-point Likert scale (0–10): average pain in the last week, maximum pain in the last week, mental distress and impairment in daily activities. Furthermore, the German Pain Questionnaire consists of a question regarding the endurance of pain (1 = not applicable, I have no pain, 2 = I can tolerate it well, 3 = I can just tolerate it, 4 = I can tolerate it badly). For the pain assessment, patients were asked to name the most predominant painful side.

2.4. tDCS

Before each local anesthetic infiltration series, a 20 min tDCS stimulation was performed using the NeuroConn DC Stimulator® with saline soaked, square sponge electrodes (surface 25cm^2) similar to Nitsche and Paulus et al. (22, 47, 48) (see Supplementary Figure 1). Following the protocol of Morosoli et al., we placed the anode electrode over the primary motor cortex (M1) contralateral to the most predominant painful side, and the cathode electrode over the contralateral supraorbital area (51). The primary motor cortex is located in the Brodman location 4 (52, 53). Electrode position of C3,4 correlates with Brodman location 4, which is located in the precentral gyms, shoulder to wrist area, caudal to middle frontal gyrus (54). We determined the C3 or C4 placement using the recommendation of Jasper (55).

The patients were divided in three subgroups with either anodal, cathodal or sham stimulation. The same stimulation setting was used in every subgroup. Due to the triple-blinding study design, electrode placement was identical in either anodal or cathodal stimulation group with inverse current flow, depending on study allocation (e.g., anodal stimulation: anode=anode and cathode=cathode whereas cathodal stimulation anode=cathode and cathode=anode).

In the active groups (anodal and cathodal), stimulation started with an initialization phase with increasing current over 30 s. Afterwards, tDCS with 2 mA was applied for 20 min, following a phase with decreasing current over another 30 s. In the sham group, patients received increasing and immediately decreasing current at the beginning and similar application at the end of the stimulation for the purpose of blinding.

2.5. Blinding and randomization

This study was performed in a triple-blinded setting. The patient, the tDCS applying physician and the person performing statistics were blinded to group allocation. Blinding of tDCS was performed using the study mode of the NeuroConn DC Stimulator®. A block-randomization was used with blocks of six to ensure comparable group sizes in case of early stop of the study. Randomization was performed using a computer-generated random list for patient allocation with four blocks with size of six provided by study statistician. After inclusion, patients were treated following the randomization list. For allocation concealment, block

sizes and study randomization list were prepared blinded to study physicians.

2.6. Historic control for comparison non-stimulation and stimulation

To explore the intrinsic effect of the stimulation setting, we compared tDCS patients with patients without tDCS obtained in a historic cohort [NCT03066037, report in (10)] with the same infiltration techniques applied in the same outpatient clinic.

2.7. Follow-up

Patients were followed-up at 1, 3, and 6 months after completion of the combined stimulation and infiltration series. Follow-Up was performed *via* telephone calls using the German Pain Questionnaire [daily report form, version 2007 (49)]. Furthermore, patients' records at the outpatient clinic were screened whether and when study patients received a new infiltration series outside the study after completion of stimulation and infiltration series.

2.8. Statistics

All statistical analyses were performed using SPSS 29. Descriptive data was summarized using mean and standard deviation or median and range depending on scale level and distribution. Analysis of immediate tDCS effect was performed using data from each session. For analyses of statistical significance, NRS-scores were explored using the exact Wilcoxon-signed-rank-test for paired data. To analyse independent groups of ordinal variables, Mann-Whitney-test or Kruskal-Wallis-test was applied, as appropriate. Distribution of continuous data was examined with graphical exploration and Kolmogorov-Smirnov-test. For binary data, Fishers exact test was applied. To describe odds between groups, Mantel-Haenszel estimation was performed. All statistical significance tests used a two-sided alpha level of <5% and were intended as exploratory in this pilot trial. Similar to previous studies, we defined responders as patients with a pain reduction measured in NRS of at least 50% (9, 10, 16). Patients treated per protocol were included into analysis ($n = 13$). The study was a priori planned to explore a clinical meaningful difference in pain reduction measured in NRS (0.33 vs. 0.5 pain, SD ±0.1) with a power of 0.8 resulting in a number of 24 patients to be randomized. In 2019, the study was temporarily *on hold* due to explore unexpected high rates of drop outs (4 out of 17), however, restart of this trial was not feasible due to ongoing restriction to perform studies during COVID-19 pandemic and thus terminated.

3. Results

Altogether, 686 cases presenting at the pain outpatient center of Charité Virchow Klinikum were pre-screened. Most of these patients did not receive invasive treatment. Patients with refractory cranial pain syndromes scheduled for local infiltration series between June 2016 and March 2019 were screened. We identified 36 patients fulfilling inclusion criteria. After excluding 19 ineligible patients, 17 patients were randomized into the three study groups (cathodal $n = 6$, sham $n = 5$, cathodal $n = 6$). Of these, four patients withdrew their study participation. Thus, thirteen patients were included into analysis (Figure 1). Last follow-up ended in May 2019.

3.1. Patients' conditions

Included patients suffered from either trigeminal neuralgia or persistent idiopathic facial pain (PIFP) (basic characteristics, Table 1).

3.2. Blockade technique

Most patients received a blockade at the sphenopalatine ganglion (SPG) $n = 11$ (84.6%) as main infiltration site. Ganglionic local opioid analgesia (GLOA) infiltration [$n = 1$ (7.7%)] and infiltrations at the N. occ. major [$n = 1$ (7.7%)] were seldom reported as main infiltration site. For SPG blockade local anesthetics (2–3 ml bupivacaine 0.25%) was applied *via* infra-zygomatic injection. For GLOA infiltration, lipophilic opioids and local anesthetics (5 ml 0.5% bupivacaine and 0.03 mg buprenorphine) were injected close to paravertebral cervical ganglions. In patients with mononeuropathic pain patterns, nerve blocks with local anesthetic (ropivacaine 0.2%, 3 ml) were used. Included patients received 2–10 infiltrations and stimulations in a series with median 9 infiltrations and stimulations (IQR 6–10). All 13 per-protocol treated patients received 20 min of tDCS before each infiltration in the series.

3.3. Change in pain

The NRS score before infiltration and stimulation series for per-protocol patients were at median 7 (IQR5.00–9.50). There was no significant difference between dropouts and non-dropouts ($p = 0.249$). Throughout series, there was a significant overall decrease of NRS scores in treated patients (before median 7 (IQR 5.00–9.50), at the end of series median 3 (IQR 1.00–4.00), $p < 0.001$; see Figure 2A).

The NRS scores before intervention were comparable between stimulation groups ($p = 0.181$). NRS scores decreased in all three study groups throughout series. The anodal stimulation group started with lowest NRS scores before series 5.50 (median, IQR 4.50–7.00) and achieved lowest NRS scores after series 1.00 (median, IQR 0.75–4.00), resulting in the highest relative NRS reduction throughout series of 73.33% (median, IQR 50.00-87.50%). The cathodal stimulation group had higher NRS scores before series 9.00 [median, (IQR 8.00–9.00)] and after series 4.00 (median, IQR 3.00–4.00) and, thus, lowest relative NRS reduction 50.00% (median, IQR 44.44–50.00%). The NRS scores in the sham group before series were 7.50 (median, IQR 4.75–9.50), after series 2.50 (median, IQR 1.25–4.50) and a consequent relative

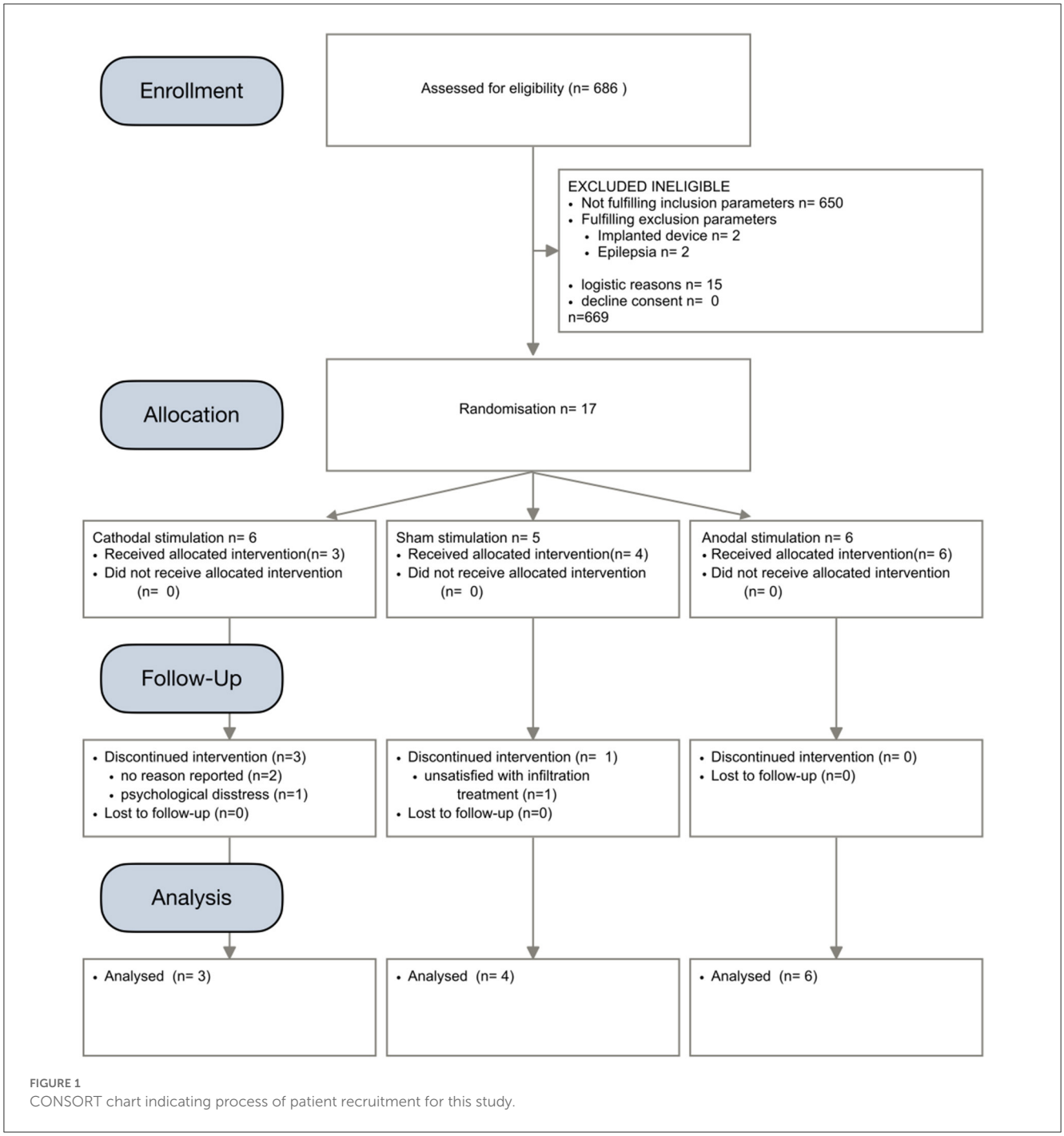


FIGURE 1
CONSORT chart indicating process of patient recruitment for this study.

NRS reduction of 68.75% (median, IQR 37.05–78.75%). The relative NRS reduction throughout series did not differ significantly between the study groups ($p = 0.532$; see Figure 2B).

3.4. Analysis of response

76.9% of patients had a 50% NRS reduction throughout series. Response of 50% NRS reduction was highest in anodal group (83.3%), followed by sham group (75.0%) and cathodal group (66.7%). Differences in response rate were non-significant ($p = 0.850$). Odds ratio in the anodal group for 50% NRS reduction was 1.667 (CI 0.074–37.728) and in the cathodal group 0.667 (CI 0.025–18.059) compared with sham group.

The time to the event of 50% NRS reduction was at Median 3 sessions (IQR 2–3). The time to event was shortest in the cathodal group (median 2, IQR 2–2), followed by sham (median 3, IQR 2.25–3) and anodal group (median 3, IQR 2.75–3.50). Differences in time to event were not significant between stimulation groups ($p = 0.644$).

With a response equalling 50% NRS reduction achieved in 75% of patients in the sham group and an odds ratio of 1.667 in the

TABLE 1 Basic characteristics for $N = 13$ patients included with refractory neuropathic pain syndromes in the head-neck area.

Variable	$N = 13$ patients
Female gender *n* (%)	7 (53.8%)
Age in years mean (±SD) median (25–75% quartile)	61.08 (±13.77) 58 (IQR 50.0-75)
Duration onset of pain until first infiltration (months) ($N = 12$), median (quartiles)	5 (0.31-19.75)
Medication at the beginning of infiltration series *n* in %	
WHO I: *n* (%)	8 (61.5%)
WHO II: *n* (%)	3 (23.1%)
WHO III: *n* (%)	2 (15.4%)
Co-analgesic drugs	
Antidepressants *n* (%)	8 (61.5%)
Antiepileptics *n* (%)	12 (92.3%)
Depressions *n* (%)	2 (15.4%)
Neuropathic pain classified following ICHD 3, given in *n* (%)	
Trigeminal neuralgia, 13.1	10 (76.9%)
Persistent idiopathic facial pain (PIFP), 13.11	3 (23.1%)

anodal group, the number needed to treat with anodal stimulation as verum treatment equals NNT = 12.

3.5. Course of pain scores throughout series

All three subgroups reported an overall NRS reduction throughout series. Course of reported median NRS scores are indicated in Figure 3.

3.6. Subgroup analysis of neuropathic pain diagnosis

Overall, 10 patients suffered from trigeminal neuralgia whereas 3 patients had a diagnosis of PIFP. Differences in relative reduction of pain intensity over time were not significant ($p = 0.469$, see Supplementary Figure 2 and Supplementary Table 1).

3.7. Effect of sole tDCS stimulation

Overall, there was a significant immediate effect of tDCS before performance of local anesthesia on pain intensity: NRS scores were reduced in median 1 point (IQR 0–2; $p < 0.001$). Nevertheless, no difference between anodal, cathodal or sham stimulation was noted ($p = 0.482$).

3.8. *Post-hoc* sample size calculation

Based on the relative NRS reduction throughout series comparing anodal treatment and sham, a sample size calculation for a confirmatory study was performed. A sample size of 93 patients is necessary to achieve level of significance in a confirmatory study. Using a conservative estimation including the drop-out rate of this study with 23.5%, altogether 120 patients would necessary to be randomized.

3.9. Analysis of side-effects

Of included per-protocol treated patients, 76.9% ($n = 10$) reported some kind of side-effects due to tDCS. A prickling (53.8%, $n = 7$) or burning sensation (53.8%, $n = 7$) was the most common side-effect. Mild local pain (15.4%, $n = 2$) and skin redness (7.7%, $n = 1$) was reported seldom. No patient reported increased headache due to stimulation. There was no severe side-effect or reported drop-out due to side-effects.

3.10. Drop-outs

Four patients dropped out of the study. One reported psychosocial distress not related to the study as the reason for dropout. One patient reported non-sufficient effect of the infiltration and two did not report a reason. Notably, most patients dropped out of the cathodal ($n = 3$) group followed by the sham group ($n = 1$). No patient dropped out of the anodal group.

3.11. Comparison non-stimulation and stimulation

The differences in relative NRS reduction between non-stimulation group ($n = 83$, Median 44.44%, IQR 0.00–70.00%) and stimulation group ($n = 13$, Median 66.66%, IQR 47.22–80.00%) were not significant ($p = 0.054$). A higher proportion of responders with 50% NRS reduction was noted in group with stimulation setting ($n = 10$, 76.9%) than in non-stimulation group ($n = 41$, 49.4%, $p = 0.079$; see Figure 4). This results in an OR of 3.41 for stimulation vs. non-stimulation setting and a subsequent NNT by stimulation setting of 3.63.

3.12. Follow-up analysis

There was no statistically significant difference in tDCS study groups regarding maximum pain measured in NRS at 1 month follow-up time point ($p = 0.645$), three-month follow-up time point ($p = 0.626$) and 6 month follow-up time point ($p = 0.835$). There was as well no statistically significant difference in tDCS study groups regarding average pain measured in NRS at 1 month follow-up time point ($p = 0.404$), 3 month follow-up time point ($p = 0.618$) and 6 month follow-up time point ($p = 0.632$).

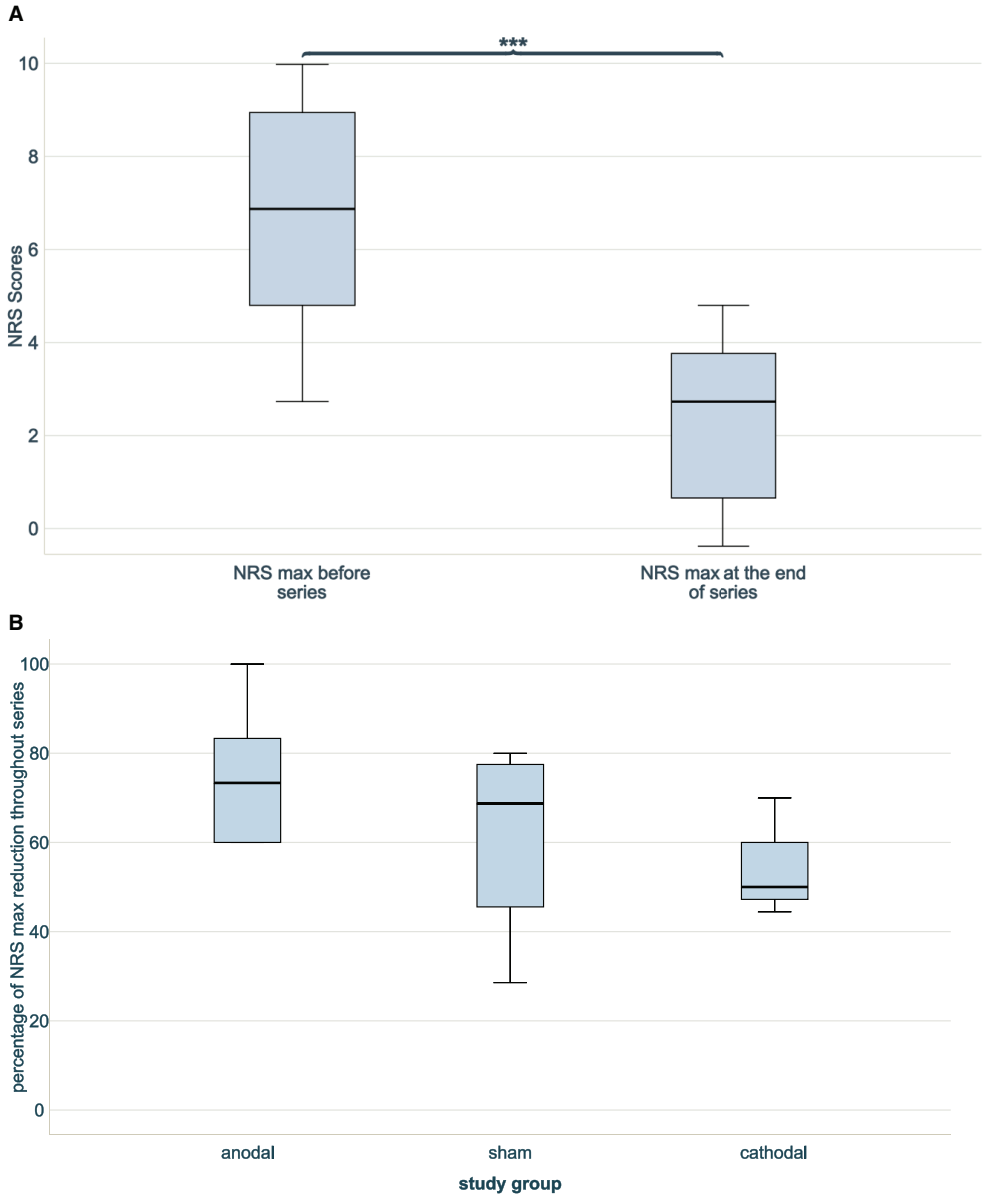


FIGURE 2
NRS scores through series without dropouts. **(A)** Two boxplots indicating NRS max at beginning and at the end of combined infiltration and stimulation series. A significant NRS reduction was achieved ($^{***}p < 0.001$), $n = 13$. **(B)** Three boxplots showing the percentages of reduction of NRS score at the end of infiltration and stimulation series compared to the beginning between blind groups (anodal $n = 6$, sham $n = 4$, cathodal $n = 3$). No difference in reduction was noted ($n = 13$, $p = 0.532$).

At 1 month follow-up, there was a significant difference in mental distress between subgroups with cathodal stimulation group having the highest rating in impairment [anodal median 3 (IQR 0–8); sham median 0 (IQR 0–0); cathodal median 8 (IQR 5–8); $p < 0.05$]. In both, impairment in daily activities [anodal 0 (IQR 0–5); sham median 1 (IQR 0.25–1.75), cathodal median 5 (IQR 2–5); $p = 0.231$] and endurance of pain [anodal median 2 (IQR 1.5–2.5); sham median 2 (IQR 1.25–2), cathodal median 3 (IQR 2–3); $p = 0.154$] cathodal stimulation apparently showed worse scores. At both, 3 and 6 months follow-up, we observed no statistical differences in impairment in daily activities, mental distress and endurance of pain.

In total, three patients received additional local infiltration series outside the study after completion of stimulation and infiltration series. The patients with additional series were equally distributed among the study groups (anodal $n = 1$, sham $n = 1$ and cathodal $n = 1$) and the time to the series (median 12, IQR 11–12) did not differ between subgroups ($p = 0.368$).

3.13. Analysis of self-assessment

To determine patient blinding, patients were asked in a self-assessment to which group they belong. Group assignment and self-assessment to active or sham stimulation did not show any statistical association ($p = 0.429$).

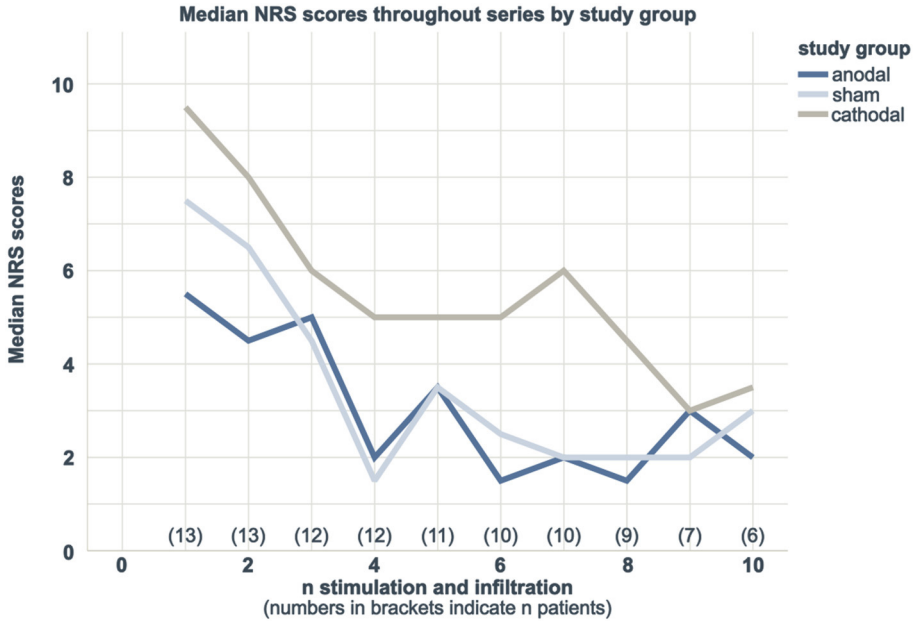


FIGURE 3
Course of median NRS max values throughout series by study group.

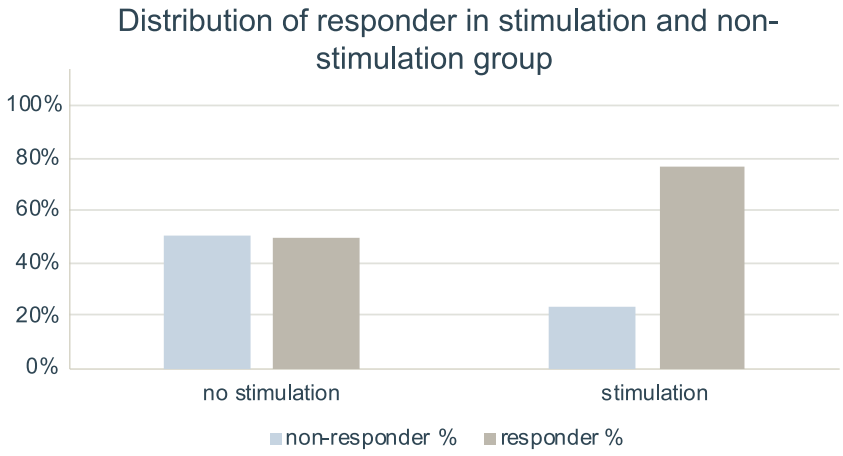


FIGURE 4
Distribution of responder in stimulation and non-stimulation setting. Bar charts indicating percentage of responder and non-responder with 50% NRS reduction in group with no stimulation setting ($n = 83$) and in group with stimulation setting ($n = 13$). Data for infiltration series without stimulation setting was taken from our previous study (10).

4. Discussion

As the main findings of this randomized controlled pilot trial, we observed tDCS to be safe and feasible applied in multimodal pain management and embedded in infiltration series for neuropathic cranial pain. Nevertheless, effect size to potentially achieve a 50% reduction in pain intensity beyond placebo effect was low with an odds ratio of 1.667 and an estimated number needed to treat of 12. Furthermore, we were able to quantify probable intrinsic placebo effects of tDCS setting with an OR of 3.41 and to show effective blinding measures for further trials in this area.

Adjunctive treatment with tDCS in pain disorders is an emerging field in pain research (18). The combination of both infiltration series and tDCS was performed in this pilot study. This approach seemed promising, since changes in resting state functional connectivity in areas relevant for pain was noted after tDCS and local anesthesia infiltration (13, 25, 39). Although there was an overall significant NRS reduction throughout series in this trial, differences of this reduction between study groups did not reach statistical level of significance. Nevertheless, highest proportion of NRS reduction was noted in the anodal tDCS group and thus, might support the use of anodal M1-stimulation 2 mA for 20 min. This finding goes along with other tDCS studies in the field,

stating that this stimulation setting seems to be standard treatment in pain studies evaluating tDCS effects (18). Most studies included in a Cochrane-Review used 2 mA stimulation over 20 min. In that review, single tDCS resulted in a reduction in pain intensity of 0.82 (95% CI 0.42–1.2) points, or a percentage change of 17% (95% CI 9% to 25%) of the control group outcome (19).

From our results, an NNT of 12 can be estimated when comparing effects of anodal tDCS vs. sham-tDCS in our specific chronic pain patient population. A randomized clinical trial with 59 participants with tDCS as add-on treatment for bipolar depression showed an NNT of 5.8 in primary outcome defined as a change from baseline 17-item Hamilton Depression Rating Scale (56). This may indicate that effects of tDCS on pain might be lower than effects in other fields. The assumed effect of tDCS in our study in patients with refractory neuropathic cranial pain syndromes goes in line with the results of other studies. Treatment with patient-conducted anodal tDCS has shown beneficial effects in patients with trigeminal neuralgia: pain intensity was significantly reduced after 2 weeks of treatment (anodal 6.7 ± 1.3 (pre) to 5.5 ± 2.3 (post); sham 7.2 ± 1.2 (pre) to 7.8 ± 1.8 (post), $p = 0.008$) (57). This study by Fitzgibbon et al. highlights another benefit of tDCS: self-applying tDCS by patients themselves and, thus, enhancing self-efficacy (18).

Effects of tDCS on pain could be partly attributed to changes in endogenous inhibitory pathways (28). In a positron-emission tomography study, Garcia-Larrea et al. showed that most changes in cerebral blood flow attributed to electrical stimulation of the precentral gyrus was noted in the ventral-lateral thalamus hypothesizing that this may reflect cortico-thalamic connections (58). Thalamo-cortical connections seem to play a crucial role in pain (59–61). A different approach explains effects by modulation of cortical plasticity (18). A resting state functional MRI study with fibromyalgia patients showed changes in cortical plasticity correlated with pain reduction in both, sham and active tDCS treatment. Hence, it was hypothesized that there might be a placebo response common to both sham and real tDCS (62). This goes together with results of a PET-MRI trial indicating that acute changes in endogenous μ-opioid receptor mediated neurotransmission are produced by sham-tDCS but enhanced at molecular and clinical levels by real tDCS (63). Although reduction of NRS scores throughout tDCS series in our study should be partly attributed to nerve block techniques (10), we could speculate that μ-opioidergic effects being subclinic in single session tDCS (64) might multiply in subsequent tDCS-series. This repetitive stimulation may be necessary to reverse changes in neuroplasticity especially related to chronic pain. The repetition of stimulation is supported by results from animal data of a chronic neuropathic pain model in rats in which repetitive anodal tDCS over the M1 areal had a longer analgesic effect than single stimulus (65). A systematic review on non-invasive brain stimulation in oro-facial pain stated that higher number of sessions seems to be accompanied by more durable effects (24).

A reduction of 50% pain intensity is common as a description for successful treatment and used in this study (9, 10, 16, 66). When compared to previous data of infiltration series without tDCS, responder rate in this tDCS trial was higher, though statistically non-significant (10). This suggests a strong placebo effect, which was calculated with an NNT of 3.6. Therefore, the overlying placebo effect seems to be stronger than the inherent effects provided by tDCS. Furthermore, we found an immediate effect of tDCS on pain intensity which did not differ between cathodal, anodal and sham stimulation. This finding supports the idea of a direct placebo effect mediated by the tDCS setting.

It has been reported that invasive procedures might have more powerful placebo effects than less invasive procedures. Expectancy is one of the most powerful causes of placebo effects. Infiltration and stimulation with tDCS enhances expectations regarding pain relief (67). Furthermore, longer studies with more than six weeks of follow-up seem to have a more profound placebo effect (68). Consequently, study designs need to acknowledge strong placebo effects. Interestingly, worse scoring for cathodal tDCS at 1 month follow-up time-point together with relatively high drop-out rate in this group could be suggestive for a deteriorating influence of cathodal M1 stimulation on pain patients. This could be due to inverse effects of excitability of the underlying cortex of anodal and cathodal tDCS stimulation (22, 29). This inverse effect might also explain the higher rated distress in cathodal group since anodal tDCS has been repeatedly reported to have a beneficial effect on depression (69).

4.1. Limitations

Although providing insights into tDCS for chronic neuropathic pain patients, this pilot study has some limitations. Especially the small sample size in pilot studies limit generalizability of results. Furthermore, individual pain perception differs between patients and other outcome measurements like change in medication would be an interesting variable to include in future protocols (70). In addition to that, the inclusion and exclusion criteria did not cover all possible confounders (e.g., the effects of pain medication). To cover such unmeasured confounders, the study was performed in a randomized-controlled design with included long term data on patients. Another limitation were differences in the baseline NRS among the different study groups. Though statistically not significant, we used relative instead of absolute NRS reduction and a definition of 50% NRS reduction as a clinically relevant response to address these differences. Regarding suitable outcome measurements, resting pain, maximum pain in exertion as well as frequency of pain attacks and change in pain medication should be assessed.

As blinding is a critical issue in tDCS, we observed sufficient blinding provided by the study mode of the NeuroConn DC-Stimulator®. There was no connection noted between the self-assessment of patients and the actual study group. Thus, our results support the use of an increasing and decreasing current at the beginning and end of a sham stimulation to imitate effects of tDCS. This goes with the results of the study by Gandiga et al. who described this sham procedure. In their pooled data analysis including several studies over 3 years with 170 stimulation sessions, there was no difference in the incidence of side-effects between tDCS and sham groups (71). This was contrary to results from a study evaluating differences between sham and active tDCS with 131 patients receiving either type of stimulation; a statistically higher rate of sensory side effects was noted in the active tDCS

group (72). Based on our finding, blinding in our tDCS population was sufficient.

4.2. Future directions

Future studies could try to lower the barriers to tDCS application with supervised stimulation at home (18). A different approaches is to combine non-invasive brain stimulation with other non-invasive approaches such as neurofeedback to further enhance possible beneficial effects (73). Not only feedback to the patient but also to the tDCS applying in real-time tool could be a new research direction. Thus ongoing brain activity could provide the base for closed-loop technology allowing the delivery of tDCS specific to an individual's internal state (18). Furthermore, future studies should address the limitations reported in our study including small sample size and unmeasured confounders. A sample size calculation for such future studies, revealed the necessity of 120 patients with refractory neuropathic cranial pain to confirm our findings. This is challenging, since infiltration series are only used in patients refractory to standard treatment and thus performed relatively rarely. In 4 years, a study in an university affiliated pain outpatient clinic reported only 74 patients receiving a ganglionic opioid analgesia (GLOA) at the superior cervical ganglion as an infiltration series (16). These numbers are supported by our previous study performed as well in a university affiliated pain outpatient clinic with 83 patients receiving infiltration series in six-and-a-half years (10). Hence, a confirmatory study could only be performed in multicentre study design.

Data availability statement

Data can be accessed upon request by contacting the last author ST via e-mail: sascha.tafelski@charite.de.

Ethics statement

This study involving human participants was reviewed and approved by Ethikkommission der Charité – Universitätsmedizin Berlin Campus Charité Mitte, Germany (EA1/031/16). The patients provided their written informed consent to participate in this study.

Author contributions

JDW: acquisition of data, analysis and interpretation of data, creating of all figures and tables, drafting the article, revising the article critically for important intellectual content, and final approval of the version to be published. JK: acquisition of data, revising the article critically for important intellectual content, and final approval of the version to be published. TF: conception of study, revising the article for important intellectual content, and final approval of the version to be published. CD: revising the article for important intellectual content and final approval of the version to be published. MS: giving advice to conception and design of study, revising the article critically for important intellectual content, and final approval of the version to be published. ST: conception and design of study, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. All authors contributed to the article and approved the submitted version.

Funding

This research was funded by the AMS Stiftung. The funder was not involved in study design, data collection, data analysis, manuscript preparation or publication decisions. We acknowledge financial support from the Open Access Publication Fund of Charité – Universitätsmedizin Berlin and the German Research Foundation (DFG).

Acknowledgments

We strongly thank the nurses and the participating patients at the pain outpatient clinic for their contribution to the study. Furthermore, we thank the AMS Stiftung for the continuous financial support of our research. We presented the main results of this study at the annual meeting of the German pain society (Deutscher Schmerzkongress 2021) and received the award for the best scientific poster.

Conflict of interest

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1069434/full#supplementary-material

References

1. Weiss AL, Ehrhardt KP, Tolba R. Atypical facial pain: a comprehensive, evidence-based review. *Curr Pain Headache Rep*. (2017). doi: 10.1007/s11916-017-0609-9

2. Rice ASC, Smith BH, Blyth FM. Pain and the global burden of disease. *PAIN*. (2016) 157:791–6. doi: 10.1097/j.pain.0000000000000454

3. Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain*. (2019) 160:53–9. doi: 10.1097/j.pain.0000000000001365

4. Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. *Nat Rev Dis Prim*. (2017) 3:17002. doi: 10.1038/nrdp.2017.2

5. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. (2015) 14:162–73. doi: 10.1016/S1474-4422(14)70251-0

6. Szok D, Tajti J, Nyári A, Vécsei L. Therapeutic Approaches for Peripheral and Central Neuropathic Pain. Trojano L, editor. *Behav Neurol*. (2019) 2019:8685954. doi: 10.1155/2019/8685954

7. Dworkin RH, O'Connor AB, Kent J, Mackey SC, Raja SN, Stacey BR, et al. Interventional management of neuropathic pain: NeuPSIG recommendations. *Pain*. (2013) 154:2249–61. doi: 10.1016/j.pain.2013.06.004

8. Vorenkamp KE. Interventional Procedures for Facial Pain. *Curr Pain Headache Rep*. (2012) 17:308. doi: 10.1007/s11916-012-0308-5

9. Tafelski S, Beutlhauser T, Gouliou-Mayerhauser E, Fritzsche T, Denke C, Schäfer M. Praxis der regionalanästhesiologischen Behandlung chronischer Schmerzpatienten in der stationären und ambulanten Versorgung. *Der Schmerz*. (2015) 29:186–94. doi: 10.1007/s00482-014-1503-6

10. Gerken JD, Fritzsche T, Denke C, Schäfer M, Tafelski S. Retrospective study on ganglionic and nerve block series as therapeutic option for chronic pain patients with refractory neuropathic pain. Gazerani P, editor. *Pain Res Manage*. (2020) 2020:6042941. doi: 10.1155/2020/6042941

11. Cousins MJ, Bridenbaugh PO, Carr DB, Horlocker TT. *Cousins and Bridenbaugh's Neural Blockade in Clinical Anesthesia and Pain Medicine. 4th ed*. Philadelphia: Lippincott Williams & Wilkins (2009). 1306 p.

12. Dosch MP. *Atlas of Neural Therapy With Local Anesthetics. 3rd ed Stuttgart*. New York: Thieme (2009).

13. Krebs K, Rorden C, Androulakis XM. Resting state functional connectivity after sphenopalatine ganglion blocks in chronic migraine with medication overuse headache: a pilot longitudinal fMRI study. *Headache J Head Face Pain*. (2018) 58:732–43. doi: 10.1111/head.13318

14. Kanai A, Suzuki A, Kobayashi M, Hoka S. Intranasal lidocaine 8% spray for second-division trigeminal neuralgia. BJA: British Journal of Anaesthesia. *Oktober*. (2006) 97:559–63. doi: 10.1093/bja/ael180

15. Newman-Norlund RD, Rorden C, Maleki N, Patel M, Cheng B, Androulakis XM. Cortical and subcortical changes following sphenopalatine ganglion blocks in chronic migraine with medication overuse headache: a preliminary longitudinal study. *Women's Midlife Health*. (2020) 6:7. doi: 10.1186/s40695-020-00055-y

16. Elsner F, Radbruch L, Gaertner J, Straub U, Sabatowski R. Efficacy of opioid analgesia at the superior cervical ganglion in neuropathic head and facial pain. *Schmerz (Berlin, Germany)*. (2006) 20:268–272, 274–276. doi: 10.1007/s00482-005-0460-5

17. Kuner R, Flor H. Structural plasticity and reorganisation in chronic pain. *Nat Rev Neurosci*. (2017) 18:20–30. doi: 10.1038/nrn.2016.162

18. Fitzgibbon BM, Schabrun SM. Transcranial direct current stimulation for pain disorders: challenges and new frontiers. clinical pharmacology & therapeutics. *Oktober*. (2019) 106:717–9. doi: 10.1002/cpt.1544

19. O'Connell N, Marston L, Spencer S, DeSouza L, Wand B. Non-invasive brain stimulation techniques for chronic pain. *Cochr Database Syst Rev*. (2018) 16:CD008208. doi: 10.1002/14651858.CD008208.pub4

20. Cirillo G, Di Pino G, Capone F, Ranieri F, Florio L, Todisco V, et al. Neurobiological after-effects of non-invasive brain stimulation. *Brain Stimul. Basic Transl. Clin. Res. Neuromodul*. (2017) 10:1–18. doi: 10.1016/j.brs.2016.11.009

21. Rahman A, Reato D, Arlotti M, Gasca F, Datta A, Parra LC, et al. Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. *J Physiol*. (2013) 591:2563–78. doi: 10.1113/jphysiol.2012.247171

22. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol*. (2000) 527:633–9. doi: 10.1111/j.1469-7793.2000.t01-1-00633.x

23. Keuters MH, Aswendt M, Tennstaedt A, Wiedermann D, Pikhovych A, Rotthues S, et al. Transcranial direct current stimulation promotes the mobility of engrafted NSCs in the rat brain. *NMR Biomed*. (2015) 28:231–9. doi: 10.1002/nbm.3244

24. Herrero Babiloni A, Guay S, Nixdorf DR, de Beaumont L, Lavigne G. Non-invasive brain stimulation in chronic orofacial pain: a systematic review. *J Pain Res*. (2018) 11:1445–57. doi: 10.2147/JPR.S168705

25. Polanía R, Paulus W, Nitsche MA. Reorganizing the intrinsic functional architecture of the human primary motor cortex during rest with non-invasive cortical stimulation. *PLoS ONE*. (2012) 7:e30971. doi: 10.1371/journal.pone.0030971

26. Fregni F, Freedman S, Pascual-Leone A. Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. *Lancet Neurol*. (2007) 6:188–91. doi: 10.1016/S1474-4422(07)70032-7

27. Gregoret L, Zamorano AM, Graven-Nielsen T. Effects of multifocal transcranial direct current stimulation targeting the motor network during prolonged experimental pain. *European J Pain*. (2021) 25:1241–53. doi: 10.1002/ejp.1743

28. Giannoni-Luza S, Pacheco-Barrios K, Cardenas-Rojas A, Mejia-Pando PF, Luna-Cuadros MA, Barouh JL, et al. Noninvasive motor cortex stimulation effects on quantitative sensory testing in healthy and chronic pain subjects: a systematic review and meta-analysis. *PAIN*. (2020) 161:1955–75. doi: 10.1097/j.pain.0000000000001893

29. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol*. (2017) 128:56–92. doi: 10.1016/j.clinph.2016.10.087

30. Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: State of the art 2008. *Brain Stimul*. (2008) 1:206–23. doi: 10.1016/j.brs.2008.06.004

31. Vaseghi B, Zoghi M, Jaberzadeh S. Does anodal transcranial direct current stimulation modulate sensory perception and pain? A meta-analysis study. *Clin Neurophysiol*. (2014) 125:1847–58. doi: 10.1016/j.clinph.2014.01.020

32. Vaseghi B, Zoghi M, Jaberzadeh S. How Does Anodal Transcranial Direct Current Stimulation of the Pain Neuromatrix Affect Brain Excitability and Pain Perception? A randomised, double-blind, sham-control study. *PLoS ONE*. (2015) 10:e0118340. doi: 10.1371/journal.pone.0118340

33. Vaseghi B, Zoghi M, Jaberzadeh S, A. Meta-Analysis of Site-Specific Effects of Cathodal Transcranial Direct Current Stimulation on Sensory Perception and Pain. *PLoS ONE*. (2015) 10:e0123873. doi: 10.1371/journal.pone.0123873

34. DaSilva AF, Volz MS, Bikson M, Fregni F. Electrode positioning and montage in transcranial direct current stimulation. *J Vis Exp*. (2011) 51:2744. doi: 10.3791/2744-v

35. Kulkarni B, Bentley DE, Elliott R, Youell P, Watson A, Derbyshire SWG, et al. Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. *Eur J Neurosci*. (2005) 21:3133–42. doi: 10.1111/j.1460-9568.2005.04098.x

36. Peyron R, Laurent B, García-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). *Neurophysiol Clin*. (2000) 30:263–88. doi: 10.1016/S0987-7053(00)00227-6

37. Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, et al. Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. *Clin Neurophysiol*. (2017) 128:1774–809. doi: 10.1016/j.clinph.2017.06.001

38. Cardenas-Rojas A, Pacheco-Barrios K, Giannoni-Luza S, Rivera-Torrejon O, Fregni F. Noninvasive brain stimulation combined with exercise in chronic pain: a systematic review and meta-analysis. *null*. (2020) 20:401–12. doi: 10.1080/14737175.2020.1738927

39. Kunze T, Hunold A, Haueisen J, Jirsa V, Spiegler A. Transcranial direct current stimulation changes resting state functional connectivity: A large-scale brain network modeling study. *Neuroimage*. (2016) 140:174–87. doi: 10.1016/j.neuroimage.2016.02.015

40. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. (2018) 38:1–211. doi: 10.1177/0333102417738202

41. Regionalanästhesie. *Stuttgart*. New York: Gustav Fischer Verlag (1988).

42. Arnold B, Brinkschmidt T, Casser HR, Gralow I, Irnich D, Klimczyk K, et al. Multimodale Schmerztherapie. *Der Schmerz*. (2009) 23:112. doi: 10.1007/s00482-008-0741-x

43. Arnold B, Brinkschmidt T, Casser HR, Diezemann A, Gralow I, Irnich D, et al. Multimodale Schmerztherapie für die Behandlung chronischer Schmerzsyndrome. *Der Schmerz*. (2014) 28:459–72. doi: 10.1007/s00482-014-1471-x

44. World Medical Association. World Medical Association declaration of helsinki: ethical principles for medical research involving human subjects. *JAMA*. (2013) 310:2191–4. doi: 10.1001/jama.2013.281053

45. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. *März*. (2010) 340:c869. doi: 10.1136/bmj.c869

46. Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. *Exp Brain Res*. (2005) 166:23–30. doi: 10.1007/s00221-005-2334-6

47. Nitsche MA, Nitsche MS, Klein CC, Tergau F, Rothwell JC, Paulus W. Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. *Clin Neurophysiol.* (2003) 114:600–4. doi: 10.1016/S1388-2457(02)00412-1

48. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology.* (2001) 57:1899–901. doi: 10.1212/WNL.57.10.1899

49. Pfingsten M, Nagel B, Emrich O, Seemann H, Lindena G, Nilges P, et al. *Deutscher Schmerz-Fragebogen.* Handbuch Berlin: DGSS. (2015).

50. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. *PAIN.* (1992) 50:133–49. doi: 10.1016/0304-3959(92)90154-4

51. Morosoli T, Amaro S, Balmagambetova S, Brando R, Coutinho L, Duarte N, et al. Adjuvant transcranial direct current stimulation in patients with chronic migraine: protocol of a randomized controlled trial. *J Contemp Med Educ.* (2015) 3:1. doi: 10.5455/jcme.20150331115109

52. Chouinard PA, Paus T. The primary motor and premotor areas of the human cerebral cortex. *Neuroscientist.* (2006) 12:143–52. doi: 10.1177/1073858405284255

53. FULTON JF, A NOTE ON THE DEFINITION OF THE. "MOTOR" AND "PREMOTOR" AREAS. *Brain.* (1935) 58:311–6. doi: 10.1093/brain/58.2.311

54. Homan RW, Herman J, Purdy P. Cerebral location of international 10-20 system electrode placement. *Electroencephalogr Clin Neurophysiol.* (1987) 66:376–82. doi: 10.1016/0013-4694(87)90206-9

55. Jasper HH. Report of the committee on methods of clinical examination in electroencephalography: 1957. *Electroencephalogr Clin Neurophysiol.* (1958) 10:370–5. doi: 10.1016/0013-4694(58)90053-1

56. Sampaio-Junior B, Tortella G, Borrione L, Moffa AH, Machado-Vieira R, Cretaz E, et al. Efficacy and safety of transcranial direct current stimulation as an add-on treatment for bipolar depression: a randomized clinical trial. *JAMA Psychiatry.* (2018) 75:158–66. doi: 10.1001/jamapsychiatry.2017.4040

57. Hagenacker T, Bude V, Naegel S, Holle D, Katsarava Z, Diener HC, et al. Patient-conducted anodal transcranial direct current stimulation of the motor cortex alleviates pain in trigeminal neuralgia. *J Headache Pain.* (2014) 15:78. doi: 10.1186/1129-2377-15-78

58. García-Larrea L, Peyron R, Mertens P, Gregoire CM, Lavenne F, Le Bars D, et al. Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. *PAIN.* (1999) 83:259–73. doi: 10.1016/S0304-3959(99)00114-1

59. Jones EG. Thalamocortical dysrhythmia and chronic pain. *PAIN.* (2010) 150:4–5. doi: 10.1016/j.pain.2010.03.022

60. Tu Y, Fu Z, Mao C, Falahpour M, Gollub RL, Park J, et al. Distinct thalamocortical network dynamics are associated with the pathophysiology of chronic low back pain. *Nat Commun.* (2020) 11:3948. doi: 10.1038/s41467-020-17788-z

61. Walton KD, Dubois M, Llinás RR. Abnormal thalamocortical activity in patients with Complex Regional Pain Syndrome (CRPS) Type I. *PAIN.* (2010) 150:41–51. doi: 10.1016/j.pain.2010.02.023

62. Cummiford CM, Nascimento TD, Foerster BR, Clauw DJ, Zubieta JK, Harris RE, et al. Changes in resting state functional connectivity after repetitive transcranial direct current stimulation applied to motor cortex in fibromyalgia patients. *Arthritis Res Ther.* (2016) 18:40. doi: 10.1186/s13075-016-0934-0

63. DosSantos MF, Martikainen IK, Nascimento TD, Love TM, DeBoer MD, Schambra HM, et al. Building up Analgesia in Humans via the Endogenous μ-Opioid System by Combining Placebo and Active tDCS: A Preliminary Report. *PLoS ONE.* (2014) 9:e102350. doi: 10.1371/journal.pone.0102350

64. DosSantos M, Love T, Martikainen I, Nascimento T, Fregni F, Cummiford C, et al. Immediate Effects of tDCS on the μ-Opioid System of a Chronic Pain Patient. *Front Psychiatry.* (2012) 3:93. doi: 10.3389/fpsyt.2012.00093

65. Wen HZ, Gao SH, Zhao YD, He WJ, Tian XL, Ruan HZ. Parameter optimization analysis of prolonged analgesia effect of tDCS on neuropathic pain rats. *Front Behav Neurosci.* (2017) 11:115. doi: 10.3389/fnbeh.2017.00115

66. Moore RA, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, et al. "Evidence" in chronic pain – establishing best practice in the reporting of systematic reviews. *Pain.* (2010) 150:386–9. doi: 10.1016/j.pain.2010.05.011

67. Locher C, Frey Nascimento A, Kirsch I, Kossowsky J, Meyer A, Gaab J. Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia. *PAIN.* (2017) 158:2320–8. doi: 10.1097/j.pain.0000000000001012

68. Tuttle AH, Tohyama S, Ramsay T, Kimmelman J, Schweinhardt P, Bennett GJ, et al. Increasing placebo responses over time in U.S. clinical trials of neuropathic pain. *PAIN.* (2015) 156:2616–26. doi: 10.1097/j.pain.0000000000000333

69. Fregni F, El-Hagrassy MM, Pacheco-Barrios K, Carvalho S, Leite J, Simis M, et al. Evidence-Based Guidelines and Secondary Meta-Analysis for the Use of Transcranial Direct Current Stimulation in Neurological and Psychiatric Disorders. *Int J Neuropsychopharmacol.* (2021) 24:256–313. doi: 10.1093/ijnp/pyaa051

70. Fillingim RB. Individual differences in pain: understanding the mosaic that makes pain personal. PAIN. 2017; 158. doi: 10.1097/j.pain.0000000000000775

71. Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin Neurophysiol.* (2006) 117:845–50. doi: 10.1016/j.clinph.2005.12.003

72. Kessler SK, Turkeltaub PE, Benson JG, Hamilton RH. Differences in the experience of active and sham transcranial direct current stimulation. *Brain Stimul.* (2012) 5:155–62. doi: 10.1016/j.brs.2011.02.007

73. Patel K, Sutherland H, Henshaw J, Taylor JR, Brown CA, Casson AJ, et al. Effects of neurofeedback in the management of chronic pain: A systematic review and meta-analysis of clinical trials. *European J Pain.* (2020) 24:1440–57. doi: 10.1002/ejp.1612

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 25 April 2023
DOI 10.3389/fneur.2023.1167029

OPEN ACCESS

EDITED BY
Jean-Pascal Lefaucheur,
Univ Paris-Est Créteil, AP-HP, France

REVIEWED BY
Moussa Antoine Chalah,
GHU Paris Psychiatrie et Neurosciences, France
Sophie Schlatter,
INSERM U1290 Recherche sur la Performance des Soins (RESHAPE), France

*CORRESPONDENCE
Paula Horczak
✉ Paula.Horczak@ugent.be

†These authors have contributed equally to this work and share first authorship

RECEIVED 15 February 2023
ACCEPTED 03 April 2023
PUBLISHED 25 April 2023

CITATION
Horczak P, Wang C, De Witte S, De Smet S, Remue J, De Raedt R, Vanderhasselt M-A, Wu G-R, Lemmens GMD and Baeken C (2023) Combining transcranial direct current stimulation with group cognitive behavioral therapy developed to treat rumination: a clinical pilot study.
Front. Neurol. 14:1167029.
doi: 10.3389/fneur.2023.1167029

Combining transcranial direct current stimulation with group cognitive behavioral therapy developed to treat rumination: a clinical pilot study

Paula Horczak[1,2*†], Chanyu Wang[1,2†], Sara De Witte[1,2,3,4,5†], Stefanie De Smet[1,2], Jonathan Remue[6], Rudi De Raedt[7], Marie-Anne Vanderhasselt[1,2], Guo-Rong Wu[8], Gilbert M. D. Lemmens[2,6] and Chris Baeken[1,2,3,4,5,6,9]

[1]Ghent Experimental Psychiatry (GHEP) Lab, Ghent University, Ghent, Belgium, [2]Department of Head and Skin – Psychiatry and Medical Psychology, Ghent University, Ghent, Belgium, [3]Department of Neurology and Bru-BRAIN, University Hospital Brussels, Brussels, Belgium, [4]Neuroprotection and Neuromodulation Research Group (NEUR), Center for Neurosciences (C4N), Vrije Universiteit Brussel (VUB), Brussels, Belgium, [5]Department of Psychiatry, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium, [6]Department of Psychiatry, Ghent University Hospital, Ghent, East Flanders, Belgium, [7]Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium, [8]Key Laboratory of Cognition and Personality, Faculty of Psychology, Southwest University, Chongqing, China, [9]Department of Electrical Engineering, Eindhoven University of Technology, Eindhoven, Netherlands

Background: As part of repetitive negative thinking (RNT), rumination is a maladaptive cognitive response style to stress or negative mood which can increase the risk of depression and may prohibit complete recovery. Cognitive behavioral therapy (CBT) and transcranial direct current stimulation (tDCS) both proved to be effective in decreasing rumination. However, the combined effects of tDCS and CBT interventions on rumination have not yet been explored. The first aim of this pilot study is to investigate whether the combination of tDCS and CBT has an accumulating positive effect on modulating state rumination. The second aim is to assess the feasibility and safety profile of the proposed combined approach.

Method: Seventeen adults aged 32–60 years, suffering from RNT, were referred by their primary care professional to participate in an 8-week group intervention for RNT ("Drop It") comprising 8 sessions of CBT. Before each CBT session, patients underwent one double-blinded prefrontal active (2mA for 20min) or sham tDCS (anode over F3, cathode over the right supraorbital region) combined with an internal cognitive attention task focused on individual RNT, i.e., online tDCS priming. During each session, the Brief State Rumination Inventory was used to assess state rumination.

Results: A mixed effects model analysis revealed no significant differences between the stimulation conditions, weekly sessions, or their interaction in terms of state rumination scores.

Conclusion: Overall, the combination of online tDCS priming followed by group CBT was found to be safe and feasible. On the other hand, no significant additional effects of this combined approach on state rumination were established. Although

our pilot study may have been too small to find significant clinical effects, future larger RCT studies on combined tDCS-CBT treatment protocols may reevaluate the selection of internal cognitive attention tasks and more objective neurophysiological measurements, consider the optimal timing of the combination (concurrently or sequentially), or may add additional tDCS sessions when following CBT.

KEYWORDS

transcranial direct current stimulation, group cognitive behavioral therapy, rumination, repetitive negative thinking, major depressive disorder, generalized anxiety disorder, NIBS, psychotherapy

Introduction

Repetitive negative thinking (RNT), such as rumination or worry, has been considered to be a transdiagnostic process for mood and anxiety disorders (1, 2). Rumination involves repetitively focusing on negative events and their potential causes and consequences and has been considered to be a maladaptive cognitive response style that can increase the risk of depression (3, 4). Worry, on the other hand, is more often associated with anxiety disorders, and is characterized by excessive and uncontrollable thoughts about potential negative outcomes or events in the future (5–7). Clinical management typically includes psychotherapy (8).

For instance, cognitive behavioral therapy (CBT) has been shown to be an effective treatment for reducing RNT in patients with major depressive disorder (MDD) and generalized anxiety disorder (GAD), this on the individual level but also when offered as group therapy (9, 10). In addition, it has been shown that RNT-focused CBT in particular has a more pronounced effect on RNT than treatments that do not specifically target rumination (11). For example, Watkins and colleagues (12) performed a randomized controlled trial which provided evidence that MDD patients in the rumination-focused CBT group ruminated significantly less compared to those in the treatment as usual group. Recently, Rogiers and colleagues (13) developed a psychoeducational CBT-based group intervention called "Drop It," specifically for the treatment of RNT. It has proven to be effective in reducing RNT and improving the quality of life for MDD patients, which remain stable up to 9 months after the intervention (14). Brain imaging observations suggest its effectiveness in reducing RNT is associated with increased prefrontal brain perfusion in the left dorsolateral prefrontal cortex (DLPFC) (15). The DLPFC is implicated in regulating affective states and in providing cognitive control over stress and emotional responsiveness (16). In a healthy population, Kühn and colleagues (17) found that DLPFC activation and unwanted self-referent ruminative thoughts were inversely correlated. Crucially, as demonstrated by Jacobs and colleagues (18), adolescents at risk for depressive relapse, who received CBT, showed a significant decrease in connectivity between brain regions related to rumination and cognitive control. Taken together, these findings imply that CBT in general, and "Drop It" intervention in particular, may act by enhancing the top-down cognitive control of negative cognition or emotions (19).

A quite different interventional approach, transcranial direct current stimulation (tDCS), is one of the emerging noninvasive brain stimulation (NIBS) techniques that can also be used to alter RNT. During the application of tDCS, a weak, direct electric current is induced through anodal and cathodal scalp electrodes. Although the exact working mechanisms underlying tDCS are not yet fully understood, it is thought that tDCS exerts its beneficial effects through the induction of polarization shifts on the resting membrane potential (20). These alterations are considered sufficient to bias neural firing, with anodal stimulation locally facilitating cortical excitability and cathodal stimulation impairing it. To modulate cognitive performance and emotion regulation in healthy and neuropsychiatric subjects, the excitability-enhancing anodal electrode is most frequently applied to the DLPFC (21, 22). The cathodal electrode is often placed over a contralateral cephalic region such as the supraorbital region (21). Within the clinical context, the effect of tDCS on reducing rumination on sadness was demonstrated in patients with drug-resistant depression (23). Studies in healthy populations indicate that (even one) left anodal DLPFC tDCS session can attenuate momentary ruminative self-referential thoughts (24, 25) as well as self-attention (26). It is hypothesized that attenuated self-referential attention specifically may be a neurocognitive mechanism through which tDCS reduces emotional reactivity (26).

More recently, NIBS has been used together with cognitive/emotional tasks to increase the clinical effects. This approach is called online stimulation and is based on the activity-selectivity hypothesis (27), meaning that NIBS interventions may depend on the neural targets that are activated through cognitive tasks or therapies at the same time (28, 29). For instance, the combination of rTMS and psychotherapy in MDD yields higher remission rates than psychotherapy alone (30). Furthermore, as demonstrated by Brunoni and colleagues (31), the combination of tDCS and cognitive control therapy is beneficial for elderly depressed patients. Similarly, in a healthy population, the combination of a neuropsychological task with tDCS has been proven to more effectively improve specific cognitive functions (32, 33) such as counterfactual thinking (34). Therefore, activating, i.e., priming, target areas with RNT during active (as compared to sham) tDCS may yield higher benefits from the CBT.

Currently there are no studies that have evaluated the potential positive or negative effects of online tDCS priming combined with a CBT-based intervention on rumination. The aim of the present pilot study is to explore whether the combination of online active or sham tDCS priming, followed by group CBT "Drop It" treatment, is feasible and safe. Moreover, we hypothesized that priming rumination-related neurocircuits with an internal cognitive attention task focused on individual RNT combined with active (as compared to sham) tDCS prior to the group CBT "Drop It" sessions, would result in supplemental decreases of RNT in terms of reducing state rumination.

Methods

Participants

Eighteen participants (88% females), divided into two groups of nine participants each, participated in this study (*M* age = 44.8; *SD* = 8.9), however 17 were included in the final analysis as one participant was absent during more than two sessions (*n* active = 9). One of the inclusion criteria for participation in the study was that participants were already in mental health care treatment (psychiatrist, psychologist or general practitioner), seeking treatment for rumination - whether or not as part of a MDD or GAD diagnosis - and were referred by their treatment provider to "Drop It" (13, 35) – a psychoeducational CBT-based group intervention for RNT - at the Ghent University Hospital. As compensation for their participation in the study, participants were not charged for the "Drop It" intervention. All participants were between 32 and 60 years old. Habitual treatment use was allowed but kept at a steady dose during the entire experimental trial. Participants were excluded from the study in case of pregnancy, skin conditions in the skull area, use of implanted medical devices (such as a pacemaker), concentration difficulties, no motivation for weekly homework, no intention of weekly attendance, cognitive impairments, substance abuse, suicide risk, the diagnosis of obsessive–compulsive disorder or severe depression. All exclusion criteria were assessed by a psychiatrist during an intake interview using the Mini International Neuropsychiatric Interview [MINI (36)] as well as the Hamilton Depression Rating Scale [HDRS (37)]. The HDRS scores were collected as part of baseline measures and no participants were excluded based on cut-off scores. After the intake, participants were asked to fill in the Leuven Adaptation of the Rumination on Sadness Scale [LARSS (38)] and Penn State Worry Questionnaire [PSWQ (39)] at home. Before the experiment, the participants signed a written informed consent form. The study was approved by the Ethical Committee of the University Hospital of Ghent University (UZ Gent).

Transcranial direct current stimulation

Stimulations were performed using a Soterix mini-CT tDCS device, which allows the double-blinding of the tDCS stimulation condition by providing individualized numeric codes. The anode was placed over the left DLPFC, located using the Beam F3 algorithm (40). Based on the distances between nasion, inion, tragus and vertex as landmarks, this algorithm estimates the coordinates for F3, resembling the left DLPFC (41). This area was selected based on our previous NIBS research in similar samples, targeting this exact same spot (29, 42). The cathode was placed on the right supraorbital region by placing the electrode 1 cm above the right eye. A current of 2 mA was delivered through carbon rubber electrodes of 4.5 × 4.5 cm that were covered by specially designed sponges soaked in a saline solution. During the active stimulation, there was a 30 s ramp-up period, followed by 20 min of stimulation, with a ramp-down of 30 s at the end. For sham tDCS, the current was directly ramped down after the initial ramp-up phase (43).

Online tDCS

Online tDCS is defined here as the performance of an internal cognitive attention task focused on individual RNT concurrently with 20 min of stimulation. This task was adapted from the sixth session of the "Drop It" intervention (i.e., the mindfulness-based attention exercise, see the description of the "Drop It" intervention below). To guide this task, the patients listened in group to an audio recording. The following fragment is the transcript of the audio recording (translated from Dutch):

> I want to ask you to visualize yourself in a situation which initiates worrying. What do you see? Where are you? What is happening? Who is involved? Which thoughts are running through your mind? Do you feel something in your body? How would you label these experiences? Are they associated with emotions? What would you call these emotions? What do you do? Stay with your attention to what you think and feel, no matter how annoying these thoughts or feelings are.

The audio recording started to play simultaneously with the start of the stimulation and lasted for 15 min. The last sentence ("*Stay with your attention …*") was given at 15 min and as a consequence, for the last 5 min of the stimulation, the patients were instructed to stay with their feelings. Online tDCS was implemented before each weekly group CBT intervention "Drop It" (see "Drop It" and Figure 1).

Importantly, this online tDCS procedure acted as 'primer' for the subsequent CBT intervention "Drop It."

Drop It

The "Drop It" intervention consists of seven weekly group sessions (groups of up to 10 patients) and a follow-up session 1 month after the

FIGURE 1
Overview of the study procedure. BSRI, Brief State Rumination Inventory; tDCS, transcranial direct current stimulation; CBT, cognitive behavioral therapy.

seventh session. All sessions lasted 90 min, were guided by CBT-trained psychotherapists and had a well-defined, following structure. All sessions started with a mindfulness-based attention exercise (15 min). Subsequently, a group discussion of the homework (15 min) followed by a "brain-talk" about relevant brain structures and neural circuits (15 min) took place. Lastly, a RNT exercise followed by a discussion (30 min) and a homework task (10 min) concluded the session. All participants received a manual for self-guided help explaining all exercises and homework tasks and a CD containing the attention training exercises. For a detailed description of the intervention see 13.

Procedure

Half of the participants were randomized to receive active tDCS, whereas the other half received sham tDCS. Both groups attended the same CBT sessions to minimize group effects. To assure effective blinding, numeric codes were generated by the tDCS, where each code represented either active or sham stimulation. Every patient had a unique code assigned to them. Patients were required to enter the code in the tDCS device in order to start the stimulation. Patients and the psychotherapist were blinded for tDCS devices conditions until the end of the study. Stimulation was applied during the internal cognitive attention task focused on individual RNT. Subsequently, the tDCS setup was removed and the participants proceeded with the "Drop It" session as described above. During each session, participants were asked to fill in the Brief State Rumination Inventory [BSRI (44)] at three time points: before (A) and after (B) the stimulation as well as at the end of the "Drop It" session (C) (see Figure 1). Given that the first tDCS group CBT session was considered a practice session, these data were not included in the statistical analysis.

Questionnaires

Hamilton depression rating scale

The HDRS is a standardized clinical interview developed to assess the severity of depression. Higher scores suggest higher levels of symptoms of depression (range 0–52). In the current study, the Dutch version of the 17-item HDRS was used (45). The calculated internal consistency was rather poor (Cronbach's alpha = 0.57) in the current study. In general, the HDRS' Cronbach's alpha varies between 0.46 and 0.97 (46).

Leuven adaptation of the rumination on sadness scale

Leuven adaptation of the rumination on sadness scale is the Dutch version of the Rumination on Sadness Scale [RSS (47)]. It contains three original subscales from the RSS (minus four items) as well as eight new items. This questionnaire contains 21 items, which are scored on a 5-point Likert scale, ranging from 1 ('totally not') to 5 ('very often'). Higher scores indicate higher levels of rumination (range 21–105). The internal consistency of the three subscales 'Causal Analysis', 'Understanding,' and 'Uncontrollability' is good to excellent, with Cronbach's alpha of, respectively, 0.87, 0.85, and 0.91.

Penn state worry questionnaire

The PSWQ consists of 16 items that assess the general disposition to worry. Participants rate statements about worry on a scale of 1 ('not at all typical of me') to 5 ('very typical of me'). Higher scores suggest a higher level of worry (range 16–80). In this study, the Dutch version of the questionnaire was used (48, 49) which has good internal consistency (Cronbach's alpha between 0.83 and 0.86).

Brief state rumination inventory

The BSRI is a self-report questionnaire designed to measure RNT at the time of answering. The questionnaire consists of 8 items, each scored on a 100-mm VAS ranging from 0 ('completely disagree') to 100 ('completely agree'). Higher scores indicate higher state rumination. In the current study, the Dutch version of the BSRI was used which has good internal consistency (Cronbach's alpha = 0.89).

Tolerability and safety

Stimulation tolerability was assessed using a custom in-house developed questionnaire. At the end of each "Drop It" intervention, patients were asked to answer eight questions concerning transient hyperactivity or irritability, transient headache, transient local pain, transient neck pain, transient dental pain, transient tingling, transient changes in hearing, irritation at the site of stimulation. Patients could rate their experiences on a scale ranging from 'never' to 'almost constantly'.

Statistical analysis

Preprocessing

All preprocessing and analyses were performed using R (50) and MATLAB (MathWorks, Natick, MA). The data and the analysis code are publicly available at https://osf.io/4xtgr/.

One participant was excluded from further analysis due to absence during more than two sessions, resulting in 17 participants included in the final analysis. Subsequently, missing data was explored and visualized. Fifteen point 3% (15.3%) of the data was missing. Little's Missing Completely at Random (MCAR) test was non-significant, $\chi^2 = 173.37$, $p > 0.5$, suggesting that the pattern of missing data was missing at random. Consequently, to handle missing values, a prediction model, i.e., multiple imputation method, using the 'mice' package (51) with default settings, was applied. The 'mice' function uses a Multivariate Imputation by Chained Equations (MICE) method to impute missing values. This method works by creating multiple imputed datasets and then pooling the results together. For sample characteristics, only complete questionnaires were considered. For the exploratory analysis using MATLAB, the amount of missing data for each participant was included as a one of the covariates. Finally, Δ (delta) rumination scores were calculated as the difference between BSRI scores at the end of the "Drop It" session and before the stimulation, i.e., C-A (*cf.* supra).

Analyses

Sample characteristics and potential group differences were explored using *independent sample t-tests* and *Fisher's exact test*.

A mixed effects model was fitted using package 'lme4' (52) to investigate the relationship between Δ rumination scores ($M = -13.24$,

TABLE 1 Baseline demographic and clinical characteristics of patients in the active versus sham tDCS condition.

Baseline characteristic	Active tDCS – CBT (n=9)		Sham tDCS – CBT (n=8)			
	M	*SD*	*M*	*SD*	*t*	*p*
Age (years)	48.56	8.49	40.50	7.62	2.06	0.06
HDRS	11.11 (9)	3.92	11.12 (8)	5.06	−0.006	0.99
LARSS	70.44 (9)	14.76	61.71 (7)	13.82	1.22	0.25
PSWQ	67.25 (8)	6.67	65.83 (6)	5.74	0.43	0.68
					95% CI	*p*
Female (%)	78		100		[0.001, 5.91]	0.47
Psychotherapy (%)					[0.07, 7.55]	1
Yes	55.56 (5)		62.50 (5)			
No psychotherapy	44.44 (4)		37.50 (3)			
Diagnosis (%)						0.33
MDD	33.33 (3)		37.50 (3)			
GAD	11.11 (1)		37.50 (3)			
Both	55.56 (5)		25.00 (2)			
Medication (%)						0.37
Antianxiety	0		12.50 (1)			
Antidepressant	22.22 (2)		50.00 (4)			
Both	44.44 (4)		12.50 (1)			
No medication	22.22 (2)		25.00 (2)			

CI, confidence interval; HDRS, the Hamilton Depression Rating Scale; LARSS, the Leuven Adaptation of the Rumination on Sadness Scale; PSWQ, the Penn State Worry Questionnaire. The number next to the mean of the three questionnaires is the sample size of each group after deleting the missing data.

SD = 286.24, range = −613 – 503) and the tDCS condition, CBT session as well as the interaction between the two. By-participant random intercepts were included to model individual differences with respect to rumination scores. Results of the model are reported using type III Wald chi-squared statistics. After fitting the model, the normality, linearity, homoscedasticity and multicollinearity assumptions were tested. No obvious violations were observed.

For the exploratory analysis, a one-way ANCOVA was used to determine whether Δ rumination scores, averaged across seven sessions, differed significantly between the active and the sham tDCS group. Age, gender, and the amount of missing data were included as covariates. A statistical significance level of $p < 0.05$, two-tailed, was adopted for all statistical tests.

Results

Sample characteristics

Participants were randomly assigned to an active tDCS ($n = 9$, 78% female, $M_{age} = 48.56$, SD = 8.49) or sham condition ($n = 8$, 100% female, $M_{age} = 40.50$, SD = 7.62). There were no significant baseline differences between the two conditions in terms of age [$t(15) = 2.06$, $p = 0.06$], gender ($p = 0.47$, *95%* CI = [0.001, 5.91]), HDRS scores [$t(13.19) = -0.006$, $p = 0.99$], LARSS scores [$t(13.44) = 1.22$, $p = 0.25$], PSWQ scores [$t(11.69) = 0.43$, $p = 0.68$], diagnosis ($p = 0.33$), pharmacological ($p = 0.37$) or psychological treatment ($p = 1$, *95%* CI = [0.07, 7.55]) (see Table 1). Patients were not able to correctly guess their assigned stimulation condition as the percentage of correct guesses was below chance (42%), indicating that blinding was effective. However, due to practical reasons, only a subset of participants was asked about guessing the stimulation condition.

Rumination scores

The mixed effect model did not reveal significant effects of condition [$\chi^2(1,115) = 0.19$, $p = 0.66$], session [$\chi^2(6,110) = 7.50$, $p = 0.28$] or the interaction between the two [$\chi^2(6,110) = 1.04$, $p = 0.98$] on Δ rumination scores (Figure 2).

Additionally, Δ rumination scores were also calculated for the difference between BSRI scores after the stimulation and at the end of the "Drop It" session, i.e., B-A. However, no significant differences were found either [condition $\chi^2(1,115) = 0.05$, $p = 0.83$], session [$\chi^2(6,110) = 5.18$, $p = 0.52$], interaction between the two [$\chi^2(6,110) = 2.07$, $p = 0.9$].

Exploratory analysis

The one-way ANCOVA revealed no significant difference in the averaged Δ rumination scores between the two groups [$F(1,13) = 0.80$, $p = 0.38$]: after receiving 8 sessions of CBT, patients in the active tDCS group ($M = 21.89$, SD = 92.49) did not ruminate less compared with the sham group ($M = -16.43$, SD = 58.97; see Figure 3).

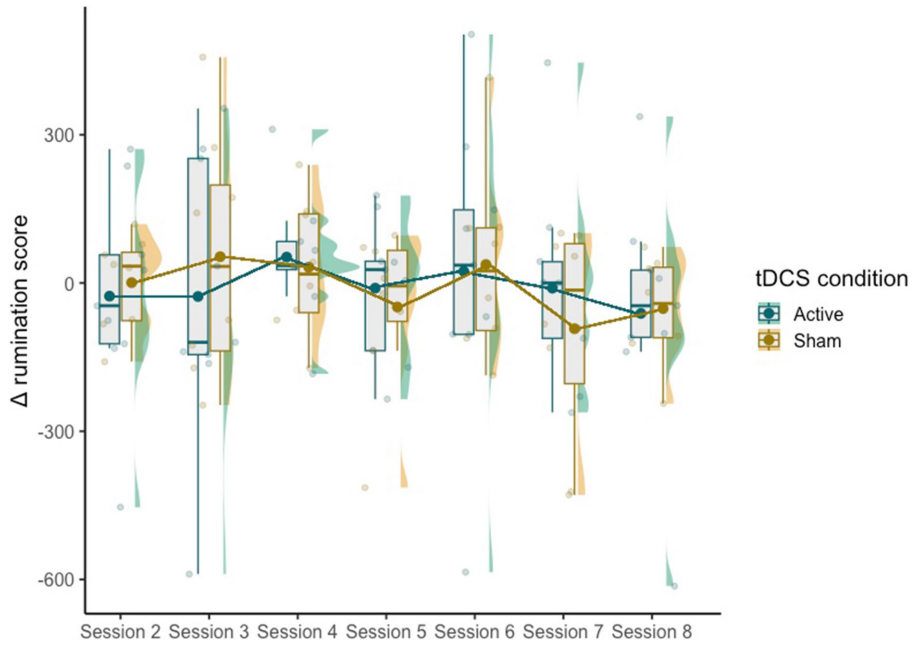


FIGURE 2
The distribution of the difference in post-CBT and pre-tDCS rumination scores.

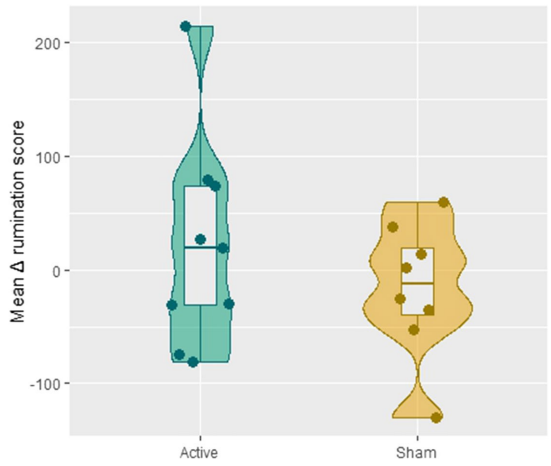


FIGURE 3
The difference in the averaged Δ rumination scores (i.e., the mean of the value C-A) across session 2–8 between the active and sham group.

Tolerability and safety

No severe short-term adverse effects were reported during the study. Long-term effects were not assessed. Participants mostly reported irritation at the site of stimulation, transient tingling, and transient headache, which is in line with previously described adverse effects of tDCS (53). Due to practical reasons, only a subset of patients was asked to fill in our tolerability questionnaire. However, given the preliminary results as well as just one drop out throughout the whole study, it seems reasonable to deduce that the combination of group CBT and tDCS was well tolerated.

Discussion

In this pilot study, we have evaluated a novel therapeutic approach aimed at reducing rumination by combining an internal cognitive attention task focused on individual RNT and tDCS, i.e., online tDCS priming, with a CBT-based group intervention "Drop It." A sham-controlled online tDCS priming followed by CBT-based group intervention was conducted in 17 depressed and/or anxious patients who mainly suffered from RNT. Statistical analysis showed no significant additional effect of online tDCS priming with group CBT on state rumination. Given no reports of severe adverse effects and just one drop out, the combination of group CBT and tDCS seems feasible, well-tolerated and safe. The minor adverse effects reported by the participants pertained to transient events and were fully in line with previously described adverse effects of tDCS. Although we were unable to detect significant differences in state rumination scores between the tDCS groups, our current findings indicate that focusing on RNT during tDCS does not negatively impact (group) CBT.

Besides the relatively small sample size, the lack of additional effects of online tDCS priming is puzzling. Firstly, it could be that the amount of primed tDCS sessions was critically too low (seven tDCS sessions over 7 weeks time and one follow-up session). Martin and colleagues (54) examined the efficacy of tDCS combined with cognitive emotional training and demonstrated significant antidepressant efficacy. However, tDCS administered during cognitive emotional training was applied three times a week for 6 weeks. In a group of alcohol dependent patients, Dubuson and colleagues (55) found that five consecutive daily sessions for 4 weeks combined with alcohol cue inhibitory control training resulted in better clinical outcomes. Although it is difficult to directly compare studies due to methodological differences, it could be that one online tDCS priming before CBT, applied on a weekly basis, is simply not sufficient to elicit meaningful clinical differences. Similarly, although

the choice of the stimulation zones in the current study (anodal left prefrontal - cathodal right supraorbital) was based on our previous research (29, 42), it could be that in the present context they were less suitable. Secondly, it is possible that using a cognitive attention task focused on individual RNT to prime the neural targets might not have been the most optimal choice. As argued before, we expected that priming rumination-related neurocircuits before CBT with active online tDCS would result in a supplemental decrease of rumination. However, notwithstanding that we could not demonstrate significance, our exploratory analysis – contrasting active and sham primed stimulation over the seven group CBT sessions – is suggestive that active online tDCS priming may result in rumination increments after CBT. It remains an open question regarding the kind of cognitive tasks used during the tDCS stimulation. For instance, Sreeraj and colleagues (56) evaluated the effect of a single session online tDCS on working memory in schizophrenia and found improved working memory performance only in the online sham condition. Moreover, an open question remains regarding the timing of the tDCS/CBT combination that consists of multiple sessions, e.g., before versus immediately after the CBT. Lastly, other negative results of combining tDCS with therapeutic interventions have been documented. For example, tDCS-enhanced inhibitory control training showed no superior efficacy on symptoms of PTSD, anxiety, or depression (57).

Limitations

Besides the relatively small sample size, we did not include clinical post-measurements. Therefore, we cannot claim that the combined active versus sham tDCS priming group CBT intervention yielded additional clinical effects on RNT in these patients. While online tDCS priming did not seem to have an augmenting effect on our primary outcome, being state rumination, we cannot rule out that it still had an effect on the trait of worry and/or rumination. This limits our conclusions about potential beneficial clinical effects of tDCS and all interpretations should be restricted to the state effect of our combined intervention on rumination. Moreover, as the first tDCS group CBT session was considered a practice session, this data was not included in the statistical analysis. However, active and sham stimulation was nevertheless applied, which could have influenced the outcomes of the following sessions. The goal of the practice session was to familiarize the patients with the devices and the structure of the sessions. However, in future studies, when including a practice session, one could consider using the tDCS devices but not turning them on, in order to prevent possible impact on the targeted neural areas. Additionally, the lack of a control condition, e.g., tDCS alone or CBT alone, limits our conclusions about the tDCS intervention.

Furthermore, we used a custom in-house developed questionnaire to assess tolerability. In future studies a standardized questionnaire should be used to assure reliable responses as well as comparability to established norms and/or other studies. Additionally, the use of only a subset of the total sample size (due to practical reasons) limited statistical options of analyzing side-effects to quantify tolerability. Similarly, asking all participants about guessing the stimulation condition, instead of only a subset, should be assured in future studies.

Finally, besides the idea that other stimulation methods, such as rTMS, could have been more appropriate, it could also be informative to examine specific cognitive subtypes of rumination, i.e., brooding and reflection. For instance, a recent rTMS study by Ehrlich and colleagues (58) showed that repetitive pulse transcranial magnetic stimulation may modulate reflection rumination rather than brooding. Additionally, an interesting approach for future studies could be to explore the influence of tDCS on more objective measures of rumination, such as cardiac activity. More specifically, both in healthy and clinical populations, it has been demonstrated that heart rate variability (HRV) is negatively correlated with rumination, such that lower levels of HRV indicate higher levels of rumination (59, 60). In the context of NIBS, the combination of tDCS and cardiac biofeedback has proven to be effective in reducing psychological and physiological stress responses (61).

Conclusion

This is the first study to explore the potential positive or negative effects of online tDCS priming combined with an 8-week group CBT-based intervention "Drop It" on state rumination. Although the experimental protocol was found to be safe, well-tolerated and feasible, we could not demonstrate superior efficacy of tDCS-augmented CBT on RNT. Future well-powered RCTs may be needed to demonstrate additional clinical effects of online tDCS priming on psychotherapeutic interventions, exploring other types of cognitive tasks paired with tDCS as well as more objective neurophysiological measurements. Additionally, it could prove to be mandatory to augment the number of primed tDCS sessions during the period patients receive (group) CBT.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: OSF repository https://osf.io/4xtgr.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee of the University Hospital of Ghent University (UZ Gent). The patients/participants provided their written informed consent to participate in this study.

Author contributions

JR, RD, M-AV, GL, and CB participated in the conception and design of this study. SDW and SDS were involved in data acquisition. PH, SDS, CW, and G-RW undertook the data preprocessing and statistical analysis. PH, CW, SDW, SDS, M-AV, G-RW, and CB participated in data interpretation and in writing the manuscript. All authors contributed to the article and approved the submitted version.

Funding

The authors acknowledge the following funding. G-RW was supported by the National Natural Science Foundation of China (Grant No. 62271415). CW was supported by fellowship funding from the China Scholarship Council (CSC). SDS was funded by a FWO-Flanders PhD fellowship (Grant Number: 11J7521N). This work was also

supported by the Queen Elisabeth Medical Foundation for Neurosciences; by the Ghent University Multidisciplinary Research Partnership "The integrative neuroscience of behavioral control"; by an Applied Biomedical (TBM) grant of the Agency for Innovation through Science and Technology (IWT); part of the Research Foundation – Flanders (FWO) PrevenD Project 2.0 (T000720N) and FWO project G011018N. M-AV received funding from the FWO and from Ghent University (Grants: G0F4619N and BOF17/STA/030, respectively).

Acknowledgments

We want to thank all participants for their willingness to be part of this study. We would also like to thank Mitchel Kappen for his help in statistical analysis using R.

Conflict of interest

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.

Publisher's note

References

1. Ehring T, Watkins ER. Repetitive negative thinking as a transdiagnostic process. *Int J Cogn Ther*. (2008) 1:192–205. doi: 10.1521/ijct.2008.1.3.192

2. Kertz SJ, Koran J, Stevens KT, Björgvinsson T. Repetitive negative thinking predicts depression and anxiety symptom improvement during brief cognitive behavioral therapy. *Behav Res Ther*. (2015) 68:54–63. doi: 10.1016/j.brat.2015.03.006

3. Alderman BL, Olson RL, Bates ME, Selby EA, Buckman JF, Brush CJ, et al. Rumination in major depressive disorder is associated with impaired neural activation during conflict monitoring. *Front Hum Neurosci*. (2015) 9:269. doi: 10.3389/fnhum.2015.00269

4. Nolen-Hoeksema S, Wisco BE, Lyubomirsky S. Rethinking rumination. *Perspect Psychol Sci*. (2008) 3:400–24. doi: 10.1111/j.1745-6924.2008.00088.x

5. Bredemeier K, Lieblich S, Foa EB. Pretreatment levels of rumination predict cognitive-behavioral therapy outcomes in a transdiagnostic sample of adults with anxiety-related disorders. *J Anxiety Disord*. (2020) 75:102277. doi: 10.1016/j.janxdis.2020.102277

6. Ruscio AM, Gentes EL, Jones JD, Hallion LS, Coleman ES, Swendsen J. Rumination predicts heightened responding to stressful life events in major depressive disorder and generalized anxiety disorder. *J Abnorm Psychol*. (2015) 124:17–26. doi: 10.1037/abn0000025

7. Newman MG, Llera SJ. A novel theory of experiential avoidance in generalized anxiety disorder: a review and synthesis of research supporting a contrast avoidance model of worry. *Clin Psychol Rev*. (2011) 31:371–82. doi: 10.1016/j.cpr.2011.01.008

8. Watkins ER, Roberts H. Reflecting on rumination: consequences, causes, mechanisms and treatment of rumination. *Behav Res Ther*. (2020) 127:103573. doi: 10.1016/j.brat.2020.103573

9. Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Huibers MJ. How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. *World Psychiatry*. (2016) 15:245–58. doi: 10.1002/wps.20346

10. Cuijpers P, Miguel C, Harrer M, Plessen CY, Ciharova M, Ebert D, et al. Cognitive behavior therapy vs. control conditions, other psychotherapies, pharmacotherapies and combined treatment for depression: a comprehensive meta-analysis including 409 trials with 52, 702 patients. *World Psychiatry*. (2023) 22:105–15. doi: 10.1002/wps.21069

11. Spinhoven P, Klein N, Kennis M, Cramer AOJ, Siegle G, Cuijpers P, et al. The effects of cognitive-behavior therapy for depression on repetitive negative thinking: a meta-analysis. *Behav Res Ther*. (2018) 106:71–85. doi: 10.1016/j.brat.2018.04.002

12. Watkins ER, Mullan E, Wingrove J, Rimes K, Steiner H, Bathurst N, et al. Rumination-focused cognitive-behavioural therapy for residual depression: phase II randomised controlled trial. *Br J Psychiatry J Ment Sci*. (2011) 199:317–22. doi: 10.1192/bjp.bp.110.090282

13. Rogiers R, Baeken C, Watkins ER, Van den Abbeele D, Remue J, De Raedt R, et al. A psychoeducational CBT-based group intervention ("drop it") for repetitive negative thinking: theoretical concepts and treatment processes. *Int J Group Psychother*. (2022) 72:257–92. doi: 10.1080/00207284.2022.2066535

14. Rogiers R, Baeken C, Van den Abbeele D, Watkins ER, Remue J, Colman R, et al. Group intervention 'drop it!' Decreases repetitive negative thinking in major depressive disorder and/or generalized anxiety disorder: a randomised controlled study. *Cogn Ther Res*. (2022) 46:182–96. doi: 10.1007/s10608-021-10240-6

15. Baeken C, Guo-Rong W, Rogiers R, Remue J, Lemmens GM, Raedt RD. Cognitive behavioral based group psychotherapy focusing on repetitive negative thinking: decreased uncontrollability of rumination is related to brain perfusion increases in the left dorsolateral prefrontal cortex. *J Psychiatr Res*. (2021) 136:281–7. doi: 10.1016/j.jpsychires.2021.02.011

16. Plewnia C, Schroeder PA, Wolkenstein L. Targeting the biased brain: non-invasive brain stimulation to ameliorate cognitive control. *Lancet Psychiatry*. (2015) 2:351–6. doi: 10.1016/S2215-0366(15)00056-5

17. Kühn S, Vanderhasselt MA, De Raedt R, Gallinat J. The neural basis of unwanted thoughts during resting state. *Soc Cogn Affect Neurosci*. (2014) 9:1320–4. doi: 10.1093/scan/nst117

18. Jacobs RH, Watkins ER, Peters AT, Feldhaus CG, Barba A, Carbray J, et al. Targeting ruminative thinking in adolescents at risk for depressive relapse: rumination-focused cognitive behavior therapy in a pilot randomized controlled trial with resting state fMRI. *PLoS One*. (2016) 11:e0163952. doi: 10.1371/journal.pone.0163952

19. Clark DA, Beck AT. Cognitive theory and therapy of anxiety and depression: convergence with neurobiological findings. *Trends Cogn Sci*. (2010) 14:418–24. doi: 10.1016/j.tics.2010.06.007

20. Brunoni AR, Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Boggio PS, et al. Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. *Prog Neuro-Psychopharmacol Biol Psychiatry*. (2011) 35:96–101. doi: 10.1016/j.pnpbp.2010.09.010

21. Baeken C, Brunelin J, Duprat R, Vanderhasselt MA. The application of tDCS in psychiatric disorders: a brain imaging view. *Socioaffect Neurosci Psychol*. (2016) 6:29588. doi: 10.3402/snp.v6.29588

22. Dedoncker J, Brunoni AR, Baeken C, Vanderhasselt MA. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. *Brain Stimul*. (2016) 9:501–17. doi: 10.1016/j.brs.2016.04.006

23. Monnart A, Vanderhasselt MA, Schroder E, Campanella S, Fontaine P, Kornreich C. Treatment of resistant depression: a pilot study assessing the efficacy of a tDCS-mindfulness program compared with a tDCS-relaxation program. *Front Psych*. (2019) 10:730. doi: 10.3389/fpsyt.2019.00730

24. Baeken C, Remue J, Vanderhasselt MA, Brunoni AR, De Witte S, Duprat R, et al. Increased left prefrontal brain perfusion after MRI compatible tDCS attenuates momentary ruminative self-referential thoughts. *Brain Stimul*. (2017) 10:1088–95. doi: 10.1016/j.brs.2017.09.005

25. De Raedt R, Remue J, Loeys T, Hooley JM, Baeken C. The effect of transcranial direct current stimulation of the prefrontal cortex on implicit self-esteem is mediated by rumination after criticism. *Behav Res Ther*. (2017) 99:138–46. doi: 10.1016/j.brat.2017.10.009

26. Allaert J, Erdogan M, Sanchez-Lopez A, Baeken C, De Raedt R, Vanderhasselt MA. Prefrontal tDCS attenuates self-referential attentional deployment: a mechanism underlying adaptive emotional reactivity to social-evaluative threat. *Front Hum Neurosci*. (2021) 15:700557. doi: 10.3389/fnhum.2021.700557

27. Bikson M, Name A, Rahman A. Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms. *Front Hum Neurosci*. (2013) 7:688. doi: 10.3389/fnhum.2013.00688

28. Sathappan AV, Luber BM, Lisanby SH. The dynamic duo: combining noninvasive brain stimulation with cognitive interventions. *Prog Neuro-Psychopharmacol Biol Psychiatry*. (2019) 89:347–60. doi: 10.1016/j.pnpbp.2018.10.006

29. Dedoncker J, Baeken C, De Raedt R, Vanderhasselt MA. Combined transcranial direct current stimulation and psychological interventions: state of the art and promising

perspectives for clinical psychology. *Biol Psychol*. (2021) 158:107991. doi: 10.1016/j.biopsycho.2020.107991

30. Donse L, Padberg F, Sack AT, Rush AJ, Arns M. Simultaneous rTMS and psychotherapy in major depressive disorder: clinical outcomes and predictors from a large naturalistic study. *Brain Stimul*. (2018) 11:337–45. doi: 10.1016/j.brs.2017.11.004

31. Brunoni AR, Boggio PS, De Raedt R, Benseñor IM, Lotufo PA, Namur V, et al. Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. *J Affect Disord*. (2014) 162:43–9. doi: 10.1016/j.jad.2014.03.026

32. Lee JH, Lee TL, Kang N. Transcranial direct current stimulation decreased cognition-related reaction time in older adults: a systematic review and meta-analysis. *Ageing Res Rev*. (2021) 70:101377. doi: 10.1016/j.arr.2021.101377

33. Vanderhasselt MA, Brunoni AR, Loeys T, Boggio PS, De Raedt R. Nosce te ipsum--Socrates revisited? Controlling momentary ruminative self-referent thoughts by neuromodulation of emotional working memory. *Neuropsychologia*. (2013) 51:2581–9. doi: 10.1016/j.neuropsychologia.2013.08.011

34. Allaert J, De Raedt R, van der Veen FM, Baeken C, Vanderhasselt MA. Prefrontal tDCS attenuates counterfactual thinking in female individuals prone to self-critical rumination. *Sci Rep*. (2021) 11:11601. doi: 10.1038/s41598-021-90677-7

35. Rogiers R, Van Parys H, Baeken C, Van den Abbeele D, Remue J, De Raedt R, et al. Treatment experiences during a cognitive behaviour therapy group intervention targeting repetitive negative thinking: a qualitative study. *Psychol Psychother*. (2022) 95:447–66. doi: 10.1111/papt.12378

36. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E. The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. (1998) 59:22–33.

37. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56

38. Raes F, Hermans D, Williams JMG, Bijttebier P, Eelen P. A "triple W"-model of rumination on sadness: why am I feeling sad, What's the meaning of my sadness, and wish I could stop thinking about my sadness (but I Can't!). *Cogn Ther Res*. (2008) 32:526–41. doi: 10.1007/s10608-007-9137-y

39. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the Penn State worry questionnaire. *Behav Res Ther*. (1990) 28:487–95. doi: 10.1016/0005-7967(90)90135-6

40. Mir-Moghtadaei A, Caballero R, Fried P, Fox MD, Lee K, Giacobbe P, et al. Concordance between BeamF3 and MRI-neuronavigated target sites for repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex. *Brain Stimul*. (2015) 8:965–73. doi: 10.1016/j.brs.2015.05.008

41. Beam W, Borckardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimul*. (2009) 2:50–4. doi: 10.1016/j.brs.2008.09.006

42. Peleman K, Van Schuerbeek P, Luypaert R, Stadnik T, De Raedt R, De Mey J, et al. Using 3D-MRI to localize the dorsolateral prefrontal cortex in TMS research. *World J Biol Psychiatry*. (2010) 11:1–6. doi: 10.1080/15622970802669564

43. Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: state of the art 2008. *Brain Stimul*. (2008) 1:206–23. doi: 10.1016/j.brs.2008.06.004

44. Marchetti I, Mor N, Chiorri C, Koster EH. The brief state rumination inventory (BSRI): validation and psychometric evaluation. *Cogn Ther Res*. (2018) 42:447–60. doi: 10.1007/s10608-018-9901-1

45. Hermans PJ, Van Ree F, Betgem P, Westenbrink A. Betrouwbaarheid en validiteit van het Hamilton interview. *Gedrag*. (1981) 9:219–33.

46. Bagby RM, Ryder AG, Schuller DR, Marshall MB. The Hamilton depression rating scale: has the gold standard become a lead weight? *Am J Psychiatry*. (2004) 161:2163–77. doi: 10.1176/appi.ajp.161.12.2163

47. Conway M, Csank PAR, Holm SL, Blake CK. On assessing individual differences in rumination on sadness. *J Pers Assess*. (2000) 75:404–25. doi: 10.1207/S15327752JPA7503_04

48. Kerkhof A, Hermans D, Figee A, Laeremans I, Aardema A, Pieters G. De Penn State worry questionnaire en de Worry domains questionnaire: Eerste resultaten bij Nederlandse en Vlaamse klinische en poliklinische populaties. (the PSWQ and the WDQ: first results from Dutch and Flemish clinical and polyclinical populations). *Gedragstherapie*. (2000) 33:135–45.

49. Van Der Heiden C, Muris P, Bos AER, Van Der Molen H, Oostra M. Normative data for the Dutch version of the Penn State Worry questionnaire. *Neth J Psychol*. (2009) 65:69–75. doi: 10.1007/BF03080129

50. R Core Team. *R: A language and environment for statistical computing*. Vienna: R Foundation for Statistical Computing (2022).

51. van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw*. (2011) 45:1–67. doi: 10.18637/jss.v045.i03

52. Bates D, Maechler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw*. (2015) 67:1–48. doi: 10.18637/jss.v067.i01

53. Brunoni AR, Amadera J, Berbel B, Volz MS, Gomes Rizzerio B, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol*. (2011) 14:1133–45. doi: 10.1017/S1461145710001690

54. Martin DM, Teng JZ, Lo TY, Alonzo A, Goh T, Iacoviello BM, et al. Clinical pilot study of transcranial direct current stimulation combined with cognitive emotional training for medication resistant depression. *J Affect Disord*. (2018) 232:89–95. doi: 10.1016/j.jad.2018.02.021

55. Dubuson M, Kornreich C, Vanderhasselt MA, Baeken C, Wyckmans F, Dousset C, et al. Transcranial direct current stimulation combined with alcohol cue inhibitory control training reduces the risk of early alcohol relapse: a randomized placebo-controlled clinical trial. *Brain Stimul*. (2021) 14:1531–43. doi: 10.1016/j.brs.2021.10.386

56. Sreeraj VS, Bose A, Chhabra H, Shivakumar V, Agarwal SM, Narayanaswamy JC, et al. Working memory performance with online-tDCS in schizophrenia: a randomized, double-blinded, sham-controlled, partial cross-over proof-of-concept study. *Asian J Psychiatr*. (2020) 50:101946. doi: 10.1016/j.ajp.2020.101946

57. Smits FM, Geuze E, Schutter DJLG, van Honk J, Gladwin TE. Effects of tDCS during inhibitory control training on performance and PTSD, aggression and anxiety symptoms: a randomized-controlled trial in a military sample. *Psychol Med*. (2021) 52:3964–74. Advance online publication. doi: 10.1017/S0033291721000817

58. Ehrlich TJ, Bhat J, Horwege AM, Mathalon DH, Glover GH, Roach BJ, et al. Ruminative reflection is associated with anticorrelations between the orbitofrontal cortex and the default mode network in depression: implications for repetitive transcranial magnetic stimulation. *Brain Imaging Behav*. (2022) 16:1186–95. doi: 10.1007/s11682-021-00596-4

59. Carnevali L, Thayer JF, Brosschot JF, Ottaviani C. Heart rate variability mediates the link between rumination and depressive symptoms: a longitudinal study. *Int J Psychophysiol*. (2018) 131:131–8. doi: 10.1016/j.ijpsycho.2017.11.002

60. Woody ML, McGeary JE, Gibb BE. Brooding rumination and heart rate variability in women at high and low risk for depression: group differences and moderation by COMT genotype. *J Abnorm Psychol*. (2014) 123:61–7. doi: 10.1037/a0035450

61. Schlatter S, Guillot A, Schmidt L, Mura M, Trama R, Di Rienzo F, et al. Combining proactive transcranial stimulation and cardiac biofeedback to substantially manage harmful stress effects. *Brain Stimul*. (2021) 14:1384–92. doi: 10.1016/j.brs.2021.08.019

frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 21 June 2023
DOI 10.3389/fneur.2023.1189034

OPEN ACCESS

EDITED BY
Jean-Pascal Lefaucheur,
Univ Paris-Est Créteil, AP-HP, France

REVIEWED BY
Robert Andrew Morrison,
The University of Texas at Dallas, United States
Qian Ding,
Guangdong Provincial People's Hospital, China

*CORRESPONDENCE
Weisheng Zhuang
✉ zhuang20062634@163.com

RECEIVED 18 March 2023
ACCEPTED 16 May 2023
PUBLISHED 21 June 2023

CITATION
Wang X, Ding Q, Li T, Li W, Yin J, Li Y, Li Y and Zhuang W (2023) Application of vagus nerve stimulation on the rehabilitation of upper limb dysfunction after stroke: a systematic review and meta-analysis. *Front. Neurol.* 14:1189034. doi: 10.3389/fneur.2023.1189034

Application of vagus nerve stimulation on the rehabilitation of upper limb dysfunction after stroke: a systematic review and meta-analysis

Xu Wang[1], Qixin Ding[1], Tianshu Li[2], Wanyue Li[3], Jialin Yin[4], Yakun Li[4], Yuefang Li[2] and Weisheng Zhuang[4]*

[1]School of Rehabilitation Medicine, Henan University of Chinese Medicine, Zhengzhou, China, [2]School of Clinical Medicine, Henan University, Zhengzhou, China, [3]Department of Rehabilitation Medicine, The First Affiliated Hospital of Jinan University, Guangzhou, China, [4]Department of Rehabilitation, Henan Provincial People's Hospital, School of Rehabilitation Medicine, Henan University of Chinese Medicine, Zhengzhou, China

Objective: This study aimed to elucidate the efficacy, safety, and long-term implications of vagus nerve stimulation (VNS) as a viable therapeutic option for patients with upper limb dysfunction following a stroke.

Methods: Data from the following libraries were searched from inception to December 2022: PubMed, Wanfang, Scopus, China Science and Technology Journal Database, Embase, Web of Science, China Biology Medicine Disc, Cochrane Library, and China National Knowledge Infrastructure. Outcomes included indicators of upper limb motor function, indicators of prognosis, and indicators of safety (incidence of adverse events [AEs] and serious AEs [SAEs]). Two of the authors extracted the data independently. A third researcher arbitrated when disputes occurred. The quality of each eligible study was evaluated using the Cochrane Risk of Bias tool. Meta-analysis and bias analysis were performed using Stata (version 16.0) and RevMan (version 5.3).

Results: Ten trials (VNS combined with rehabilitation group vs. no or sham VNS combined with rehabilitation group) with 335 patients were included in the meta-analysis. Regarding upper extremity motor function, based on Fugl–Meyer assessment scores, VNS combined with other treatment options had immediate (mean difference [MD] = 2.82, 95% confidence interval [CI] = 1.78–3.91, I^2 = 62%, $p < 0.00001$) and long-term (day-30 MD = 4.20, 95% CI = 2.90–5.50, $p < 0.00001$; day-90 MD = 3.27, 95% CI = 1.67–4.87, $p < 0.00001$) beneficial effects compared with that of the control treatment. Subgroup analyses showed that transcutaneous VNS (MD = 2.87, 95% CI = 1.78–3.91, I^2 = 62%, $p < 0.00001$) may be superior to invasive VNS (MD = 3.56, 95% CI = 1.99–5.13, I^2 = 77%, $p < 0.0001$) and that VNS combined with integrated treatment (MD = 2.87, 95% CI = 1.78–3.91, I^2 = 62%, $p < 0.00001$) is superior to VNS combined with upper extremity training alone (MD = 2.24, 95% CI = 0.55–3.93, I^2 = 48%, $p = 0.009$). Moreover, lower frequency VNS (20 Hz) (MD = 3.39, 95% CI = 2.06–4.73, I^2 = 65%, $p < 0.00001$) may be superior to higher frequency VNS (25 Hz or 30 Hz) (MD = 2.29, 95% CI = 0.27–4.32, I^2 = 58%, $p = 0,03$). Regarding prognosis, the VNS group outperformed the control group in the activities of daily living (standardized MD = 1.50, 95% CI = 1.10–1.90, I^2 = 0%, $p < 0.00001$) and depression reduction. In contrast, quality of life did not improve ($p = 0.51$). Safety was not significantly different between the experimental and control groups (AE $p = 0.25$; SAE $p = 0.26$).

Conclusion: VNS is an effective and safe treatment for upper extremity motor dysfunction after a stroke. For the functional restoration of the upper extremities, noninvasive integrated therapy and lower-frequency VNS may be more effective. In the future, further high-quality studies with larger study populations, more comprehensive indicators, and thorough data are required to advance the clinical application of VNS.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier: CRD42023399820.

KEYWORDS

vagus nerve stimulation (vns), stroke, rehabilitation, meta-analysis, upper limb dysfunction

1. Introduction

Stroke is a severe health risk that represents a great burden to society and healthcare systems. Approximately 60% of the individuals who experience a stroke have long-lasting upper extremity dysfunction that hinders their activities of daily living and compromises their mental wellbeing (1–4). It has been predicted that, by 2050, there will be ∼200 million stroke victims worldwide. Hence, it is paramount that more effective treatment strategies are developed (5). Alternative approaches are required because standard rehabilitation therapy may not successfully restore function after a stroke (6). Ideally, future therapies for stroke should combine thrombolysis with antithrombotic, neuroprotective, and neuroplasticity-enhancing interventions (7). One possible treatment for enhancing neuroplasticity of the upper limb following a stroke is vagus nerve stimulation (VNS). VNS is an adjunctive therapy approved by the Food and Drug Administration for the treatment of partial epilepsy, depression, and primary headache disorders (8). VNS refers to any method that stimulates the vagus nerve. The methods are divided into invasive VNS (iVNS) and transcutaneous VNS (tVNS). Furthermore, tVNS can be further divided into transcutaneous cervical VNS (tcVNS) and transcutaneous auricular VNS (taVNS) (9, 10). The number of publications related to VNS has tripled in the last 10 years. In particular, the number of published studies has exponentially increased over the last few years (11). Numerous preclinical studies have documented positive poststroke recovery following a combination of VNS and physical therapy. Numerous clinical studies have also produced encouraging findings (12).

Animal studies involving rats with cerebral ischemia have suggested that VNS combined with rehabilitation can significantly alleviate neurological impairment, reduce cerebral infarction volume, and improve forelimb function, as well as memory and cognition (13–17). The mechanism of action may include enhancing angiogenesis, controlling blood-brain barrier permeability, minimizing the spread of depolarization, preventing neuroinflammation, and facilitating poststroke axonal plasticity (18–22). An increasing number of clinical trials have also demonstrated the beneficial effects of VNS combined with rehabilitation for patients with stroke. However, most clinical trials have been limited by small sample sizes (23, 24). Several meta-analyses have concluded based on the available clinical trials that VNS may improve the recovery of upper limb function following a stroke (25–32). Additionally, some researchers have reported that tVNS may be more effective than iVNS (26, 28, 29, 31, 32). These published meta-analyses had a risk of publication bias due to the absence of funnel plots. Many of these meta-analyses have also highlighted the need for more welldesigned studies to verify the long-term efficacy of VNS, including the stimulation settings, prognostic scores, integrated rehabilitation training methods, adverse events (AEs), and other factors. The analyses conducted by Liu et al. (28) and Zhao et al. (32) also restricted the studies to specific languages. In light of the potential clinical significance of VNS and the currently weak evidence from quantitative analyses, this study aimed to conduct a comprehensive and up-to-date meta-analysis on VNS for upper limb dysfunction after a stroke, including the efficacy, safety, and long-term implications.

2. Data and methods

This study was a systematic review of previously published studies. Therefore, both patient consent and ethical approval were not required (33). The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and previously published protocols (34). The detailed protocol used to perform this systematic evaluation has been registered in PROSPERO (reference number: CRD42023399820).

2.1. Search strategy

The following databases were searched from the time of inception to December 2022: PubMed, Scopus, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Wanfang, China Science and Technology Journal Database, and China Biology Medicine. The following search terms were used: (Stroke OR Cerebrovascular Accident OR CVA OR Cerebrovascular Apoplexy OR Vascular Accident OR Cerebral Stroke) AND (VNS OR Vagal Nerve Stimulation OR Vagal Nerve Stimulation). To identify further relevant articles, we traced

the references included in the identified articles and conducted manual searches.

2.2. Inclusion and exclusion criteria

We searched for studies without language restrictions. The inclusion criteria were as follows: (1) Studies with patients with stroke and upper limb disorders; (2) the experimental group received VNS combined with other treatment approaches, and the control group received no VNS or sham stimulation combined with other treatment approaches. The other treatment approaches were the same in the experimental and control groups; (3) studies that were randomized controlled trials (RCT); and (4) the study included at least one of the following pretraining or follow-up outcome indicators: motor function, quality of life, activities of daily living (ADL), and/or AEs. The exclusion criteria were as follows: (1) Patients who experienced a non-primary stroke; (2) relevant data required for meta-analysis were not available; (3) the full text of the paper could not be obtained even after contacting the corresponding author.

2.3. Data extraction

The following data were gathered: author, location, publication year, disease course, disease type, the number of samples, intervention modes, the type of combined therapy, stimulus parameters, stimulus time, evaluation time, and outcomes. Two researchers independently screened the papers and extracted and crosschecked the data. Any dispute was resolved through discussion or negotiation with an independent researcher. We used the Java program GetData Graph Digitizer (http://www.getdata-graph-digitizer.com) to determine the numerical values from the plotted data if no values were originally provided. If there were no pre- and post-treatment differences in the included randomized controlled trials or post-treatment data, the corresponding author was contacted to obtain the missing details. Where necessary, we manually calculated the mean and standard deviation (SD) using the Cochrane Handbook formulas based on the available baseline and outcome data.

2.4. Outcome measures

The outcome measures in this study were the efficacy and safety of VNS for the treatment of upper limb dysfunction after a stroke. Efficacy referred to the improvement of upper limb motor function and its impact on patient prognosis, while safety included the number of AEs and serious AEs (SAEs). The main indicator of upper limb motor function was the Fugl–Meyer Assessment for Upper Extremity (FMA-UE) score after VNS treatment at different frequencies combined with different treatment methods. The secondary indicators were the Wolf Motor Function Test (WMFT) score and FMA-UE effective rate. The prognosis was defined as improvement in ADL, quality of life, and mental wellbeing (e.g., mood).

2.5. Quality assessment

The quality of all the articles was assessed independently by the two researchers who reviewed the findings. When a disagreement occurred, a third researcher was consulted for arbitration. The quality of the included RCTs was assessed using the Cochrane risk-of-bias tool (35). This involved evaluating seven different types of biases: attrition bias (incomplete outcome data), selection bias (unbiased sequence generation and allocation concealment), reporting bias (selective result reporting), blinding bias (unbiased performance and detection), and other bias. The risk of bias for each item was rated as low, unclear, or high.

2.6. Statistical analysis

The evaluation index data of the included studies were processed using RevMan software (version 5.3; Cochrane Collaboration, Software Update, Oxford, UK). The mean difference (MD) and 95% confidence interval (CI) were used to express continuous variables. For continuous variables with different units, the standardized MD (SMD) and 95% CI were applied to exclude the influence of units (36). Dichotomous variables were expressed as risk ratios using the Mantel–Haenszel method. The degree of study heterogeneity was represented using I^2. A random-effects model was applied if I^2 exceeded 50%. Otherwise, a fixed-effects model was used. Values >75% indicated high heterogeneity. Sensitivity and subgroup analyses were utilized to pinpoint the source of heterogeneity and also to examine the stability of the results, as well as compare the effects of different clinical factors. Descriptive analysis was performed if the cause of the heterogeneity was not identified. Stata software (version 16.0, http://www.stata.com) was used to construct a funnel plot to determine publication bias. Finally, we used GRADE profiler software (https://gradeprofifiler.software.informer.com/) to evaluate the quality of the evidence based on the analyzed outcome indicators of the present study.

3. Results

3.1. Search results, study characteristics, and quality assessment

The flowchart of the search and article selection process is shown in Figure 1. Initially, 1,335 articles were identified as potentially relevant. Ten articles (three written in Chinese and seven in English) (23, 24, 37–44), involving 335 participants, were finally included in this study. The basic details of the 10 included articles are shown in Table 1. All 10 articles were RCTs with an experimental group and a control group. The experimental groups underwent VNS with different stimulus parameters combined with other treatment approaches. Eight of the 10 studies utilized a placebo in the control group, while the other two were blank controls (no VNS) (Table 1). The combined treatment methods employed with VNS included upper limb therapy alone in six studies and comprehensive therapy in three studies. The

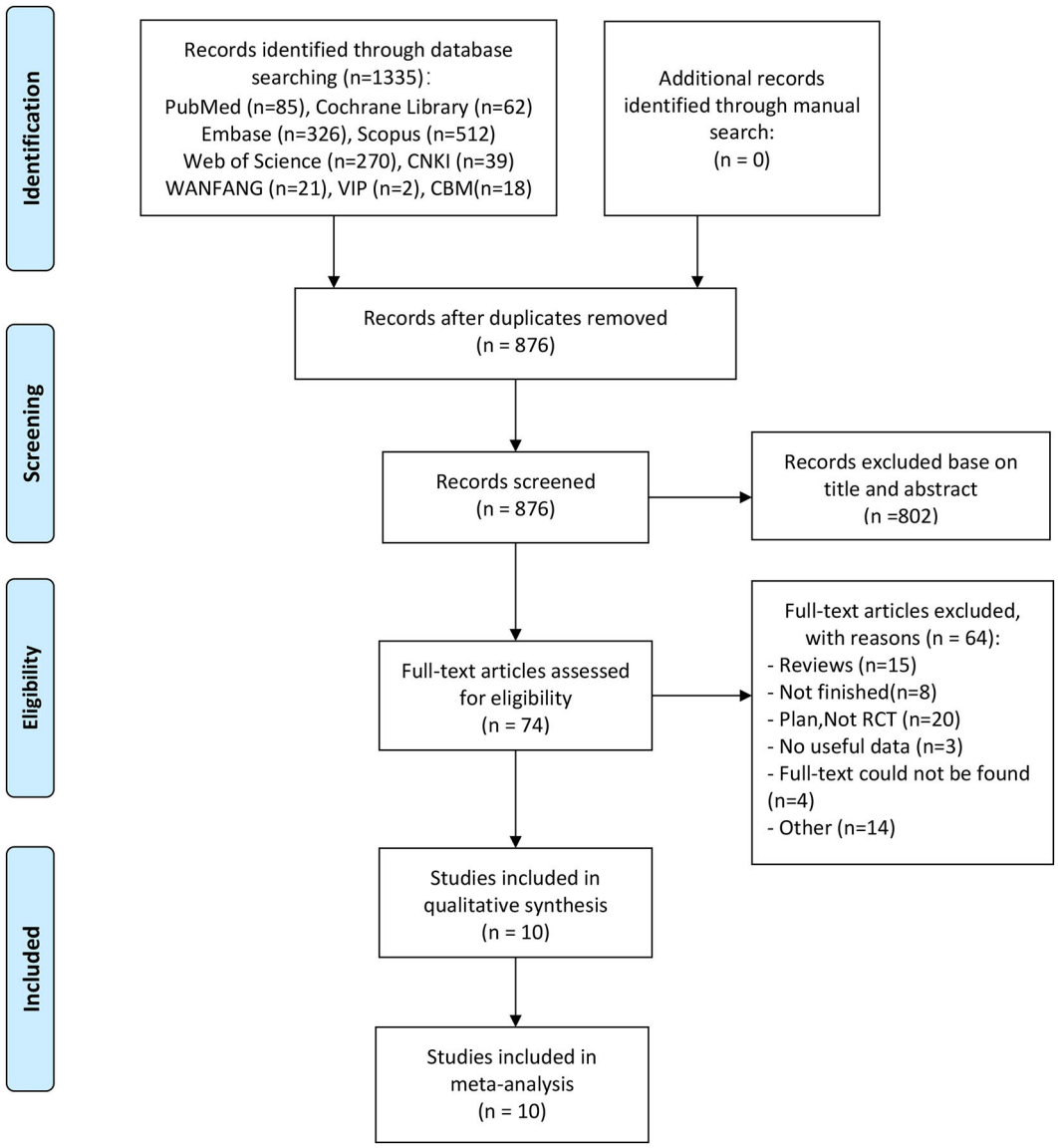


FIGURE 1
The flowchart of the literature search and screening process.

interventions lasted for 2–4 weeks, and evaluations were performed 1–90 days after the treatment. Wu et al. (41) and Dawson et al. (23) did not blind the outcome assessments (detection bias), but the remaining eight studies were blinded (Figure 2).

3.2. The efficacy of VNS used in stroke treatment

3.2.1. The primary indicator of upper limb motor function measured by the FMA-UE score

Nine articles reported the FMA-UE scores a day after treatment (immediate effect). The available results indicated that the VNS group significantly improved upper limb motor function compared with the control group (MD = 2.84, 95% CI = 1.78–3.91, I^2 = 62%, $p < 0.00001$; Figure 3) (23, 24, 37, 39–44). Three articles reported FMA-UE scores at 30- and 90-day posttreatment (long-term effects) (24, 41, 43). The pooled findings indicated that the scores in the VNS group were significantly higher than those in the control group at 30- (MD = 4.20, 95% CI = 2.90–5.50) and 90-day posttreatment (MD = 3.27, 95% CI = 1.67–4.87) (Figure 3). Based on these results, VNS demonstrated immediate and long-term effects on upper limb motor function.

A subgroup analysis was conducted to compare various aspects that may influence efficacy, such as disease stage, combination protocol, stimulation modality, and other stimulation parameters.

TABLE 1 Basic information of the included studies.

Author year	Location	Disease	Type	N (E/C)	Mode (E/C)	Combined therapy	Stimulus parameters and time	Evaluation time (day)	Effective index	Safe index
Dawson et al. (26)	England 2 centers	IC	>6 months	9/11	iVNS	Upper limb training	30 Hz, 0.1 ms, 0.8 mA, 0.5 s/10 s 120 min per day, 3 times per week, 6 w	1, 30, 90	FMA-UE, ARAT, grip strength, NHPT, Box and Block test	AE, SAE
Capone et al. (24)	Italy	IC/ICH	>1 year	7/5	taVNS/ sham	Upper limb robot training	20 Hz, 0.3 ms, patients' tolerance (1.1 ± 9.0 mA), 30 s/5 min, 60 min per day, 10 days	1	FMA-UE	sBP, dBP, HR
Kimberley et al. (39)	America	IC	4 months to 3 years	8/9	iVNS/ sham	Upper limb training	30 Hz, 0.1 ms, 0.8 mA, 0.5 s/10 s, 120 min per day, 3 times per week, 6 w	1, 30, 90	FMA-UE, WMFT, Nine-hole test, MAL, SIS	AE, SAE
Zhenguo (38)	China	NA	>2 months	40/40	VNS	Comprehensive therapy	3 months, NA	1	FMA, MBI, NIHSS	
Wu et al. (40)	China	IC	subacute	10/11	taVNS/ sham	Comprehensive rehabilitation training	20 Hz, 0.3 ms, patients' tolerance (1.66 ± 0.40 mA), 30 s/2 min 30 min per day, 10 consecutive days	1, 30, 90	FMA-UE, WMFT, FIM, Brunstrom	HR, sBP, dBP, AE
Wei et al. (30)	China	IC	2 weeks to 3 months	13/13	taVNS/sham	Upper limb training	25 Hz, 0.1 ms, patients' tolerance, 60 min per day, 5 times per week, 4 w	1, 30	FMA-UE, Brunstrom, MFAS, MAS, BI	HR, AE
Liping (37)	China	IC	>24 hours <3 months	21/21	taVNS/ sham	Medical treatment and comprehensive rehabilitation training	20 Hz, 0.5 mA, 30 s/2 min 30 min per time, 5 times per week, 3 w	1	FMA-UE, WMFT, FIM	AE
Chang et al. (44)	America	NA	>6 months	14/15	taVNS/ sham	Upper limb robot training	30 Hz, 0.3 ms, patients' tolerance (0.1–0.5 mA), 0.5 s/10 s, 60 min per time, 3 times per week, 3 w	1	FMA-UE, MRC, WMFT	AE
Dawson et al. (43)	America, 19 centers	IC	>9 months	53/55	iVNS/ sham	Upper limb training	30 Hz, 0.1 ms, 0.8 mA, 0.5 s/10 s, 120 min per day, 3 times per week, 6 w	1, 90	FMA-UE, WMFT, MAL, SIS, SS-QOL, EQ-D, BDI	AE, SAE
Li et al. (6)	China	IC/ICH	<1 month	28/28	taVNS/ sham	Comprehensive rehabilitation	20 hz, 0.3 ms, patients' tolerance (1.71 ± 0.5 mA), 30 s/5 min, 20 min per time, 5 times per week, 4 w	1	WMFT, FMA-UE, FMA-L, FMA-S, HADS, SIS	HR, sBP, dBP, AE

E, experiment group; C, control group; NA, no answer; IC, ischemic cerebral infraction; ICH, hemorrhage cerebral infraction; tVNS, transcutaneous vagus nerve stimulation; taVNS, transcutaneous auricular vagus nerve stimulation; tcVNS, transcutaneous cervical VNS; iVNS, invasive vagus nerve stimulation; FMA-UE, Fugl-Meyer Assessment for Upper Extremity; FMA-L, Fugl-Meyer Assessment for lower limb function; FMA-S, Fugl-Meyer Assessment for sensory; SIS, Stroke Impact Scale; ARAT, Action Research Arm Test; WMFT, Wolf Motor Function Test; MAL, Motor Activity Log; FIM, Functional Independence Measurement; EQ-D, EuroQol Five Dimensions Questionnaire; BDI, Beck Depression Inventory; HADS, Hospital Anxiety, and Depression Scale; SS-QOL, Stroke-Specific Quality of Life; BDI, Beck Depression Inventory; AE, adverse events; SAE, serious AEs; HR, heart rate; sBP, systolic blood pressure; dBP, diastolic blood pressure.

10.3389/fneur.2023.1189034

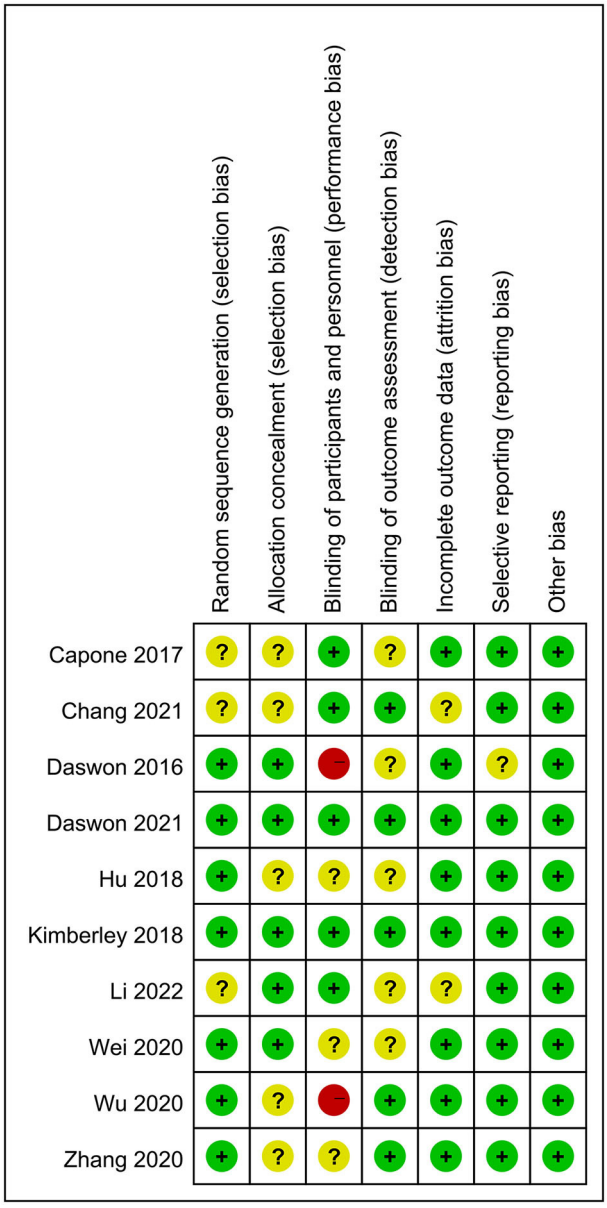


FIGURE 2
Risk of bias summary of RCTs. RCT, Randomized controlled experiment.

The results revealed that tVNS (MD = 2.87, 95% CI = 1.78–3.91, I^2 = 62%, p < 0.00001) may be superior to iVNS (MD = 3.56, 95% CI = 1.99–5.13, I^2 = 77%, p < 0.0001, Figure 4A). Moreover, VNS in conjunction with combination therapy (MD = 2.87, 95% CI = 1.78–3.91, I^2 = 62%, p < 0.00001) outperforms VNS in conjunction with upper extremity training alone (MD = 2.24, 95% CI = 0.55–3.93, I^2 = 48%, p = 0.009, Figure 4B). Furthermore, lower frequency VNS (<25 Hz) (MD = 3.39, 95% CI = 2.06–4.73, I^2 = 65%, p < 0.00001) may be superior to higher frequency VNS (≥25 Hz) (MD = 2.29, 95% CI = 0.27–4.32, I^2 = 58%, p = 0.03) (Figure 4C).

3.2.2. Secondary indicators of upper extremity motor function measured by the FMA-UE efficiency and WMFT score

FMA-UE efficiency was defined as an increase in the FMA-UE score by >6. Three articles (23, 24, 39) reported the FMA-UE scores at 1 day posttreatment (immediate effect), and two articles (39, 43) reported the FMA-UE scores at 90 days posttreatment (long-term effect) (Figure 5). Pooled analyses indicated that both the immediate (MD = 4.06, 95% CI = 1.18–13.89) and long-term (MD = 3.37, 95% CI = 1.56–7.28) effects had little heterogeneity. The fixed-effects model was employed, and the results indicated that FMA-UE efficiency was higher in the experimental group than that in the control group.

Three articles (39, 41, 43) reported the immediate effect as indicated by the WMFT score. The pooled analysis indicated that the WMFT score was higher in the experimental group than that in the control group (MD = 0.37, 95% CI = 0.06–0.81, I^2 = 89%) (Figure 6A). A subgroup analysis was conducted due to high heterogeneity. The results showed that lower frequency VNS (<25 Hz) (MD = 3.59, 95% CI = 1.97–5.51) was more effective than higher frequency VNS (≥25 Hz) (MD = 0.17, 95% CI = 0.07–0.27) (Figure 6B). Three articles (39, 43, 44) reported the long-term effect as indicated by the WMFT score in the absence of heterogeneity (i.e., I^2 = 0) and found that the VNS group had significantly higher scores than the control group at 90-day posttreatment (MD = 0.30, 95% CI = 0.19–0.47) (Figure 6A).

3.3.3. Prognosis

To determine the prognosis, we examined the ADL, quality of life, and depression status scores. Four studies (37, 38, 40, 41) included indicators that assessed ADL, including BI, MBI, and FIM. After aggregation, it was found that I^2 was 88% (Figure 7A), indicating excessive heterogeneity. The sensitivity analysis indicated that after excluding the study of Zhang et al. (37), the heterogeneity decreased to 0%. Thus, this indicator was excluded from the analysis. Subsequently, the reanalyzed results indicated that the ADL score was significantly higher after VNS (SMD = 1.50, 95% CI = 1.10–1.90, I^2 = 0%, p < 0.00001) (Figure 7B). Two articles (42, 43) included life quality assessment scales, including the Stroke-Specific Quality of Life Scale and EuroQol five-dimensional questionnaire. No significant difference was found between the experimental and control groups after the summary analysis (SMD = 0.10; 95% CI = −0.2 to 0.41, I^2 = 0%; p = 0.51) (Figure 7C). Two articles included a scale for assessing depression status, namely, the Beck Depression Inventory (BDI) and the depression domain of the Hospital Anxiety and Depression Scale (HADS). Li et al. (42) found that the HADS score decreased in the experimental group after VNS, while Dawson et al. (43) found a decrease in the BDI score 1 day (−1.6 [SD = 6.2] vs. 0.8 [SD = 5.0]) and 90 days posttreatment (−1.8 [SD = 5.6] vs. 0.2 [SD = 4.1]) compared with that of the control group.

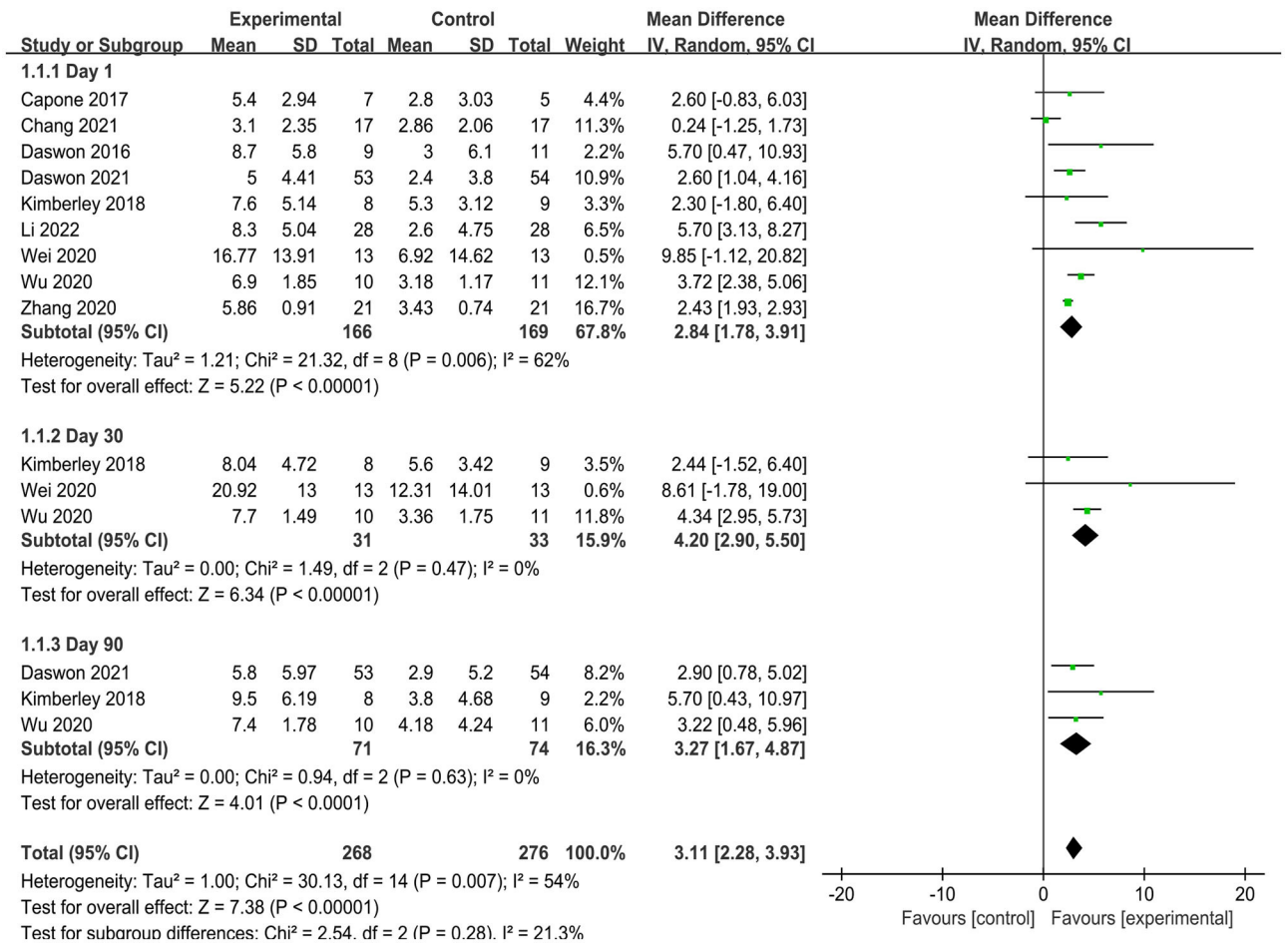


FIGURE 3
Frost plot of the immediate and long-term effects of FMA-UE.

3.3. Safety of VNS used in stroke treatment

The AE incidence was reported in seven papers (23, 24, 40–44), and the SAE incidence was reported in three papers (23, 39, 43). As shown in the pooled analysis in Figure 8, there was no significant difference between the experimental and control groups in the incidence of AEs ($p = 0.25$, Figure 8A) or SAEs ($p = 0.26$) (Figure 8B). These results indicate that VNS combined with rehabilitation therapy is safe for the treatment of upper limb dysfunction after stroke.

3.4. Publication bias and sensitivity analysis

Quantitative evaluation of the FMA-UE scores using Egger's test indicated no bias ($p = 0.266$). The publication bias chart is shown in Figure 9. Sensitivity analysis was performed by excluding publications one by one. The heterogeneity decreased significantly after removing the study by Chang et al. (44). The bias was presumably related to the intervention duration, which differed from those of other studies. However, Chang et al.'s study did not affect the pooled results or the subgroup analysis results, which were stable.

3.5. GRADE quality evaluation

The key outcome indicators (FMA-UE score, ADL score, and the number of AEs and SAEs) of the 10 included studies were evaluated using the GRADE software. The GRADE system evaluates five factors: risk of bias, inconsistency, imprecision, indirectness, and publication bias, and divides the quality of the evidence into four categories: high, medium, low, and very poor. The results according to the GRADE system indicated that the evidence was of high quality for the FMA-UE score, medium quality for the number of AEs and ADL, and low quality for the number of SAEs.

4. Discussion

This study included 10 RCTs, which is a larger sample size than the previous meta-analyses that examined the use of VNS in stroke

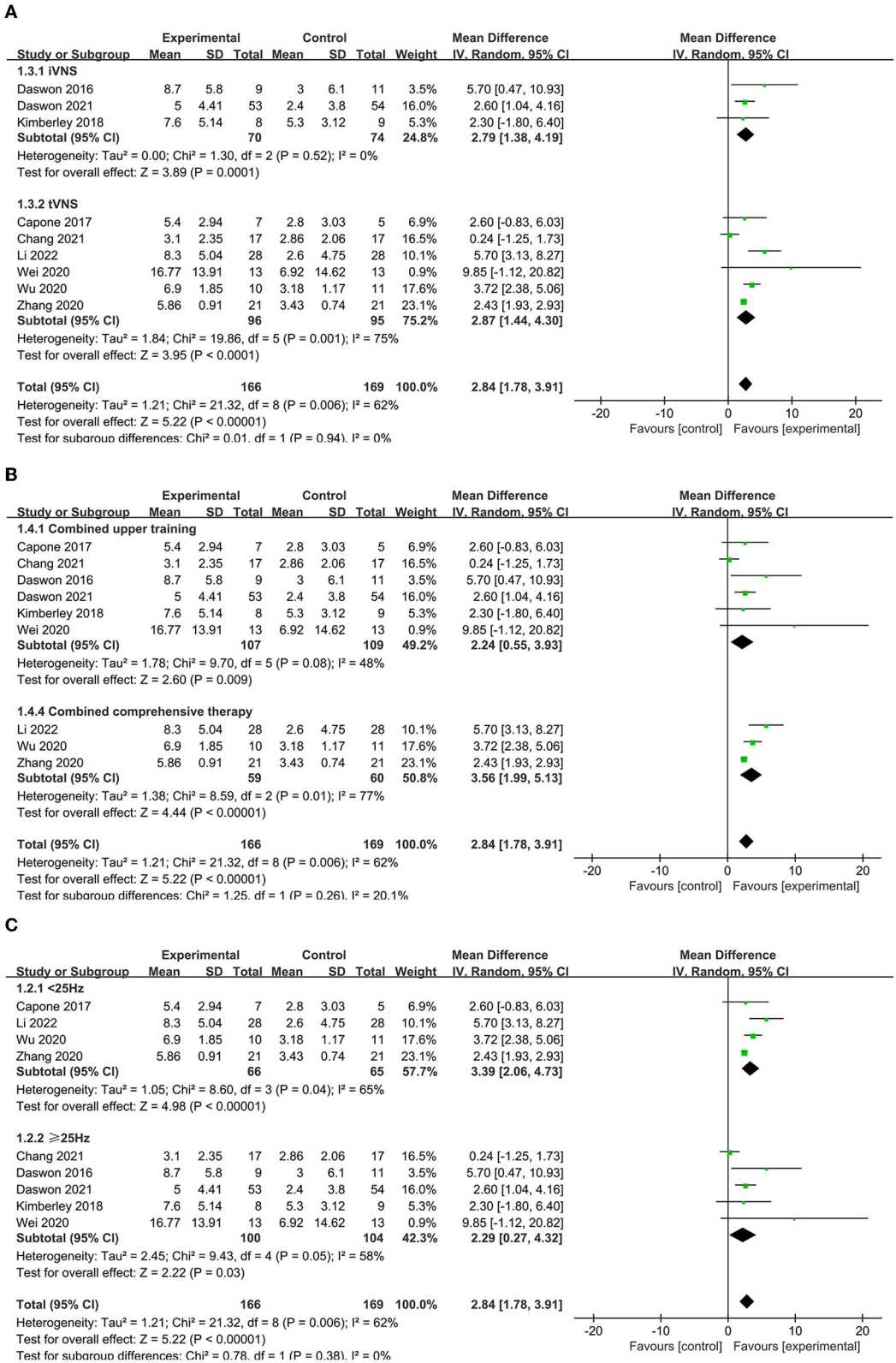


FIGURE 4
(A) Subgroup analysis of different modes of VNS in FMA-UE scores. **(B)** Subgroup analysis of VNS combined with different treatments. tVNS, transcutaneous vagus nerve stimulation; iVNS, invasive vagus nerve stimulation. **(C)** Subgroup analysis of VNS with different frequencies in FMA-UE scores.

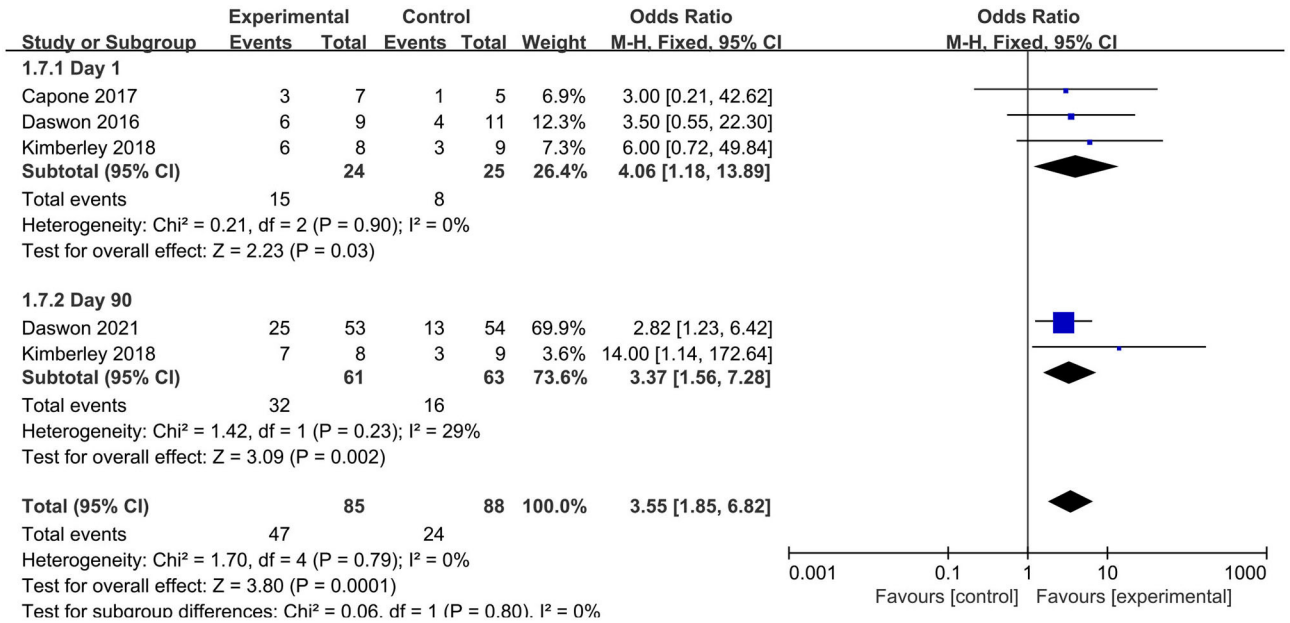


FIGURE 5
Forest plot of FMA-UE efficiency.

treatment. Publication bias, stimulation parameters, combination regimens, long-term efficacy, and prognosis were integrated and discussed in this study. The results and differences were as follows: (1) Regarding motor function, VNS exerted immediate and long-term effects when combined with comprehensive treatment as indicated by the FMA-UE score, WMFT score, and FMA-UE efficiency, which was consistent with the findings of other meta-analyses. However, the results showed that the FMA-UE pre- and post-treatment difference after 90 days of treatment was lower than that after 1 day of treatment, whereas the WMFT score was the opposite. Therefore, we could only confirm that VNS combined with rehabilitation therapy had a long-term effect and were unable to pinpoint the specific long-term changes. To further investigate this aspect, further clinical studies are warranted. The results of the subgroup analyses suggest that the tVNS mode combined combination therapy and lower frequency of VNS resulted in better outcomes. (2) Prognosis in terms of quality of life was not significant in this study. This result is consistent with the findings of previous studies. In contrast, the increased ability to perform ADL and the remission of depression contradicted the results of Gao et al. (26). For depression, the same two articles were included. The present study used a qualitative analysis considering its excessive heterogeneity. Hence, the effect of VNS on depression needs to be further demonstrated by including future studies. Regarding ADL, Gao et al. (26) included two articles that used the Stroke Impact Scale (hand function) only. In this study, we included more articles and assessed additional indicators, resulting in less heterogeneity. Our results indicated that VNS improved ADL. (3) The present study quantified the occurrence of AEs and SAEs separately to evaluate safety. This has not been considered in previous studies. Based on our results, VNS used in stroke treatment is safe.

Although supported by numerous preclinical and clinical trials, treatment with VNS-targeted plasticity remains challenging due to various factors (6). In the present study, a subgroup analysis of multiple factors was performed. First, we resulted that tVNS was superior to iVNS, which is consistent with the findings of earlier meta-analyses. In this study, all tVNS were taVNS, as tcVNS clinical trials were sparse. Hence, in the future, further investigation of tcVNS is necessary. The results stayed the same after removing the 2016 article by Dawson et al. (23) to eliminate the placebo effect. Second, we conducted a subgroup analysis of the combined VNS protocols, an important factor overlooked in previous meta-analyses, and found that VNS combined with comprehensive training had a better effect on upper limb function than upper limb training alone. We hypothesized that there is a mutually beneficial relationship between different neuroprotective and neuroplastic treatment modalities, suggesting that VNS is a suitable adjunctive therapy for stroke treatment. Furthermore, VNS combined with comprehensive training is recommended in clinical practice. Finally, the ideal parameters for optimizing VNS have long been a highly controversial issue. Optimizing these parameters is crucial for efficacy comparisons (12). One of the major limitations of VNS is its large parameter variations. Variable pulse widths, frequencies, and stimulation currents make it difficult to determine what parameters are more important and which are the best matches or combinations (45). Currently, of the many different parameters, the current intensity is the most studied. Several studies have shown that intensity and plasticity have an inverted U-shape relationship, with medium intensity being superior, and that intensity is inversely proportional to pulse width, with low intensity compensated by wide pulses (46–49). Compared with intensity, frequency is less affected by individualization; therefore, it is easier

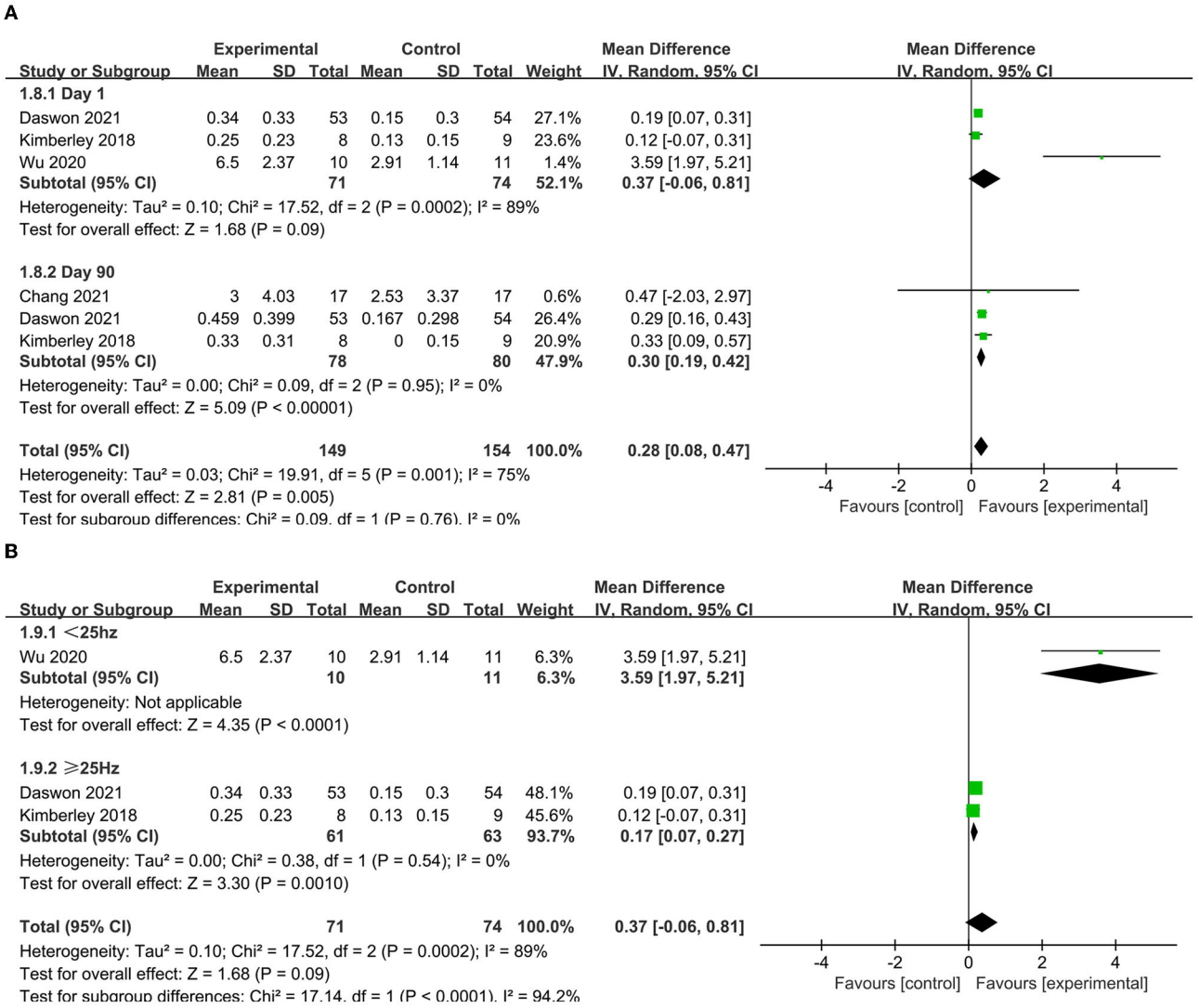


FIGURE 6
(A) Forest plot of WMFT. **(B)** Subgroup analysis of VNS with different frequencies in WMFT scores.

to optimize, although little research has been conducted to date (10). Buell et al. (50) in their biological experiments verified that frequency and plasticity have an inverted U-shape relationship and that frequencies of ∼30 Hz are more effective. Currently, VNS at 20–30 Hz is commonly used in clinical practice. Results from our subgroup analyses demonstrated that VNS at lower frequencies (<25 Hz) may be more effective than higher frequencies (≥25 Hz), which complements the findings of Buell et al. (50). Additionally, in a study that utilized taVNS for migraines (51), 1 Hz was shown to be more effective than 25 Hz (51). Taken together, these findings imply that lower frequencies may produce superior clinical outcomes. However, owing to diverse clinical applications and the limited number of frequency studies, we cannot exclude the influence of other parameters or factors on frequency. Interestingly, a study (52) has suggested that lower frequencies in tcVNS can be compensated by higher intensities. However, this is inconsistent with our subgroup analysis results on iVNS and taVNS. In the future, more vigilant investigations, including basic experiments and clinical trials, are warranted to verify and validate current findings. In summary, each of these parameters may contribute to the therapeutic effect, and one or more parameters may be altered according to the optimization of the clinical effects in individual patients.

Of note, previous studies on VNS have consistently suggested that the results obtained are influenced by individual differences that inhibit the optimization of stimulation parameters. Theoretically, advanced age is associated with reduced neuroplasticity. Moreover, stroke is dichotomized according to sex and different underlying diseases or drugs may change the effects of VNS through neuroregulatory pathway activation (4). However, preclinical trials have demonstrated that age does not limit the use of VNS in stroke treatment (16); Dawson et al. (53) have conducted further detailed subgroup analyses of their patients after their clinical trials in 2021 and found

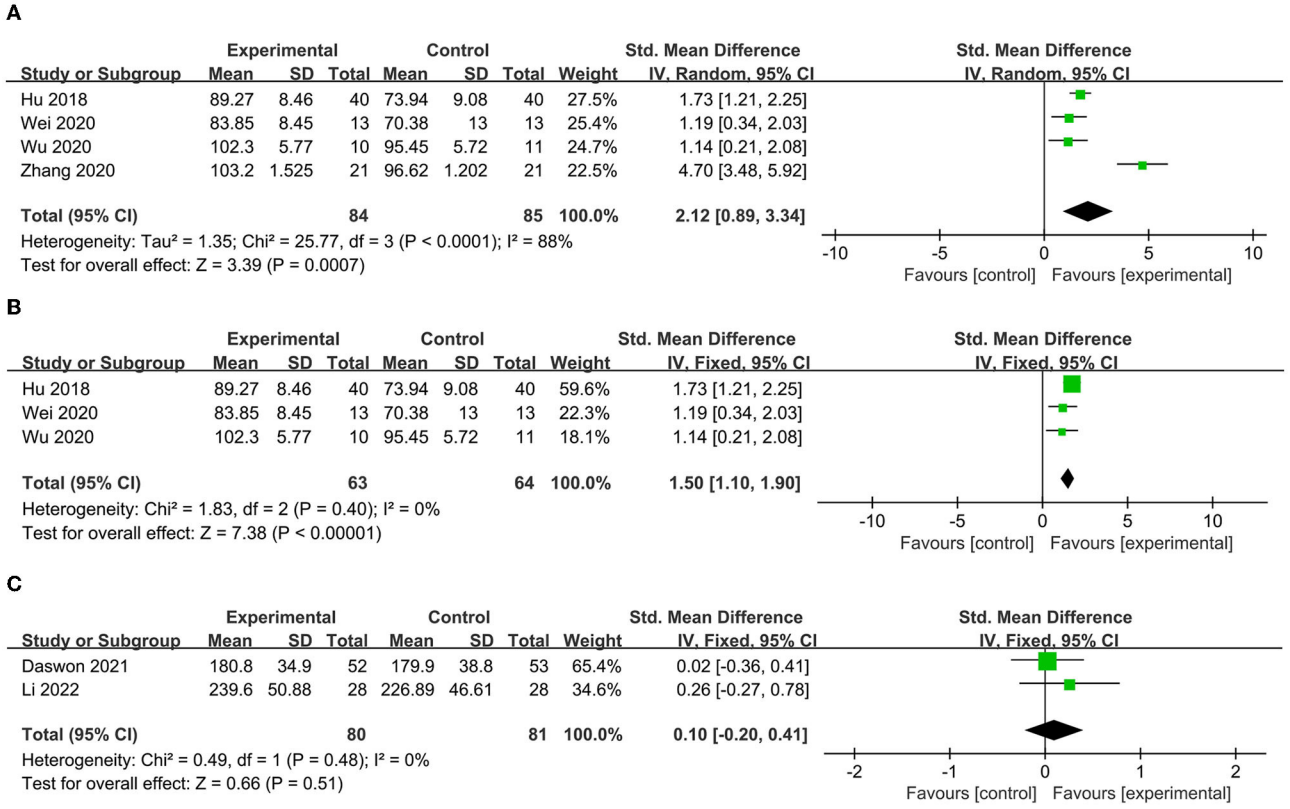


FIGURE 7
(A) Forest map of ADL score before elimination. **(B)** Forest map of ADL score after elimination. **(C)** Forest map of life quality.

that differences among different subgroups, including age, sex, residence location, stroke severity, stroke duration, side of the palsy, and cortical involvement, did not affect patient outcomes. An exploratory study by David et al. (54) examined various predictors in combination with two clinical trials and led to the hypothesis that VNS provides additional benefits for patients with more severe upper extremity disability at baseline and unfavorable imaging outcomes (e.g., higher cerebrospinal fluid volume), with no other findings inconsistent with previous speculations. These studies were restricted to specific baseline ranges, and the between-group differences and sample sizes were small. As such, further investigations, especially clinical studies, are needed to justify the above hypothesis and optimize stimulation parameters. Other studies have suggested that relationships exist between stimulation parameters and side effects that may also influence stimulation parameter optimization. These relationships require further clarification. Hence, further studies are needed (55).

This study had some limitations. First, VNS and stroke are both intrinsically heterogeneous situations. Therefore, the variables considered in the subgroup analyses were not entirely homogeneous, which could have interfered with the results. Second, only a few prognostic studies have been published, leading to insufficient evidence for drawing definitive conclusions. Future studies should include a greater number of welldesigned RCTs with high-quality samples. Third, because we did not analyze any objective indicators, future studies should consider the evaluation of neuroimaging and neurophysiological technologies.

5. Conclusion

VNS for poststroke upper extremity dysfunction is effective and safe in the long term. It improves upper extremity motor function, increases daily activity capacity, and improves mental state. The results of the subgroup analyses showed that tVNS, combined with integrated rehabilitation and a lower frequency of VNS are superior for the management of poststroke upper extremity function. This study had some limitations that need a comprehensive index and uniform stimulation parameters to further explore the use of VNS in patients with upper limb dysfunction following a stroke.

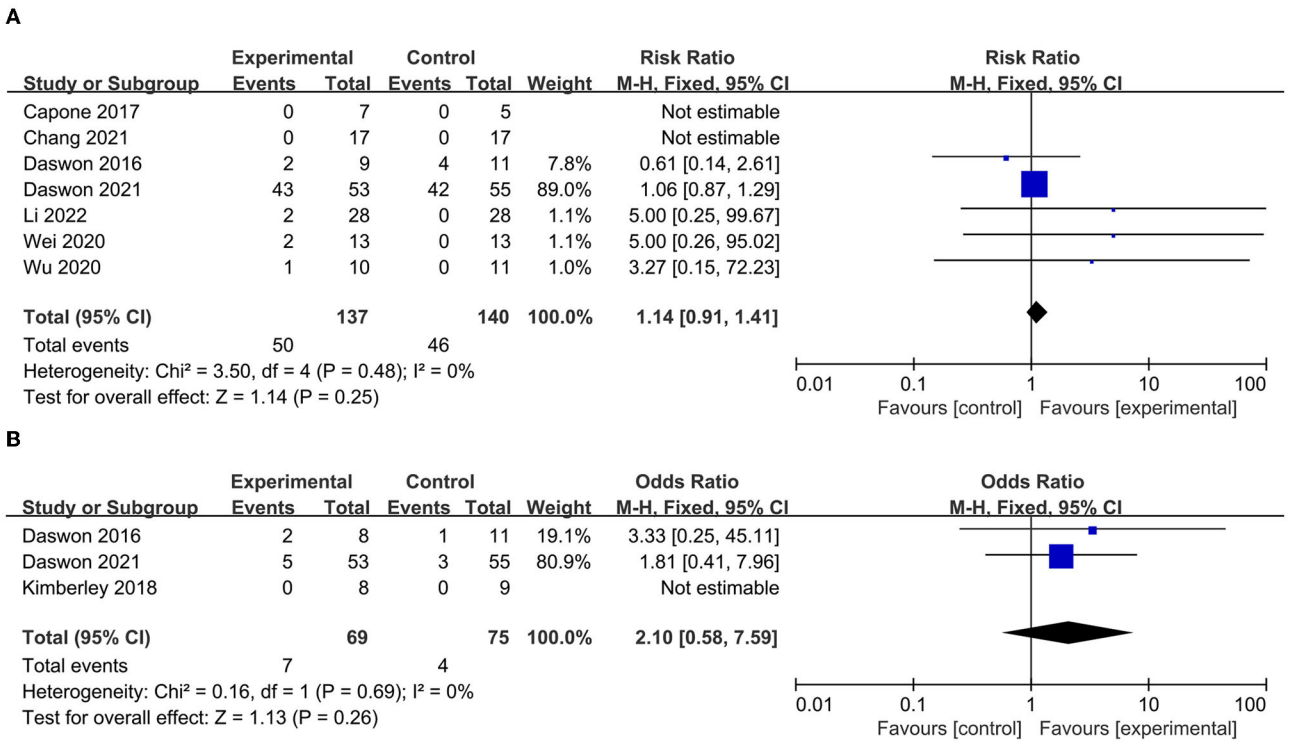


FIGURE 8
(A) Forest plot for the meta-analysis of atrial fibrillations (AEs). **(B)** Forest plot for the meta-analysis of several atrial fibrillations (SAEs).

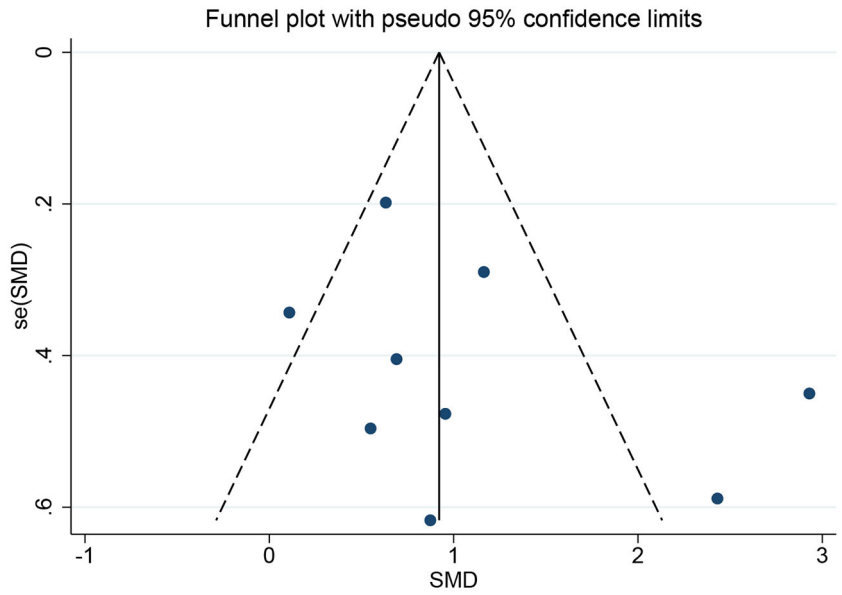


FIGURE 9
Funnel plots of upper limb motor function.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

QD and YFL accepted accountability for their analysis's accuracy and the data's reliability. The study's inception, design, and manuscript writing were all assisted by XW and WZ. The tables and figures were created by TL and WL. The literature search, data extraction and analysis, data interpretation, and quality assessment were significantly aided by YKL and JY. All authors reviewed and approved the article's submission.

Funding

This paper was funded by Henan Province Medical Science and Technology Research Program (SBGJ20210203).

Acknowledgments

We would like to express our heartfelt gratitude to WZ and WL for their valuable suggestions on the meta-analysis. We also hope to express our appreciation to the experts for editing and proofreading this manuscript.

Conflict of interest

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.

Publisher's note

References

1. Chun HY, Ford A, Kutlubaev MA, Almeida OP, Mead GE. Depression, anxiety, and suicide after stroke: a narrative review of the best available evidence. *Stroke.* (2022) 53:1402–10. doi: 10.1161/STROKEAHA.121.035499

2. Collaborators GBDS. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol.* (2021) 20:795–820. doi: 10.1016/S1474-4422(21)00252-0

3. Crichton SL, Bray BD, McKevitt C, Rudd AG, Wolfe CD. Patient outcomes up to 15 years after stroke: survival, disability, quality of life, cognition and mental health. *J Neurol Neurosurg Psychiatry.* (2016) 87:1091–8. doi: 10.1136/jnnp-2016-313361

4. Engineer ND, Kimberley TJ, Prudente CN, Dawson J, Tarver WB, Hays SA. Targeted vagus nerve stimulation for rehabilitation after stroke. *Front Neurosci.* (2019) 13:280. doi: 10.3389/fnins.2019.00280

5. Brainin M, Feigin VL, Norrving B, Martins SCO, Hankey GJ, Hachinski V, et al. Global prevention of stroke and dementia: the wso declaration. *Lancet Neurol.* (2020) 19:487–8. doi: 10.1016/S1474-4422(20)30141-1

6. Li L, Wang D, Pan H, Huang L, Sun X, He C, et al. Non-invasive vagus nerve stimulation in cerebral stroke: current status and future perspectives. *Front Neurosci.* (2022) 16:820665. doi: 10.3389/fnins.2022.820665

7. Moretti A, Ferrari F, Villa RF. Neuroprotection for ischaemic stroke: current status and challenges. *Pharmacol Ther.* (2015) 146:23–34. doi: 10.1016/j.pharmthera.2014.09.003

8. Ma J, Qiao P, Li Q, Wang Y, Zhang L, Yan LJ, et al. Vagus nerve stimulation as a promising adjunctive treatment for ischemic stroke. *Neurochem Int.* (2019) 131:104539. doi: 10.1016/j.neuint.2019.104539

9. Howland RH. Vagus nerve stimulation. *Curr Behav Neurosci Rep.* (2014) 1:64–73. doi: 10.1007/s40473-014-0010-5

10. Farmer AD, Strzelczyk A, Finisguerra A, Gourine AV, Gharabaghi A, Hasan A, et al. International consensus based review and recommendations for minimum reporting standards in research on transcutaneous vagus nerve stimulation (Version 2020). *Front Hum Neurosci.* (2020) 14:215. doi: 10.3389/fnhum.2020.568051

11. Li R, Hu H, Luo N, Fang J. Bibliometric analysis of publication trends and research hotspots in vagus nerve stimulation: a 20-year panorama. *Front Neurol.* (2022) 13:1045763. doi: 10.3389/fneur.2022.1045763

12. Cheng K, Wang Z, Bai J, Xiong J, Chen J, Ni J. Research advances in the application of vagus nerve electrical stimulation in ischemic stroke. *Front Neurosci.* (2022) 16:1043446. doi: 10.3389/fnins.2022.1043446

13. Sun Z, Baker W, Hiraki T, Greenberg JH. The effect of right vagus nerve stimulation on focal cerebral ischemia: an experimental study in the rat. *Brain Stimul.* (2012) 5:1–10. doi: 10.1016/j.brs.2011.01.009

14. Khodaparast N, Kilgard MP, Casavant R, Ruiz A, Qureshi I, Ganzer PD, et al. Vagus nerve stimulation during rehabilitative training improves forelimb recovery after chronic ischemic stroke in rats. *Neurorehabil Neural Repair.* (2016) 30:676–84. doi: 10.1177/1545968315616494

15. Khodaparast N, Hays SA, Sloan AM, Hulsey DR, Ruiz A, Pantoja M, et al. Vagus nerve stimulation during rehabilitative training improves forelimb strength following ischemic stroke. *Neurobiol Dis.* (2013) 60:80–8. doi: 10.1016/j.nbd.2013.08.002

16. Hays SA, Ruiz A, Bethea T, Khodaparast N, Carmel JB, Rennaker RL, et al. Vagus nerve stimulation during rehabilitative training enhances recovery of forelimb function after ischemic stroke in aged rats. *Neurobiol Aging.* (2016) 43:111–8. doi: 10.1016/j.neurobiolaging.2016.03.030

17. Hays SA, Khodaparast N, Hulsey DR, Ruiz A, Sloan AM, Rennaker RL, et al. Vagus nerve stimulation during rehabilitative training improves functional recovery after intracerebral hemorrhage. *Stroke.* (2014) 45:3097–100. doi: 10.1161/STROKEAHA.114.006654

18. Ay I, Nasser R, Simon B, Ay H. Transcutaneous cervical vagus nerve stimulation ameliorates acute ischemic injury in rats. *Brain Stimul.* (2016) 9:166–73. doi: 10.1016/j.brs.2015.11.008

19. Du L, Yang Z, Sheng H, Liu M, Sun Q. Effects of long-term vagus nerve electrical stimulation therapy on acute cerebral infarction and neurological function recovery in post mcao mice. *Oxid Med Cell Longev.* (2022) 2022:8131391. doi: 10.1155/2022/8131391

20. Lindemann J, Rakers C, Matuskova H, Simon BJ, Kinfe T, Petzold GC. Vagus nerve stimulation reduces spreading depolarization burden and cortical infarct volume in a rat model of stroke. *PLoS One.* (2020) 15:e0236444. doi: 10.1371/journal.pone.0236444

21. Meyers EC, Solorzano BR, James J, Ganzer PD, Lai ES, Rennaker RL, et al. Vagus nerve stimulation enhances stable plasticity and generalization of stroke recovery. *Stroke.* (2018) 49:710–7. doi: 10.1161/STROKEAHA.117.019202

22. Yang Y, Yang LY, Orban L, Cuylear D, Thompson J, Simon B, et al. Non-invasive vagus nerve stimulation reduces blood-brain barrier disruption in a rat model of ischemic stroke. *Brain Stimul.* (2018) 11:689–98. doi: 10.1016/j.brs.2018.01.034

23. Dawson J, Pierce D, Dixit A, Kimberley TJ, Robertson M, Tarver B, et al. Safety, feasibility, and efficacy of vagus nerve stimulation paired with upper-limb rehabilitation after ischemic stroke. *Stroke.* (2016) 47:143–50. doi: 10.1161/STROKEAHA.115.010477

24. Capone F, Miccinilli S, Pellegrino G, Zollo L, Simonetti D, Bressi F, et al. Transcutaneous vagus nerve stimulation combined with robotic rehabilitation improves upper limb function after stroke. *Neural Plast.* (2017) 2017:6. doi: 10.1155/2017/7876507

25. Ananda R, Roslan MHB, Wong LL, Botross NP, Ngim CF, Mariapun J. Efficacy and safety of vagus nerve stimulation in stroke rehabilitation: a systematic review and meta-analysis. *Cerebrovasc Dis.* (2022). doi: 10.1159/000526470

26. Gao Y, Zhu Y, Lu X, Wang N, Zhu S, Gong J, et al. Vagus nerve stimulation paired with rehabilitation for motor function, mental health and activities of daily living after stroke: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry.* (2022) 22:2975. doi: 10.1136/jnnp-2022-329275

27. Li H, Yan L, Qian YL. Transcutaneous vagus nerve stimulation combined with rehabilitation training in the intervention of upper limb movement disorders after stroke: a systematic review. *Neuropsychiatr Dis Treat.* (2022) 18:2095–106. doi: 10.2147/NDT.S376399

28. Liu YL, Zhang LP, Zhang X, Ma JX, Jia GW. Effect of combined vagus nerve stimulation on recovery of upper extremity function in patients with stroke: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis.* (2022) 31:11. doi: 10.1016/j.jstrokecerebrovasdis.2022.106390

29. Ramos-Castaneda JA, Barreto-Cortes CF, Losada-Floriano D, Sanabria-Barrera SM, Silva-Sieger FA, Garcia RG. Efficacy and safety of vagus nerve stimulation on upper limb motor recovery after stroke. *A Systematic Review and Meta-Analysis Front Neurol.* (2022) 13:12. doi: 10.3389/fneur.2022.889953

30. Wei J, Zhang C, Wang JX, Sun FH, Xie YJ, Ou X, et al. The effect of Vns on the rehabilitation of stroke: a meta-analysis of randomized controlled studies. *J Clin Neurosci.* (2020) 81:421–5. doi: 10.1016/j.jocn.2020.09.022

31. Xie YL, Wang S, Wu Q, Chen X. Vagus nerve stimulation for upper limb motor impairment after ischemic stroke a meta-analysis. *Medicine (Baltimore).* (2021) 100:10. doi: 10.1097/MD.0000000000027871

32. Zhao KH, Yang JE, Huang JP, Zhao ZQ, Qu Y. Effect of vagus nerve stimulation paired with rehabilitation for upper limb function improvement after stroke: a systematic review and meta-analysis of randomized controlled trials. *Int J Rehabil Res.* (2022) 45:99–108. doi: 10.1097/MRR.0000000000000509

33. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* (2002) 21:1539–58. doi: 10.1002/sim.1186

34. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the prisma statement. *Annals of internal medicine.* (2009) 151:264–9. doi: 10.7326/0003-4819-151-4-200908180-00135

35. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. Rob 2: A revised tool for assessing risk of bias in randomised trials. *Bmj.* (2019) 366:l4898. doi: 10.1136/bmj.l4898

36. Murad MH, Wang Z, Chu H, Lin L. When continuous outcomes are measured using different scales: guide for meta-analysis and interpretation. *BMJ.* (2019) 364:k4817. doi: 10.1136/bmj.k4817

37. Liping Z MY, Sanrong W, Botao T, Lang J, Gongwei J. Effects of transcutaneous vagus nerve stimulation on the recovery of upper limb motor function in patients with ischemic stroke. *Chin J Rehabil Med.* (2020) 35:1316–20. doi: 10.3969/j.issn.1001-1242.2020.11.007

38. Zhenguo H LS, Wen Y, Qiaoli D. Effect of vagus nerve stimulation and chinese medicine comprehensive physiotherapy on the recovery of limb function in patients with hemiplegia after stroke. *Chinese J Integrat Med Cardio-Cerebrovascul Dis.* (2018) 16:1974–6.

39. Kimberley TJ, Pierce D, Prudente CN, Francisco GE, Yozbatiran N, Smith P, et al. Vagus nerve stimulation paired with upper limb rehabilitation after chronic stroke: a blinded randomized pilot study. *Stroke.* (2018) 49:2789–92. doi: 10.1161/STROKEAHA.118.022279

40. Xing W. *Effect of trausauricular vagus nerve stimulation combined with limb training on upper limb motor function and brain plasticity in stroke patient. [Master's degree] [China(Tianjin)]Tianjin Institute of Physical Education* (2020).

41. Wu DD, Ma JX, Zhang LP, Wang SR, Tan BT, Jia GW. Effect and safety of transcutaneous auricular vagus nerve stimulation on recovery of upper limb motor function in subacute ischemic stroke patients: a randomized pilot study. *Neural Plast.* (2020) 2020:9. doi: 10.1155/2020/8841752

42. Li JN, Xie CC Li CQ, Zhang GF, Tang H, Jin CN, et al. Efficacy and safety of transcutaneous auricular vagus nerve stimulation combined with conventional rehabilitation training in acute stroke patients: a randomized controlled trial conducted for 1 year involving 60 patients. *Neural Regen Res.* (2022) 17:1809–13. doi: 10.4103/1673-5374.332155

43. Dawson J, Liu CY, Francisco GE, Cramer SC, Wolf SL, Dixit A, et al. Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (vns-rehab): a randomised, blinded, pivotal, device trial. *Lancet.* (2021) 397:1545–53. doi: 10.1016/S0140-6736(21)00475-X

44. Chang JL, Coggins AN, Saul M, Paget-Blanc A, Straka M, Wright J, et al. Transcutaneous auricular vagus nerve stimulation (tavns) delivered during upper limb interactive robotic training demonstrates novel antagonist control for reaching movements following stroke. *Front Neurosci.* (2021) 15:11. doi: 10.3389/fnins.2021.767302

45. Badran BW, Yu AB, Adair D, Mappin G, DeVries WH, Jenkins DD, et al. Laboratory administration of transcutaneous auricular vagus nerve stimulation (Tavns): technique, targeting, and considerations. *J Vis Exp.* (2019) doi: 10.3791/58984

46. Borland MS, Engineer CT, Vrana WA, Moreno NA, Engineer ND, Vanneste S, et al. The interval between Vns-Tone pairings determines the extent of cortical map plasticity. *Neuroscience.* (2018) 369:76–86. doi: 10.1016/j.neuroscience.2017.11.004

47. Hulsey DR, Riley JR, Loerwald KW, Rennaker RL. 2nd, Kilgard MP, Hays SA. Parametric characterization of neural activity in the locus coeruleus in response to vagus nerve stimulation. *Exp Neurol.* (2017) 289:21–30. doi: 10.1016/j.expneurol.2016.12.005

48. Morrison RA, Hulsey DR, Adcock KS, Rennaker RL. 2nd, Kilgard MP, Hays SA. Vagus nerve stimulation intensity influences motor cortex plasticity. *Brain Stimul.* (2019) 12:256–62. doi: 10.1016/j.brs.2018.10.017

49. Pruitt DT, Danaphongse TT, Lutchman M, Patel N, Reddy P, Wang V, et al. Optimizing dosing of vagus nerve stimulation for stroke recovery. *Transl Stroke Res.* (2021) 12:65–71. doi: 10.1007/s12975-020-00829-6

50. Buell EP, Loerwald KW, Engineer CT, Borland MS, Buell JM, Kelly CA, et al. Cortical map plasticity as a function of vagus nerve stimulation rate. *Brain Stimul.* (2018) 11:1218–24. doi: 10.1016/j.brs.2018.07.045

51. Andreas Straube1* JE, 3, Eren1 O, Blum B, Ruscheweyh R. *Treatment of Chronic Migraine with Transcutaneous Stimulation of the Auricular Branch of the Vagal Nerve (Auricular T-Vns): A Randomized, Monocentric Clinical Trial.* (2015).

52. Loerwald KW, Borland MS, Rennaker RL, Hays SA, Kilgard MP. The interaction of pulse width and current intensity on the extent of cortical plasticity evoked by vagus nerve stimulation. *Brain Stimul.* (2018) 11:271–7. doi: 10.1016/j.brs.2017.11.007

53. Dawson J, Liu C, Francisco GE, Cramer SC, Wolf SL, Dixit A, et al. Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke: sub-group analysis of the randomised, blinded, pivotal, vns-rehab device trial. *Stroke.* (2022) 53:2. doi: 10.1161/str.53.suppl_1.1

54. Dickie DA, Kimberley TJ, Pierce D, Engineer N, Tarver WB, Dawson J. An exploratory study of predictors of response to vagus nerve stimulation paired with upper-limb rehabilitation after ischemic stroke. *Sci Rep.* (2019) 9:15902. doi: 10.1038/s41598-019-52092-x

55. Redgrave J, Day D, Leung H, Laud PJ, Ali A, Lindert R, et al. Safety and tolerability of transcutaneous vagus nerve stimulation in humans; a systematic review. *Brain Stimul.* (2018) 11:1225–38. doi: 10.1016/j.brs.2018.08.010

frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 11 July 2023
DOI 10.3389/fneur.2023.1156987

OPEN ACCESS

EDITED BY
Julien Nizard,
Université de Nantes, France

REVIEWED BY
Vincenzo Di Lazzaro,
Campus Bio-Medico University, Italy
Zeynab Rezaee,
National Institute of Mental Health (NIH), United States
Jean Paul Buu Cuong Nguyen,
Centre Hospitalier Universitaire (CHU) de Nantes, France

*CORRESPONDENCE
Lijuan Wang
✉ wanglijuan@bsu.edu.cn
Duanwei Wang
✉ wren925@163.com

RECEIVED 03 February 2023
ACCEPTED 26 June 2023
PUBLISHED 11 July 2023

CITATION
Qi F, Nitsche MA, Ren X, Wang D and Wang L (2023) Top-down and bottom-up stimulation techniques combined with action observation treatment in stroke rehabilitation: a perspective.
Front. Neurol. 14:1156987.
doi: 10.3389/fneur.2023.1156987

Top-down and bottom-up stimulation techniques combined with action observation treatment in stroke rehabilitation: a perspective

Fengxue Qi[1], Michael A. Nitsche[2], Xiping Ren[3], Duanwei Wang[4]* and Lijuan Wang[5,6]*

[1]Sports, Exercise and Brain Sciences Laboratory, Beijing Sport University, Beijing, China, [2]Department of Psychology and Neurosciences, Leibniz Research Centre for Working Environment and Human Factors, Dortmund, Germany, [3]College of Physical Education and Health Sciences, Zhejiang Normal University, Jinhua, China, [4]Shandong Mental Health Center, Shandong University, Jinan, Shandong, China, [5]Key Laboratory of Exercise and Physical Fitness, Ministry of Education, Beijing Sport University, Beijing, China, [6]School of Sports Medicine and Rehabilitation, Beijing Sport University, Beijing, China

Stroke is a central nervous system disease that causes structural lesions and functional impairments of the brain, resulting in varying types, and degrees of dysfunction. The bimodal balance-recovery model (interhemispheric competition model and vicariation model) has been proposed as the mechanism of functional recovery after a stroke. We analyzed how combinations of motor observation treatment approaches, transcranial electrical (TES) or magnetic (TMS) stimulation and peripheral electrical (PES) or magnetic (PMS) stimulation techniques can be taken as accessorial physical therapy methods on symptom reduction of stroke patients. We suggest that top-down and bottom-up stimulation techniques combined with action observation treatment synergistically might develop into valuable physical therapy strategies in neurorehabilitation after stroke. We explored how TES or TMS intervention over the contralesional hemisphere or the lesioned hemisphere combined with PES or PMS of the paretic limbs during motor observation followed by action execution have super-additive effects to potentiate the effect of conventional treatment in stroke patients. The proposed paradigm could be an innovative and adjunctive approach to potentiate the effect of conventional rehabilitation treatment, especially for those patients with severe motor deficits.

KEYWORDS

transcranial direct current stimulation, transcranial random noise stimulation, transcranial alternating current stimulation, transcranial magnetic stimulation, peripheral electrical stimulation, peripheral magnetic stimulation, action observation

Introduction

Stroke is a neurological syndrome caused by an acute vascular injury of the central nervous system. The syndrome incorporates the cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage (1). It is one of the primary causes of mortality and severe long-term disability. Among all causes of death, stroke ranks fifth following heart disease, cancer, chronic lower respiratory disease, and unintentional injuries/accidents (2). In 2019, the prevalence of

stroke was 101 million cases and there were 6.55 million deaths in global (3). As a major concern of global health, stroke poses great social economic burden, for example, the overall expenses of stroke in US was $52.8 billion in 2017–2018, with mean direct expenses of $8,242 for each patient (4). Stroke ranks second among all the contributors to disability-adjust life-years globally (5). Long-term complications of stroke include pain syndromes, depression and anxiety, cognitive decline and dementia, as well as falls and fractures due to gait instability (2). Motor impairment of the contralateral limb (e.g., loss or limitation of muscle control, mobility, power, and dexterity) is one of the commonest and most detrimental consequences after stroke (6, 7). Dysfunctional motor control affects functional independence of activities of daily living, and thus reduces the quality of life.

Neurorehabilitation after a stroke includes multidisciplinary rehabilitation methods to compensate for the motor deficit, restore motor functions, and improve the life quality of patients (8, 9). Despite intensive therapeutic efforts during stroke rehabilitation, a relevant amount of stroke survivors failed to regain their motor functions that are important for activities of daily living completely (10). Therefore new/advanced approaches are required to optimize motor functions and reduce disability in stroke patients. Based on basic behavioral science and neuroscientific knowledge, novel rehabilitative approaches have been developed to ameliorate perceptual abilities and improve motor functions after stroke in the last few years (11, 12). These novel rehabilitative intervention modalities included action observation treatment (AOT), non-invasive brain stimulation (NIBS) as well as repetitive peripheral electrical or magnetic stimulation (13). These tools share features of targeted modulation of central nervous system activity, and neuroplasticity induction, and might hereby generate therapeutic benefits (11, 14). In this perspective paper, we aimed to discuss how combinations with these novel stimulation techniques and approaches can be taken as potential rehabilitation methods for stroke patients.

Theoretical background and rationale

Brain structural damage of areas and connections, as well as inhibition of the ipsilesional primary motor and sensory cortex disrupts functional connectivity of the motor network and impairs functional network flexibility after stroke (15). A bimodal balance-recovery model has been proposed as the mechanism of functional recovery after a stroke. The extent of structural reserve of the lesioned hemisphere is related to functional reorganization and the involvement of the affected hemisphere in motor control (16). The interhemispheric competition model dominates in stroke patients with high structural reserve (less impairment) (16). Functional neuroimaging studies showed a dysbalance of motor cortex excitability in post-stroke, which is relative hypo-excitability in the ipsilesional hemisphere and hyper-excitability in the contralesional hemisphere (16–18). The hyperactive contralesional hemisphere inhibits cortical excitability of the ipsilesional hemisphere *via* transcallosal inhibition, and compromises motor output (19, 20). Based on the inter-hemispheric competition model, upregulating the excitability of the lesioned hemisphere and/or downregulating the excitability of the intact hemisphere may facilitate recovery in stroke patients (21). In patients with little structural reserve (more severe impairment), the vicariation model predicts stroke recovery. Activity in the contralesional hemisphere compensates for functional loss by the affected hemisphere (16). In this case, instead of predicting a worse outcome on the basis of the interhemispheric competition model, interhemispheric imbalance facilitates vicarious activity of the intact hemisphere, allowing substitutional plasticity (16). A recent longitudinal study by Lin et al. has verified this bimodal balance recovery hypothesis, indicating that the contralesional hemisphere modulates differently across chronic stroke patients with different levels of ipsilesional hemisphere reserve (22).

Neuroplasticity is an important physiological foundation for the neurorehabilitation of stroke patients. It refers to the life-long ability of the central nervous system for reorganization and adaptation, which includes strengthening and weakening synaptic connections, as well as the formation of new neural pathways. Neuroplasticity is a crucial foundation for learning and memory formation, and recovery of motor functions after neurological injuries (9). Modifying neural circuit function in response to external/environmental stimuli and subsequently affecting behavior, cognition, and motor function is a crucial property of the mammalian brain (23, 24). Functional plasticity and structural plasticity are two types of plasticity mechanisms (25). Functional plasticity refers to alterations in the strength of preexisting synaptic transmission, whereas structural plasticity incorporates the growth and deletion of synaptic connections (23, 25, 26). Synaptic plasticity can occur from the ultrastructure level to the brain network level along with short- and long-term alternations in Ca^{2+} dynamics, modulation of neurotransmission as well as expression of protein and gene (27). Synaptic plasticity is classified into Hebbian and homeostatic synaptic plasticity (25, 28). Hebbian synaptic plasticity is a positive feedback loop and unrestricted dynamics *via* strengthening (long-term potentiation, LTP) or weakening (long-term depression, LTD) of synaptic transmission (24, 26, 29). In contrast, homeostatic synaptic plasticity is a negative feedback loop and stabilized neural dynamics in which synaptic efficacy decreases in the case of high neuronal activities and increases when activities are low (25, 30). Animal studies largely contributed to our knowledge about physiological plasticity mechanisms and led to further investigations of neuroplasticity in humans. In the neocortex, studies in animal models demonstrated a close association between motor learning and LTP-like plasticity (31–33). In humans, LTP-like plasticity was explored in the primary motor cortex (M1) concerning use-dependent plasticity (34–37), its involvement in motor learning (38), and its relevance for compensation of motor cortex dysfunctions after brain lesions (39). Post-transcriptional modifications of pe-existing protein account for LTP in the early phase, whereas alternations in the expression of genes and protein relate to LTP in the late phase (27). It has been shown that for studying the plasticity of the human brain, sensory inputs and non-invasive brain stimulation (NIBS) are able to alter respective cortical properties such as the strength of neural network connections, and movement representations (40, 41). Beyond its relevance to the learning formation of the healthy brain, cortical reorganization and adaptive plasticity apply to the field of neurorehabilitation (42–44).

Multimodal therapies in rehabilitation

Action observation treatment

Action observation and execution networks were found first in macaque monkeys. These networks are based on mirror neurons

which are all-important to comprehending the actions of other individuals (45). The notion of mirror mechanisms displays that individuals observing an action could not only activate an identical or similar motor or motor-related cortical network but also automatically promote execution and motor skill acquisition in an observer (46, 47). Functional neuroimaging studies showed an observation-execution-dependent cortical network in human brains and revealed the overlapping of motor observation and motor execution in some brain regions. These networks incorporate M1, the primary somatosensory cortex, the ventral premotor cortex, several parietal areas, and the inferior frontal gyrus (48–52).

Respective observation-related network activation *via* observing a goal-directed movement of others promotes motor skill learning abilities and attainment of observers (53–55). Since long-term potentiation-like (LTP) plasticity is elevated by enhanced task-dependent motor cortex excitability (31, 56), the underlying mechanism of acquisition of a new motor skill *via* action observation might include LTP-like plasticity of these specific brain regions and network (57–60). Motor cortex activation by action observation might thus have the potential to develop into an effective rehabilitative strategy. In healthy humans, action observation enhances motor skill learning (46, 61–63), and action-related motor capacity with the untrained hand (64). AOT, in which action observation followed by execution of an identical task, has been used to alleviate motor function deficits in patients with neurological disorders (65). A typical rehabilitation session of AOT consists of an observation phase and an execution phase. A video clip of an actor and an actress performing object-directed daily action from different perspectives is presented on a computer screen. Specific action can be divided into three to four motor acts. Patients need to observe the motor act and execute the observed act afterwards (65, 66). In patients with acute ischemic stroke, AOT for 10 days facilitates relearning of upper extremity motor skills (67). For patients diagnosed with cerebral ischemic or hemorrhagic stroke in the subacute phase, AOT potentiated upper extremity motor function recovery, improved manual dexterity, and increased quality of life (68). AOT for 4 weeks improved upper extremity function and daily living performance in chronic stroke patients, and AOT of first-person perspective showed more beneficial effects in comparison with AOT of third-person perspective (69). AOT for 4 weeks has also been shown to promote gait ability in chronic stroke patients, and functional AOT was more effective than general AOT (70).

Repetitive transcranial magnetic stimulation

TMS produces a time-varying magnetic field perpendicular to the stimulating coil, inducing electric currents in the cortical tissue beneath the scalp, and eliciting action potentials in targeted neuronal populations. As a neuromodulatory tool, repetitive TMS (rTMS) induces frequency-dependent after-effects. Low-frequency rTMS (LF-rTMS, ≤1 Hz) induces a prolonged decrease in cortical excitability, whereas high-frequency stimulation (HF-rTMS, ≥5 Hz) enhances cortical excitability (10, 71). Theta burst stimulation (TBS) is a subtype of rTMS, including intermittent (iTBS) and continuous (cTBS) stimulation that enhances and suppresses cortical excitability, respectively (72–74). HF-rTMS delivered to M1 concurrent with motor learning practice accelerated the rate of motor skill acquisition and improved motor performance in healthy individuals (75). It is assumed that the effect of this combined intervention is accomplished by the induction of LTP-like processes in the motor network, which promotes task-specific plasticity (75). In subacute hemorrhagic and ischemic stroke patients, delivery of HF-rTMS in the affected hemisphere facilitated motor function recovery of the paralytic hand (76). HF-rTMS over ipsilesional M1 promoted upper extremity motor recovery and daily living ability in acute stroke patients suffering from unilateral subcortical infarction in the middle cerebral artery (77). In subacute ischemic stroke patients, iTBS over the lesioned M1 prior to physiotherapy increased network connectivity between bilateral motor areas and M1, which is correlated with grip strength improvement (78). Resting-state interhemispheric motor network connectivity gradually decreases early after ischemic stroke and subsequently re-increases in the progress of motor function recovery (79). Application of iTBS facilitates reorganization of the motor network and induces neuronal plasticity, contributing to motor function recovery (78). It is proposed that HF-rTMS (76) and iTBS (78) over the ipsilesional M1 up-regulates the activity of the lesioned cortex. LF-rTMS applied over the unaffected motor cortex promoted motor function recovery and improved daily living ability in patients with cerebral infarction (80). LF-rTMS (80) and cTBS applied over the unaffected motor cortex down-regulates the excitability of the unaffected hemisphere and alleviates the interhemispheric inhibition imposed on the affected side. However, these approaches fail to induce beneficial effects in all stroke patients, and individuals respond differently to various stimulation parameters (81). Sankarasubramanian and co-workers demonstrated that upper limb reaching ability was facilitated by HF-rTMS over contralesional dorsal premotor cortex rather than standard stimulation approach (LF-rTMS over contralesional M1) in severely affected stroke patients (82). Therefore, classifying stroke patients into different subgroups (less affected vs. more affected) based on bimodal balance-recovery model is necessary for designing targeted and effective treatments.

Transcranial electrical stimulation

Some studies showed that transcranial electrical stimulation (tES), including transcranial direct current (tDCS), transcranial random noise (tRNS), and transcranial alternating current (tACS) stimulation can increase the acquisition and retention of motor skills and improve motor functions in healthy humans, and rehabilitation (83, 84). These intervention tools elicit long-lasting augments or decrements of motor cortical excitability, and these effects are dependent on brain state and cognitive task performance before and/or during the intervention (85, 86).

tDCS modulates motor cortex excitability and/or activity *via* a weak electrical current (87), which de- or hyperpolarizes neuronal resting membrane potentials (86, 88). tDCS has a polarity-dependent influence on motor cortex excitability and/or activity. When the anode is positioned over M1, the amplitude of motor-evoked potentials (MEP) is increased (89, 90), whereas cathodal tDCS decreases MEPs with standard dosages (89, 91). Dependent on stimulation duration, tDCS can induce after-effects, which resemble LTP-like or LTD-like plasticity (85, 86, 92). In healthy humans, anodal tDCS over M1 during task execution improves motor learning (93–96). This effect is

likely accomplished via modulation of LTP-like plasticity, and enhancement of functional connectivity of respective brain networks via anodal tDCS, resulting in motor performance improvement. Some studies reported that cathodal tDCS over M1 reduced motor performance speed (95, 97), but improved motor learning under specific conditions (98, 99). It is proposed that cathodal tDCS diminishes cortical excitability ("noise reduction") via induction of LTD-like plasticity, thus focusing cortical activity on the neurons relevant to motor learning (93, 98, 99). In patient populations, this intervention has the potential to relieve maladaptive neuroplasticity and improve the neurophysiological state of the targeted brain regions as well as motor functions. The effects of tDCS on stroke patients were not consistently reported in different studies. Ojardias and co-authors reported that one session of anodal tDCS over ipsilesional M1 had a significant beneficial effect on gait endurance in chronic hemiplegic patients (100). In chronic ischemic and hemorrhagic stroke patients, two sessions of anodal tDCS applied over the lesioned M1 improved movement planning and preparation in a standing reaching task (101). Likewise, cathodal tDCS can also induce some positive effects in patients with stroke. Zimerman and co-works reported that cathodal tDCS applied to the non-lesioned M1 facilitated hand motor skill acquisition and retention in patients with subcortical ischemic stroke (102). Cathodal tDCS positioned over the unaffected motor cortex enhanced dual-task gait performance in chronic stroke patients (103). Seamon and co-works, however, indicated that neither anodal tDCS over the lesioned M1 nor cathodal tDCS over the non-lesioned M1 induced any significant effect on walking performance in chronic stroke patients (104). The variable effects of tDCS might be due to the inherent heterogeneity of the stroke patients, the variability of the stimulation parameters and the choice of motor paradigms (105). For stroke patients who benefit from tDCS, the interhemispheric balancing model has been proposed as the mechanism for motor function improvement. Anodal tDCS upregulates ipsilesional cortical excitability, improves network connectivity, and leads to alterations in interhemispheric balance (10). Cathodal tDCS over the contralesional M1 leads to downregulation of the contralesional cortical excitability and upregulation of the ipsilesional cortical excitability *via* reduced transcallosal inhibition (10, 106). Restoration of interhemispheric balance might be a relevant mechanism of tDCS-induced motor control improvement (107). As heterogeneity exists regarding the effect of tDCS on stroke patients, stratifying patients into different subgroups according to the etiology, the damage extent, and the phase of stroke is required to provide personalized therapeutic interventions.

tRNS is a relatively new neuromodulatory electrical stimulation method, which produces a white noise of a Gaussian or bell-shaped alternating current from 0.1 Hz to 640 Hz in a full-frequency spectrum or between 101 and 640 Hz in a high-frequency spectrum (108). Its random electrical oscillation spectrum in a full frequency spectrum or a high frequency spectrum applied to specific brain regions modulates neuronal membrane potentials, induces neuroplasticity, and results in an increase in motor cortex excitability (109–111). Proposed mechanisms of action are modulation of the neural signal-to-noise ratio *via* stochastic resonance (112, 113), and stimulation effects involve voltage-gated sodium channels (114–116). tRNS facilitates motor skill acquisition and consolidation in healthy humans (111, 117). Regarding the impact of tRNS in neurorehabilitation, Hayward and co-authors demonstrated that tRNS over ipsilesional M1 during reaching training improved clinical motor outcomes in chronic stroke patients suffering from severe arm dysfunction (118). tRNS combined with the Graded Arm Supplementary Program promoted upper extremity motor function recovery in ischemic stroke patients in the subacute phase (119). This implied that tRNS can boost functional adaptations of cortical tissue (118).

In tACS, another electrical non-invasive brain stimulation protocol, weak alternating sinusoidal currents over the cortical target region can entrain endogenous brain oscillations at some frequency brand (120). tACS enhanced either motor functions or cognitive functions via associated brain functions with stimulation frequencies matched to the natural dominant rhythm of the underlying brain area (121, 122). Antal et al. showed that tACS over M1 promoted motor learning in healthy humans (123). Beta-tACS over the lesioned M1 reduced the variance of sensorimotor beta-oscillations in stroke patients (124). With respect to motor rehabilitation, beta-tACS might be suitable for facilitating the specificity of brain self-regulation-based neurofeedback *via* interference with endogenous cortical rhythms and intrinsic brain oscillations in stroke patients (124).

In the human brain, regions are interconnected in complex functional networks, incorporating multiple anatomically remote but functionally interlinked areas (125–127). Some studies demonstrated that tES modulates brain activity and/or excitability in both local areas under the stimulation electrodes and remote interlinked brain regions (10, 128). Brain hubs have a critical impact on dynamic interactions between brain areas and integrate the information from different brain regions of the network (127, 129, 130). The effects of tES involving a node or hub of a specific cortical network can spread to functionally connected brain areas (128, 131, 132). Due to activity-dependent network models, tES-generated cortical activity and/or excitability alterations are furthermore sensitive to the specific state of brain networks, and dependent on the level of the ongoing activity of the stimulated cortical networks (128, 133). A wealth of studies has reported that tES can modulate behavior dependent on the neural activity level of brain networks involved in a task (98, 99, 134–137).

Repetitive peripheral electrical and magnetic stimulation

Beyond non-invasive brain stimulation, peripheral stimulation techniques are also explored for their ability to improve neurorehabilitation. Non-invasive peripheral stimulation uses external devices to generate muscle contractions and sensory afferents that can be used in clinical settings to reduce pain and promote recovery of sensorimotor functions (138). Successful goal-directed movements necessary for interaction with the environment rely on the integration of sensory and motor information (139). Stroke is a common neurological disorder leading to compromised sensorimotor integration (140). Accurate sensorimotor integration of afferent and efferent signals in the cerebral cortex contributes to precise motor control and efficient action execution, and plays a critical role in motor learning. To target sensorimotor integration in stroke patients, either enhancement of afferent input to M1 by peripheral electrical stimulation (PES) or peripheral magnetic stimulation (PMS) to modulate motor output, or reduction of sensory input by temporary deafferentation, might be the potential therapeutic interventions (139).

PES activates not only superficial cutaneous receptors but also somatosensory nerve fibers (141, 142). PES over a muscle belly or a

nerve at motor threshold intensity induces muscle contractions by depolarization of motor axons and facilitates motor unit recruitment (143). Modulation of afferent input by PES at motor threshold induces neuroplastic alternations and organizational changes in the sensorimotor cortex, and increases cortical excitability that produces adaptations in central motor pathways (144–147). PES over a nerve at sensory threshold intensity enhances somatosensory input, improves corticomotor excitability (148), facilitates connectivity in sensorimotor regions (149), and induces reorganization of cortical maps (150). Some studies reported that PES improves motor learning (151), motor memory consolidation (152), and inter-limb transfer of motor skills (149) in healthy individuals. In stroke patients, PES at motor threshold increased wrist range of motion and hand muscle strength, improved muscle tone and muscle electrical activity, enhanced functional performance of the upper extremity, and promoted daily living capacity (153, 154). In patients with subacute and chronic stroke, PES at motor threshold decreased muscle spasticity, increased muscle strength, facilitated gait performance, and promoted motor function recovery of the lower extremity (155, 156). One session of PES at sensory threshold reduced muscle spasticity, enhanced muscle strength and proprioception, and improved balance and gait ability in chronic stroke patients (157–159).

In comparison to PES, PMS is deemed to stimulate deeper tissue regions and induce strong muscle contractions for neuromuscular stimulation, with less pain, and fewer side effects with respect to stimulation of the spinal root, muscle belly, or nerve (160, 161). PMS increases peripheral venous blood flow (162), induces muscle contractions with minimal cutaneous sensations (138), and reduces spasticity and muscle hyperreflexia (163). PMS effects depend on the induction of the activity of proprioceptive afferents to the central nervous system, which results in modulation of the excitability of specific spinal circuits and the motor cortex (142, 164–166). PMS improved motor functions in healthy humans (167). In stroke patients, PMS can also induce some beneficial effects. It is reported that in patients with severe upper extremity paresis during the early acute and subacute phase of stroke, PMS prior to standard care promoted upper limb functions, improved daily living abilities, and accelerated the progress rate of motor function recovery (168, 169). In chronic stroke patients with ankle impairment, PMS improved ankle joint mobility and muscle strength, increased M1 transsynaptic excitability in the contralesional hemisphere, and decreased short-interval intracortical inhibition in both hemispheres (170, 171). It is hypothesized that proprioceptive afferents generated by PMS reduce GABAergic inhibition, and the induction of brain plasticity in the sensorimotor cortex may contribute to the increase of muscle strength (171). Furthermore, a single session of PMS significantly reduced spasticity along with decreased event-related desynchronization of mu rhythm in the contralesional hemisphere in subacute or chronic stroke patients (172). It is proposed that the reduction of spasticity might be related to cortical activity alternations in the contralesional hemisphere (172).

Combined intervention therapies in neurorehabilitation

Action observation treatment, transcranial electrical or magnetic stimulation, and peripheral electrical or magnetic stimulation are important components for the development of new treatment methods in the field of neurorehabilitation.

The combined intervention of NIBS and action observation can modulate neuroplasticity and motor functions in both healthy and stroke patients. Our previous studies showed that tRNS over M1 paired with mirror-matching action observation enhances observation-dependent motor cortex excitability, and then this effect promotes execution-dependent motor cortex excitability (137). Some studies reported that action observation improves connectivity between the ventral premotor cortex and M1, and movement execution promotes connections either between the dorsal premotor cortex and M1 or the supplementary motor region and M1 (55, 173). tRNS and motor observation might have synergistic effects in improving cortical excitability *via* premotor mirror neurons to directly and/or indirectly activate M1 neurons. Vice versa, 20 Hz tACS with target electrode over the left M1 and return electrode over the contralateral supraorbital region during movement observation inhibits motor cortex excitability and subsequently inhibits action execution-dependent cortical excitability (174). As a neurophysiological biomarker of functional reorganization, suppression of beta power oscillations is associated with motor learning and consolidation (175). These findings indicated that action observation combined with TES resulted in changes of task-dependent motor cortex activity, which could be advantageous to prevent pathological alterations in stroke sickness (65). In stroke patients with ideomotor apraxia, AOT combined with LF-TMS over the intact hemisphere increased motor cortex excitability and facilitated the recovery of hand motor function (176). LF-TMS over contralesional M1 during observation of complex hand movements improved distal upper extremity functions in the subacute phase following stroke (177). Action observation coupled with PES induced a long-lasting increase in primary motor cortex excitability (178) and improved spontaneous movement tempo (179) in healthy persons. It is proposed that PES paired with action observation might be a promising treatment technique in neurorehabilitation. PES is thought to provide movement-related afferent stimulation to consolidate the kinematic information learned from action observation and lead to neuroplastic adaptations (179).

Some studies explored the effects of transcranial magnetic or electrical stimulation combined with peripheral electrical or magnetic stimulation techniques in neurorehabilitation. In healthy individuals, the effects of combined brain and peripheral stimulation were inconsistently reported. Anodal tDCS (1 mA) alone for 5 min transiently increased cortical excitability, whereas anodal tDCS paired with PES prolonged the facilitating effect for up to 60 min (180). Likewise, cathodal tDCS (1 mA) alone for 5 min decreased the cortical excitability immediately after the stimulation, and the changes were prolonged for up to 60 min when combined with PES (180). The proposed mechanism is that anodal tDCS paired with PES induces LTP-like plasticity and cathodal tDCS combined with PES evoked LTD-like plasticity (180). Schabrun and co-authors, however, failed to find any summative effects after concurrent application of 1 mA tDCS and peripheral nerve electrical stimulation for 20 min, which might be explained by the homeostatic plasticity mechanism (181). In another study, 2 mA anodal tDCS significantly increased MEP amplitude, whereas tDCS combined with PES did not induce any changes in MEP amplitude, indicating a suppression effect following combined stimulation (182). In patients within the first few days

following a stroke, anodal tDCS over the ipsilesional M1 coupled with PES of the paretic hand for 5 consecutive days promoted hand motor function recovery (183). In chronic stroke patients, tDCS over the ipsilesional M1 combined with PES prior to motor training potentiated the beneficial effects of motor learning beyond levels reached with tDCS or PES alone (184). This might be that tDCS paired with PES produces additive effects on motor functions through different pathways where anodal tDCS depolarizes neuronal membrane potential and modulates Glutamate as well as GABA concentrations (86, 185), whereas PES modulates GABAergic interneurons activity (184, 186). In contrast, Menezes and co-authors reported that one session of combined stimulation (PES of the paretic arm and tDCS over the ipsilesional M1) prior to motor training did not facilitate training effects on range of motion, gasp and pinch strength in chronic stroke patients with moderate to severe upper extremity motor deficits (187). As discrepancy exists, more studies are needed to optimize the simulation parameters to induce the beneficial effects of this combined intervention. Paired associative stimulation (PAS) modulates motor cortex excitability based on associative LTP/LTD mechanism governed by Hebbian principles (188–190). When PES was applied 10 ms prior to TMS, motor cortex excitability was increased (facilitatory PAS), whereas motor cortex excitability was inhibited when PES is delivered 25 ms preceding TMS (inhibitory PAS) (190). Facilitatory PAS enhanced motor learning in healthy humans (191). It is suggested that PAS induces LTP-like plasticity, and triggers alterations in synaptogenesis and structure connectivity, leading to the facilitation of motor learning (191). Furthermore, facilitatory PAS can promote motor functions in stroke patients *via* the upregulation of motor cortex excitability in the ipsilesional hemisphere (192). Other forms of associative stimulation, though with limited investigations, showed some promise in treating neurological diseases. Kumru et al. reported that repetitive TMS at 0.1 Hz combined with rPMS at 10 Hz increased motor cortex excitability and reduced intracortical inhibition that might be mediated by GABA-ergic inhibition, but repetitive TMS at 0.1 Hz or rPMS at 10 Hz, respectively, did not improve motor cortex excitability (193).

Both central and peripheral stimulation protocols modulate cortical activity in a state-dependent manner (194–197). The cortical activity in action observation and execution network can be modulated by AOT and synchronously central and peripheral stimulation techniques. Combined top-down with bottom-up stimulation approaches could synergistically modulate cortical activity, spinal networks as well as motor unit recruitment in muscle, reduce spasticity and muscle hyperreflexia, and develop into physical therapy strategies in neurorehabilitation of stroke patients (Figure 1).

Both top-down and bottom-up stimulation techniques have shown some promise in promoting stroke recovery. However, as studies vary in the extent of the structural reserve, the simulation parameters, the phase of stroke, the duration of follow-up, and the outcome measurements, the therapeutic efficacy of different simulation techniques are inconsistently reported. The existing evidence is insufficient to make clinical recommendations in different phases post-stroke, and the way to appropriately apply these techniques in the clinical setting remains to be clarified. Top-down and bottom-up stimulation combined with AOT may have synergistic effects to reach a clinically meaningful level in stroke patients, which need to be investigated in well-designed randomized controlled trial studies with prolonged follow-up.

There are a few limitations that should be mentioned in this perspective. First, we did not differentiate the results following the time windows post-stroke. The neuromodulating effect of variable techniques may change in different stages of stroke. In addition, we did not discuss other neurorehabilitation approaches such as mirror therapy, motor imagery and constraint-induced movement therapy. Last, we did not include other new forms of neuromodulation techniques for instance vagal nerve stimulation and extremely low-frequency magnetic fields (11).

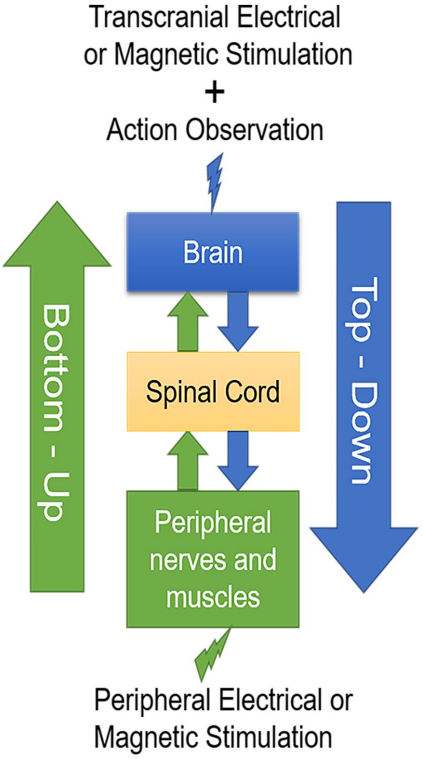


FIGURE 1
A schematic drawing of the two-stage stimulation model. Transcranial electrical or magnetic stimulation during action observation in a top-down manner combined with peripheral electrical or magnetic stimulation in a bottom-up manner develop into valuable physical therapy strategies in neurorehabilitation after stroke.

Conclusion and future perspectives

Functional recovery after a stroke depends on the extent of structural reserve of the lesioned hemisphere. The interhemispheric competition model dominates in stroke patients with high structural reserve, whereas the vicariation model dominates in those with little structural reserve. In line with this bimodal balance-recovery model, future studies should explore the effects of (1) anodal tDCS, beta tACS, high-frequency tRNS, HF-TMS, or iTBS over the contralesional hemisphere combined with PES or PMS of the paretic limbs during motor observation followed by motor execution of an identical task on subsequent motor execution-dependent motor cortex excitability in the stroke patients of the severe lesioned hemisphere; (2) anodal tDCS, beta tACS, HF-tRNS or HF-TMS over the lesioned hemisphere and cathodal tDCS, LF-TMS, or cTBS over the non-lesioned hemisphere combined with PES or PMS of the paretic limbs during motor observation followed by motor execution of an identical task

on subsequent motor execution-dependent motor cortex excitability in stroke patients with high structural reserve of the lesioned hemisphere. Further research also considers its feasibility for recovery of motor functions in upper and lower limbs in stroke patients. The combination of these techniques followed by motor execution may have a synergic effect to optimize neuroplastic changes and improve motor recovery. The task-dependent neuronal network might be efficiently connected when participants observed the correspondingly complex movement under the combination stimulation techniques, which then promoted task-dependent network activity during performance of the identical task. The proposed paradigms are an innovative approach and could be an adjunctive therapy to potentiate the effect of conventional rehabilitation treatment, especially for those patients with severe motor deficit. Future studies are required to improve the efficacy of the respective interventions, and to validate these results in larger multicenter clinical trials.

Author contributions

FQ, MN, LW, and DW contributed to the conception and design. FQ, LW, and DW drafted the paper. MN and XR revised it critically for important intellectual content. All authors have read and agreed to the published version of the manuscript.

Funding

This research was funded by the Special Fund for Fundamental Research Funds of the Central Universities (Sports Rehabilitation Science Laboratory), the Fundamental Research Funds for the Central Universities (2022QN001), and the Research Foundation for Advanced Talents of Beijing Sport University.

Conflict of interest

MN is member of the scientific advisory board of Neuroelectrics.

The remaining 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.

Publisher's note

References

1. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. (2013) 44:2064–89. doi: 10.1161/STR.0b013e318296aeca

2. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke Statistics-2021 update: a report from the American Heart Association. *Circulation*. (2021) 143:e254–743. doi: 10.1161/CIR.0000000000000950

3. Leigh J, John O, Fischer F, Rabiee N, Mirzaei Alavijeh M. Global burden of 369 diseases and injuries In 204 countries and territories 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet*. (2020) 396:1223–49. doi: 10.1016/S0140-6736(20)30752-2

4. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart disease and stroke Statistics-2022 update: a report from the American Heart Association. *Circulation*. (2022) 145:e153–639. doi: 10.1161/CIR.0000000000001052

5. Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, et al. Update on the global burden of ischemic and hemorrhagic stroke in 1990-2013: the GBD 2013 study. *Neuroepidemiology*. (2015) 45:161–76. doi: 10.1159/000441085

6. Pollock A, Baer G, Campbell P, Choo PL, Forster A, Morris J, et al. *Physical rehabilitation approaches for the recovery of function and mobility following stroke*. New York: John Wiley & Sons, Ltd (2014).

7. Ward N. Assessment of cortical reorganisation for hand function after stroke. *J Physiol*. (2011) 589:5625–32. doi: 10.1113/jphysiol.2011.220939

8. Angerova Y, Svestkova O, Sussova J, Vele F, Sladkova P, Lippertova-Grunerova M. *Neurorehabilitation*. Ceska A Slovenska Neurologie a Neurochirurgie, No. 73, pp. 131–135. (2010).

9. Krupinski J, Secades J, Shiraliyeva R. Towards effective neurorehabilitation for stroke patients. *Int J Phys Med Rehabil*. (2014) 2:183. doi: 10.4172/2329-9096.1000183

10. Liew SL, Santarnecchi E, Buch ER, Cohen LG. Non-invasive brain stimulation in neurorehabilitation: local and distant effects for motor recovery. *Front Hum Neurosci*. (2014) 8:378. doi: 10.3389/fnhum.2014.00378

11. Motolese F, Capone F, Di Lazzaro V. New tools for shaping plasticity to enhance recovery after stroke. *Handb Clin Neurol*. (2022) 184:299–315. doi: 10.1016/B978-0-12-819410-2.00016-3

12. Taub E, Uswatte G, Elbert T. New treatments in neurorehabiliation founded on basic research. *Nat Rev Neurosci*. (2002) 3:228. doi: 10.1038/nrn754

13. Abboud H, Hill E, Siddiqui J, Serra A, Walter B. Neuromodulation in multiple sclerosis. *Mult Scler J*. (2017) 23:1663–76. doi: 10.1177/1352458517736150

14. Jackson A, Zimmermann JB. Neural interfaces for the brain and spinal cord—restoring motor function. *Nat Rev Neurol*. (2012) 8:690. doi: 10.1038/nrneurol.2012.219

15. Lariviere S, Ward NS, Boudrias MH. Disrupted functional network integrity and flexibility after stroke: relation to motor impairments. *Neuroimage Clin*. (2018) 19:883–91. doi: 10.1016/j.nicl.2018.06.010

16. Di Pino G, Pellegrino G, Assenza G, Capone F, Ferreri F, Formica D, et al. Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nat Rev Neurol*. (2014) 10:597–608. doi: 10.1038/nrneurol.2014.162

17. Rehme AK, Grefkes C. Cerebral network disorders after stroke: evidence from imaging-based connectivity analyses of active and resting brain states in humans. *J Physiol*. (2013) 591:17–31. doi: 10.1113/jphysiol.2012.243469

18. Xerri C, Zennou-Azogui Y, Sadlaoud K, Sauvajon D. Interplay between intra- and interhemispheric remodeling of neural networks as a substrate of functional recovery after stroke: adaptive versus maladaptive reorganization. *Neuroscience*. (2014) 283:178–201. doi: 10.1016/j.neuroscience.2014.06.066

19. Coppens MJM, Staring WHA, Nonnekes J, Geurts ACH, Weerdesteyn V. Offline effects of transcranial direct current stimulation on reaction times of lower extremity movements in people after stroke: a pilot cross-over study. *J Neuroeng Rehabil*. (2019) 16:10. doi: 10.1186/s12984-019-0604-y

20. Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol*. (2004) 55:400. doi: 10.1002/ana.10848

21. Di Lazzaro V, Dileone M, Capone F, Pellegrino G, Ranieri F, Musumeci G, et al. Immediate and late modulation of interhemipheric imbalance with bilateral transcranial direct current stimulation in acute stroke. *Brain Stimul*. (2014) 7:841–8. doi: 10.1016/j.brs.2014.10.001

22. Lin YL, Potter-Baker KA, Cunningham DA, Li M, Sankarasubramanian V, Lee J, et al. Stratifying chronic stroke patients based on the influence of contralesional motor cortices: an inter-hemispheric inhibition study. *Clin Neurophysiol*. (2020) 131:2516–25. doi: 10.1016/j.clinph.2020.06.016

23. Citri A, Malenka RC. Synaptic plasticity: multiple forms, functions, and mechanisms. *Neuropsychopharmacology*. (2008) 33:18. doi: 10.1038/sj.npp.1301559

24. Karabanov A, Ziemann U, Hamada M, George MS, Quartarone A, Classen J, et al. Consensus paper: probing homeostatic plasticity of human cortex with non-invasive

transcranial brain stimulation. *Brain Stimul*. (2015) 8:442–54. doi: 10.1016/j.brs.2015.01.404

25. Fauth M, Tetzlaff C. Opposing effects of neuronal activity on structural plasticity. *Front Neuroanat*. (2016) 10:75. doi: 10.3389/fnana.2016.00075

26. Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. *Neuron*. (2004) 44:5–21. doi: 10.1016/j.neuron.2004.09.012

27. Cirillo G, Di Pino G, Capone F, Ranieri F, Florio L, Todisco V, et al. Neurobiological after-effects of non-invasive brain stimulation. *Brain Stimul*. (2017) 10:1–18. doi: 10.1016/j.brs.2016.11.009

28. Yee AX, Hsu YT, Chen L. A metaplasticity view of the interaction between homeostatic and Hebbian plasticity. *Philos Trans R Soc Lond Ser B Biol Sci*. (2017) 372:20160155. doi: 10.1098/rstb.2016.0155

29. Hebb DO. *The organization of behavior: A neuropsychological theory*. London: Psychology Press (2005).

30. Toyoizumi T, Kaneko M, Stryker MP, Miller KD. Modeling the dynamic interaction of Hebbian and homeostatic plasticity. *Neuron*. (2014) 84:497–510. doi: 10.1016/j.neuron.2014.09.036

31. Rioult-Pedotti MS, Friedman D, Donoghue JP. Learning-induced LTP in neocortex. *Science*. (2000) 290:533–6. doi: 10.1126/science.290.5491.533

32. Rioult-Pedotti MS, Friedman D, Hess G, Donoghue JP. Strengthening of horizontal cortical connections following skill learning. *Nat Neurosci*. (1998) 1:230–4. doi: 10.1038/678

33. Rosenzweig ES, Barnes CA. Impact of aging on hippocampal function: plasticity, network dynamics, and cognition. *Prog Neurobiol*. (2003) 69:143–79. doi: 10.1016/S0301-0082(02)00126-0

34. Butefisch CM, Davis BC, Wise SP, Sawaki L, Kopylev L, Classen J, et al. Mechanisms of use-dependent plasticity in the human motor cortex. *Proc Natl Acad Sci U S A*. (2000) 97:3661–5. doi: 10.1073/pnas.97.7.3661

35. Classen J, Liepert J, Wise SP, Hallett M, Cohen LG. Rapid plasticity of human cortical movement representation induced by practice. *J Neurophysiol*. (1998) 79:1117–23. doi: 10.1152/jn.1998.79.2.1117

36. Cohen LG, Ziemann U, Chen R, Classen J, Hallett M, Gerloff C, et al. Studies of neuroplasticity with transcranial magnetic stimulation. *J Clin Neurophysiol*. (1998) 15:305–24. doi: 10.1097/00004691-199807000-00003

37. Ziemann U, Muellbacher W, Hallett M, Cohen LG. Modulation of practice-dependent plasticity in human motor cortex. *Brain*. (2001) 124:1171–81. doi: 10.1093/brain/124.6.1171

38. Pascual-Leone A, Nguyet D, Cohen LG, Brasil-Neto JP, Cammarota A, Hallett M. Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *J Neurophysiol*. (1995) 74:1037–45. doi: 10.1152/jn.1995.74.3.1037

39. Bütefisch CM. Neurobiological bases of rehabilitation. *Neurol Sci*. (2006) 27:s18–23. doi: 10.1007/s10072-006-0540-z

40. Berardelli A, Inghilleri M, Rothwell J, Romeo S, Curra A, Gilio F, et al. Facilitation of muscle evoked responses after repetitive cortical stimulation in man. *Exp Brain Res*. (1998) 122:79–84. doi: 10.1007/s002210050493

41. Brasil-Neto J, Cohen L, Pascual-Leone A, Jabir F, Wall R, Hallett M. Rapid reversible modulation of human motor outputs after transient deafferentation of the forearm: a study with transcranial magnetic stimulation. *Neurology*. (1992) 42:1302–2. doi: 10.1212/WNL.42.7.1302

42. Duffau H. Brain plasticity: from pathophysiological mechanisms to therapeutic applications. *J Clin Neurosci*. (2006) 13:885–97. doi: 10.1016/j.jocn.2005.11.045

43. Kuo H-I, Qi F-X, Paulus W, Kuo M-F, Nitsche MA. Noradrenergic enhancement of motor learning, attention, and working memory in humans. *Int J Neuropsychopharmacol*. (2021) 24:490–8. doi: 10.1093/ijnp/pyab006

44. Ziemann U, Hallett M, Cohen LG. Mechanisms of deafferentation-induced plasticity in human motor cortex. *J Neurosci*. (1998) 18:7000–7. doi: 10.1523/JNEUROSCI.18-17-07000.1998

45. Huntley MK, Muller S, Vallence AM. Corticospinal excitability is modulated by distinct movement patterns during action observation. *Exp Brain Res*. (2018) 236:1067–75. doi: 10.1007/s00221-018-5199-1

46. Mattar A, Gribble PL. Motor learning by observing. *Neuron*. (2005) 46:153–60. doi: 10.1016/j.neuron.2005.02.009

47. Rizzolatti G, Craighero L. The mirror-neuron system. *Annu Rev Neurosci*. (2004) 27:169–92. doi: 10.1146/annurev.neuro.27.070203.144230

48. Gazzola V, Keysers C. The observation and execution of actions share motor and somatosensory voxels in all tested subjects: single-subject analyses of unsmoothed fMRI data. *Cereb Cortex*. (2008) 19:1239–55. doi: 10.1093/cercor/bhn181

49. Hari R, Forss N, Avikainen S, Kirveskari E, Salenius S, Rizzolatti G. Activation of human primary motor cortex during action observation: a neuromagnetic study. *Proc Natl Acad Sci U S A*. (1998) 95:15061–5. doi: 10.1073/pnas.95.25.15061

50. Kilner JM, Lemon RN. What we know currently about Mirror neurons. *Curr Biol*. (2013) 23:R1057–62. doi: 10.1016/j.cub.2013.10.051

51. Molenberghs P, Cunnington R, Mattingley JB. Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. *Neurosci Biobehav Rev*. (2012) 36:341–9. doi: 10.1016/j.neubiorev.2011.07.004

52. Shmuelof L, Zohary E. A mirror representation of others' actions in the human anterior parietal cortex. *J Neurosci*. (2006) 26:9736–42. doi: 10.1523/JNEUROSCI.1836-06.2006

53. Heyes CM, Foster CL. Motor learning by observation: evidence from a serial reaction time task. *Q J Exp Psychol A*. (2002) 55:593–607. doi: 10.1080/02724980143000389

54. Nielsen JB, Cohen LG. The olympic brain. Does corticospinal plasticity play a role in acquisition of skills required for high-performance sports? *J Physiol*. (2008) 586:65–70. doi: 10.1113/jphysiol.2007.142661

55. Stefan K, Classen J, Celnik P, Cohen LG. Concurrent action observation modulates practice-induced motor memory formation. *Eur J Neurosci*. (2008) 27:730–8. doi: 10.1111/j.1460-9568.2008.06035.x

56. Spampinato D, Celnik P. Temporal dynamics of cerebellar and motor cortex physiological processes during motor skill learning. *Sci Rep*. (2017) 7:40715. doi: 10.1038/srep40715

57. Celnik P, Stefan K, Hummel F, Duque J, Classen J, Cohen LG. Encoding a motor memory in the older adult by action observation. *NeuroImage*. (2006) 29:677–84. doi: 10.1016/j.neuroimage.2005.07.039

58. Loporto M, Mcallister C, Williams J, Hardwick R, Holmes P. Investigating central mechanisms underlying the effects of action observation and imagery through transcranial magnetic stimulation. *J Mot Behav*. (2011) 43:361–73. doi: 10.1080/00222895.2011.604655

59. Rioult-Pedotti M-S, Donoghue JP, Dunaevsky A. Plasticity of the synaptic modification range. *J Neurophysiol*. (2007) 98:3688–95. doi: 10.1152/jn.00164.2007

60. Sanes JN, Donoghue JP. Plasticity and primary motor cortex. *Annu Rev Neurosci*. (2000) 23:393–415. doi: 10.1146/annurev.neuro.23.1.393

61. Bazzini MC, Nuara A, Scalona E, De Marco D, Rizzolatti G, Avanzini P, et al. The proactive synergy between action observation and execution in the Acquisition of new Motor Skills. *Front Hum Neurosci*. (2022) 16:793849. doi: 10.3389/fnhum.2022.793849

62. Mcgregor HR, Gribble PL. Functional connectivity between somatosensory and motor brain areas predicts individual differences in motor learning by observing. *J Neurophysiol*. (2017) 118:1235–43. doi: 10.1152/jn.00275.2017

63. Stefan K, Cohen LG, Duque J, Mazzocchio R, Celnik P, Sawaki L, et al. Formation of a motor memory by action observation. *J Neurosci*. (2005) 25:9339–46. doi: 10.1523/JNEUROSCI.2282-05.2005

64. Bähr F, Ritter A, Seidel G, Puta C, Gabriel HH, Hamzei F. Boosting the motor outcome of the untrained hand by action observation: Mirror visual feedback, video therapy, or both combined–what is more effective? *Neural Plast* 2018. (2018) 2018:1–10. doi: 10.1155/2018/8369262

65. Buccino G. Action observation treatment: a novel tool in neurorehabilitation. *Philos Trans R Soc Lond Ser B Biol Sci*. (2014) 369:20130185. doi: 10.1098/rstb.2013.0185

66. Rossi F, Savi F, Prestia A, Mongardi A, Demarchi D, Buccino G. Combining action observation treatment with a brain-computer Interface system: perspectives on neurorehabilitation. *Sensors (Basel)*. (2021) 21:8504. doi: 10.3390/s21248504

67. Gaowgeh RAM, Neelam S, Subramanian SS, Regan R, Selvaraj SK, Anandan AD. Efficacy of action observation for upper limb motor deficit in acute stroke participants. *J Pharm Res Int*. (2021) 33:227–33. doi: 10.9734/jpri/2021/v33i56A33905

68. Hsieh YW, Lin YH, Zhu JD, Wu CY, Lin YP, Chen CC. Treatment effects of upper limb action observation therapy and Mirror therapy on rehabilitation outcomes after subacute stroke: a pilot study. *Behav Neurol*. (2020) 2020:6250524. doi: 10.1155/2020/6250524

69. Yu JA, Park J. The effect of first-person perspective action observation training on upper extremity function and activity of daily living of chronic stroke patients. *Brain Behav*. (2022) 12:e2565. doi: 10.1002/brb3.2565

70. Oh SJ, Lee JH, Kim DH. The effects of functional action-observation training on gait function in patients with post-stroke hemiparesis: a randomized controlled trial. *Technol Health Care*. (2019) 27:159–65. doi: 10.3233/THC-181388

71. Klomjai W, Katz R, Lackmy-Vallee A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Ann Phys Rehabil Med*. (2015) 58:208–13. doi: 10.1016/j.rehab.2015.05.005

72. Demirtas-Tatlidede A, Vahabzadeh-Hagh AM, Bernabeu M, Tormos JM, Pascual-Leone A. Noninvasive brain stimulation in traumatic brain injury. *J Head Trauma Rehabil*. (2012) 27:274. doi: 10.1097/HTR.0b013e318217df55

73. Di Lazzaro V, Pilato F, Saturno E, Oliviero A, Dileone M, Mazzone P, et al. Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex. *J Physiol*. (2005) 565:945–50. doi: 10.1113/jphysiol.2005.087288

74. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. (2005) 45:201–6. doi: 10.1016/j.neuron.2004.12.033

75. Narayana S, Zhang W, Rogers W, Strickland C, Franklin C, Lancaster JL, et al. Concurrent TMS to the primary motor cortex augments slow motor learning. *NeuroImage*. (2014) 85:971–84. doi: 10.1016/j.neuroimage.2013.07.024

76. Hosomi K, Morris S, Sakamoto T, Taguchi J, Maruo T, Kageyama Y, et al. Daily repetitive transcranial magnetic stimulation for Poststroke upper limb paresis in the subacute period. *J Stroke Cerebrovasc Dis*. (2016) 25:1655–64. doi: 10.1016/j.jstrokecerebrovasdis.2016.02.024

77. Guan YZ, Li J, Zhang XW, Wu S, Du H, Cui LY, et al. Effectiveness of repetitive transcranial magnetic stimulation (rTMS) after acute stroke: a one-year longitudinal randomized trial. *CNS Neurosci Ther*. (2017) 23:940–6. doi: 10.1111/cns.12762

78. Volz LJ, Rehme AK, Michely J, Nettekoven C, Eickhoff SB, Fink GR, et al. Shaping early reorganization of neural networks promotes motor function after stroke. *Cereb Cortex*. (2016) 26:2882–94. doi: 10.1093/cercor/bhw034

79. Park C-H, Chang WH, Ohn SH, Kim ST, Bang OY, Pascual-Leone A, et al. Longitudinal changes of resting-state functional connectivity during motor recovery after stroke. *Stroke*. (2011) 42:1357–62. doi: 10.1161/STROKEAHA.110.596155

80. Meng ZY, Song WQ. Low frequency repetitive transcranial magnetic stimulation improves motor dysfunction after cerebral infarction. *Neural Regen Res*. (2017) 12:610–3. doi: 10.4103/1673-5374.205100

81. Kindred JH, Wonsetler EC, Charalambous CC, Srivastava S, Marebwa BK, Bonilha L, et al. Individualized responses to Ipsilesional high-frequency and Contralesional low-frequency rTMS in chronic stroke: a pilot study to support the individualization of neuromodulation for rehabilitation. *Front Hum Neurosci*. (2020) 14:578127. doi: 10.3389/fnhum.2020.578127

82. Sankarasubramanian V, Machado AG, Conforto AB, Potter-Baker KA, Cunningham DA, Varnerin NM, et al. Inhibition versus facilitation of contralesional motor cortices in stroke: deriving a model to tailor brain stimulation. *Clin Neurophysiol*. (2017) 128:892–902. doi: 10.1016/j.clinph.2017.03.030

83. Reis J, Fritsch B. Modulation of motor performance and motor learning by transcranial direct current stimulation. *Curr Opin Neurol*. (2011) 24:590–6. doi: 10.1097/WCO.0b013e32834c3db0

84. Tanaka S, Sandrini M, Cohen LG. Modulation of motor learning and memory formation by non-invasive cortical stimulation of the primary motor cortex. *Neuropsychol Rehabil*. (2011) 21:650–75. doi: 10.1080/09602011.2011.605589

85. Polania R, Nitsche MA, Ruff CC. Studying and modifying brain function with non-invasive brain stimulation. *Nat Neurosci*. (2018) 21:174–87. doi: 10.1038/s41593-017-0054-4

86. Stagg CJ, Antal A, Nitsche MA. Physiology of transcranial direct current stimulation. *J ECT*. (2018) 34:144–52. doi: 10.1097/YCT.0000000000000510

87. Nitsche MA, Paulus W. Transcranial direct current stimulation - update 2011. *Restor Neurol Neurosci*. (2011) 29:463–92. doi: 10.3233/RNN-2011-0618

88. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. *Neuroscientist*. (2011) 17:37–53. doi: 10.1177/1073858410386614

89. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol*. (2000) 527:633–9. doi: 10.1111/j.1469-7793.2000.t01-1-00633.x

90. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*. (2001) 57:1899–901. doi: 10.1212/WNL.57.10.1899

91. Nitsche MA, Nitsche MS, Klein CC, Tergau F, Rothwell JC, Paulus W. Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. *Clin Neurophysiol*. (2003) 114:600–4. doi: 10.1016/S1388-2457(02)00412-1

92. Qi F, Nitsche MA, Zschorlich VR. Modulating observation-execution-related motor cortex activity by cathodal transcranial direct current stimulation. *J Brain Sci*. (2019) 9:121. doi: 10.3390/brainsci9050121

93. Nitsche MA, Schauenburg A, Lang N, Liebetanz D, Exner C, Paulus W, et al. Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. *J Cogn Neurosci*. (2003) 15:619–26. doi: 10.1162/089892903321662994

94. Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, et al. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proc Natl Acad Sci U S A*. (2009) 106:1590–5. doi: 10.1073/pnas.0805413106

95. Stagg C, Jayaram G, Pastor D, Kincses Z, Matthews P, Johansen-Berg H. Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning. *Neuropsychologia*. (2011) 49:800–4. doi: 10.1016/j.neuropsychologia.2011.02.009

96. Waters S, Wiestler T, Diedrichsen J. Cooperation not competition: bihemispheric tDCS and fMRI show role for ipsilateral hemisphere in motor learning. *J Neurosci*. (2017) 37:7500–12. doi: 10.1523/JNEUROSCI.3414-16.2017

97. Schmidt S, Fleischmann R, Bathe-Peters R, Irlbacher K, Brandt SA. Evolution of premotor cortical excitability after cathodal inhibition of the primary motor cortex: a sham-controlled serial navigated TMS study. *PLoS One*. (2013) 8:e57425. doi: 10.1371/journal.pone.0057425

98. Focke J, Kemmet S, Krause V, Keitel A, Pollok B. Cathodal transcranial direct current stimulation (tDCS) applied to the left premotor cortex (PMC) stabilizes a newly learned motor sequence. *Behav Brain Res*. (2017) 316:87–93. doi: 10.1016/j.bbr.2016.08.032

99. Zhu FF, Yeung AY, Poolton JM, Lee TM, Leung GK, Masters RS. Cathodal transcranial direct current stimulation over left dorsolateral prefrontal cortex area promotes implicit motor learning in a golf putting task. *Brain Stimul*. (2015) 8:784–6. doi: 10.1016/j.brs.2015.02.005

100. Ojardias E, Aze OD, Luneau D, Mednieks J, Condemine A, Rimaud D, et al. The effects of anodal transcranial direct current stimulation on the walking performance of chronic hemiplegic patients. *Neuromodulation*. (2020) 23:373–9. doi: 10.1111/ner.12962

101. Yang CL, Gad A, Creath RA, Magder L, Rogers MW, Waller SM. Effects of transcranial direct current stimulation (tDCS) on posture, movement planning, and execution during standing voluntary reach following stroke. *J Neuroeng Rehabil*. (2021) 18:5. doi: 10.1186/s12984-020-00799-8

102. Zimerman M, Heise KF, Hoppe J, Cohen LG, Gerloff C, Hummel FC. Modulation of training by single-session transcranial direct current stimulation to the intact motor cortex enhances motor skill acquisition of the paretic hand. *Stroke*. (2012) 43:2185–91. doi: 10.1161/STROKEAHA.111.645382

103. Wong PL, Yang YR, Tang SC, Huang SF, Wang RY. Comparing different montages of transcranial direct current stimulation on dual-task walking and cortical activity in chronic stroke: double-blinded randomized controlled trial. *BMC Neurol*. (2022) 22:119. doi: 10.1186/s12883-022-02644-y

104. Seamon BA, Bowden MG, Kindred JH, Embry AE, Kautz SA. Transcranial direct current stimulation electrode montages may differentially impact variables of walking performance in individuals Poststroke: a preliminary study. *J Clin Neurophysiol*. (2021) 40:71–8. doi: 10.1097/WNP.0000000000000848

105. Lefebvre S, Liew SL. Anatomical parameters of tDCS to modulate the motor system after stroke: a review. *Front Neurol*. (2017) 8:29. doi: 10.3389/fneur.2017.00029

106. Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? *Lancet Neurol*. (2006) 5:708–12. doi: 10.1016/S1474-4422(06)70525-7

107. Bolognini N, Pascual-Leone A, Fregni F. Using non-invasive brain stimulation to augment motor training-induced plasticity. *J Neuroeng Rehabil*. (2009) 6:8. doi: 10.1186/1743-0003-6-8

108. Antal A, Alekseichuk I, Paulus W. The new modalities of transcranial electric stimulation: tACS, tRNS, and other approaches In: . *Transcranial direct current stimulation in neuropsychiatric disorders*. Berlin: Springer (2016). 21–8.

109. Moliadze V, Atalay D, Antal A, Paulus W. Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. *Brain Stimul*. (2012) 5:505–11. doi: 10.1016/j.brs.2011.11.004

110. Moliadze V, Fritzsche G, Antal A. Comparing the efficacy of excitatory transcranial stimulation methods measuring motor evoked potentials. *Neural Plast*. (2014) 2014:837141–1. doi: 10.1155/2014/837141

111. Terney D, Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. *J Neurosci*. (2008) 28:14147–55. doi: 10.1523/JNEUROSCI.4248-08.2008

112. Antal A, Ambrus GG, Chaieb L. The impact of electrical stimulation techniques on behavior. *Wiley Interdiscip Rev Cogn Sci*. (2014) 5:649–59. doi: 10.1002/wcs.1319

113. Pavan A, Ghin F, Contillo A, Milesi C, Campana G, Mather G. Modulatory mechanisms underlying high-frequency transcranial random noise stimulation (hf-tRNS): a combined stochastic resonance and equivalent noise approach. *Brain Stimul*. (2019) 12:967–77. doi: 10.1016/j.brs.2019.02.018

114. Antal A, Chaieb L, Moliadze V, Monte-Silva K, Poreisz C, Thirugnanasambandam N, et al. Brain-derived neurotrophic factor (BDNF) gene polymorphisms shape cortical plasticity in humans. *Brain Stimul*. (2010) 3:230–7. doi: 10.1016/j.brs.2009.12.003

115. Chaieb L, Antal A, Paulus W. Transcranial random noise stimulation-induced plasticity is NMDA-receptor independent but sodium-channel blocker and benzodiazepines sensitive. *Front Neurosci*. (2015) 9:125. doi: 10.3389/fnins.2015.00125

116. Remedios L, Mabil P, Flores-Hernandez J, Torres-Ramírez O, Huidobro N, Castro G, et al. Effects of short-term random noise electrical stimulation on dissociated pyramidal neurons from the cerebral cortex. *Neuroscience*. (2019) 417:107–8. doi: 10.1016/j.neuroscience.2019.07.034

117. Prichard G, Weiller C, Fritsch B, Reis J. Effects of different electrical brain stimulation protocols on subcomponents of motor skill learning. *Brain Stimul*. (2014) 7:532–40. doi: 10.1016/j.brs.2014.04.005

118. Hayward KS, Brauer SG, Ruddy KL, Lloyd D, Carson RG. Repetitive reaching training combined with transcranial random noise stimulation in stroke survivors with chronic and severe arm paresis is feasible: a pilot, triple-blind, randomised case series. *J Neuroeng Rehabil*. (2017) 14:46. doi: 10.1186/s12984-017-0253-y

119. Arnao V, Riolo M, Carduccio F, Tuttolomondo A, D'amelio M, Brighina F, et al. Effects of transcranial random noise stimulation combined with graded repetitive arm supplementary program (GRASP) on motor rehabilitation of the upper limb in sub-acute ischemic stroke patients: a randomized pilot study. *J Neural Transm (Vienna)*. (2019) 126:1701–6. doi: 10.1007/s00702-019-02087-9

120. Lee TL, Lee H, Kang N. A meta-analysis showing improved cognitive performance in healthy young adults with transcranial alternating current stimulation. *NPJ Sci Learn*. (2023) 8:1. doi: 10.1038/s41539-022-00152-9

121. Vosskuhl J, Struber D, Herrmann CS. Non-invasive brain stimulation: a paradigm shift in understanding brain oscillations. *Front Hum Neurosci*. (2018) 12:211. doi: 10.3389/fnhum.2018.00211

122. Wischnewski M, Schutter D, Nitsche MA. Effects of beta-tACS on corticospinal excitability: a meta-analysis. *Brain Stimul*. (2019) 12:1381–9. doi: 10.1016/j.brs.2019.07.023

123. Antal A, Boros K, Poreisz C, Chaieb L, Terney D, Paulus W. Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. *Brain Stimul*. (2008) 1:97–105. doi: 10.1016/j.brs.2007.10.001

124. Naros G, Gharabaghi A. Physiological and behavioral effects of beta-tACS on brain self-regulation in chronic stroke. *Brain Stimul*. (2017) 10:251–9. doi: 10.1016/j.brs.2016.11.003

125. Fornito A, Zalesky A, Breakspear M. Graph analysis of the human connectome: promise, progress, and pitfalls. *NeuroImage*. (2013) 80:426–44. doi: 10.1016/j.neuroimage.2013.04.087

126. To, W.TDe Ridder D, Hart J, Vanneste S. Changing brain networks through non-invasive neuromodulation. *Front Hum Neurosci*. (2018) 12:128. doi: 10.3389/fnhum.2018.00128

127. Van Den Heuvel MP, Sporns O. Rich-club organization of the human connectome. *J Neurosci*. (2011) 31:15775–86. doi: 10.1523/JNEUROSCI.3539-11.2011

128. Fertonani A, Miniussi C. Transcranial electrical stimulation: what we know and do not know about mechanisms. *Neuroscientist*. (2017) 23:109–23. doi: 10.1177/1073858416631966

129. Cocchi L, Sale MV, Lord A, Zalesky A, Breakspear M, Mattingley JB. Dissociable effects of local inhibitory and excitatory theta-burst stimulation on large-scale brain dynamics. *J Neurophysiol*. (2015) 113:3375–85. doi: 10.1152/jn.00850.2014

130. Van Den Heuvel MP, Sporns O. An anatomical substrate for integration among functional networks in human cortex. *J Neurosci*. (2013) 33:14489–500. doi: 10.1523/JNEUROSCI.2128-13.2013

131. Polania R, Paulus W, Nitsche MA. Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. *Hum Brain Mapp*. (2012) 33:2499–508. doi: 10.1002/hbm.21380

132. Polanía R, Paulus W, Nitsche MA. Reorganizing the intrinsic functional architecture of the human primary motor cortex during rest with non-invasive cortical stimulation. *PLoS One*. (2012) 7:e30971. doi: 10.1371/journal.pone.0030971

133. Polania R, Nitsche MA, Paulus W. Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. *Hum Brain Mapp*. (2011) 32:1236–49. doi: 10.1002/hbm.21104

134. Benwell CS, Learmonth G, Miniussi C, Harvey M, Thut G. Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: evidence from biparietal tDCS influence on lateralized attention bias. *Cortex*. (2015) 69:152–65. doi: 10.1016/j.cortex.2015.05.007

135. Bortoletto M, Pellicciari MC, Rodella C, Miniussi C. The interaction with task-induced activity is more important than polarization: a tDCS study. *Brain Stimul*. (2015) 8:269–76. doi: 10.1016/j.brs.2014.11.006

136. Gill J, Shah-Basak PP, Hamilton R. It's the thought that counts: examining the task-dependent effects of transcranial direct current stimulation on executive function. *Brain Stimul*. (2015) 8:253–9. doi: 10.1016/j.brs.2014.10.018

137. Qi FX, Nitsche MA, Zschorlich VR. Interaction between transcranial random noise stimulation and observation-execution matching activity promotes motor cortex excitability. *Front Neurosci*. (2019) 13:10. doi: 10.3389/fnins.2019.00069

138. Beaulieu LD, Schneider C. Repetitive peripheral magnetic stimulation to reduce pain or improve sensorimotor impairments: a literature review on parameters of application and afferents recruitment. *Neurophysiol Clin*. (2015) 45:223–37. doi: 10.1016/j.neucli.2015.08.002

139. Edwards LL, King EM, Buetefisch CM, Borich MR. Putting the "sensory" into sensorimotor control: the role of sensorimotor integration in goal-directed hand movements after stroke. *Front Integr Neurosci*. (2019) 13:16. doi: 10.3389/fnint.2019.00016

140. Rubakova AA, Ivanova GE, Bulatova MA. *Activation of sensorimotor integration processes with a brain-computer interface*. Moscow: Bulletin of Russian State Medical University (2021).

141. Masse-Alarie H, Beaulieu L-D, Preuss R, Schneider C. Repetitive peripheral magnetic neurostimulation of multifidus muscles combined with motor training influences spine motor control and chronic low back pain. *Clin Neurophysiol*. (2017) 128:442–53. doi: 10.1016/j.clinph.2016.12.020

142. Struppler A, Binkofski F, Angerer B, Bernhardt M, Spiegel S, Drzezga A, et al. A fronto-parietal network is mediating improvement of motor function related to repetitive peripheral magnetic stimulation: a PET-H2O15 study. *NeuroImage*. (2007) 36:T174–86. doi: 10.1016/j.neuroimage.2007.03.033

143. Bergquist AJ, Wiest MJ, Collins DF. Motor unit recruitment when neuromuscular electrical stimulation is applied over a nerve trunk compared with a muscle belly: triceps surae. *J Appl Physiol*. (2012) 113:78. doi: 10.1152/japplphysiol.00074.2011

144. Everaert DG, Thompson AK, Su LC, Stein RB. Does functional electrical stimulation for foot drop strengthen corticospinal connections? *Neurorehabil Neural Repair*. (2010) 24:168–77. doi: 10.1177/1545968309349939

145. Mang CS, Clair JM, Collins DF. Neuromuscular electrical stimulation has a global effect on corticospinal excitability for leg muscles and a focused effect for hand muscles. *Exp Brain Res*. (2011) 209:355–63. doi: 10.1007/s00221-011-2556-8

146. Ridding MC, Brouwer B, Miles TS, Pitcher JB, Thompson PD. Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects. *Exp Brain Res*. (2000) 131:135–43. doi: 10.1007/s002219900269

147. Ridding MC, Mckay DR, Thompson PD, Miles TS. Changes in corticomotor representations induced by prolonged peripheral nerve stimulation in humans. *Clin Neurophysiol*. (2001) 112:1461–9. doi: 10.1016/S1388-2457(01)00592-2

148. Kaelin-Lang A, Luft AR, Sawaki L, Burstein AH, Sohn YH, Cohen LG. Modulation of human corticomotor excitability by somatosensory input. *J Physiol*. (2010) 540:623–33. doi: 10.1113/jphysiol.2001.012801

149. Veldman MP, Maurits NM, Inge Z, Maffiuletti NA, Stella VM, Chris MJ, et al. Somatosensory electrical stimulation improves skill acquisition, consolidation, and transfer by increasing sensorimotor activity and connectivity. *J Neurophysiol*. (2018) 120:281–90. doi: 10.1152/jn.00860.2017

150. Meesen RLJ, Cuypers K, Rothwell JC, Swinnen SP, Levin O. The effect of long-term TENS on persistent neuroplastic changes in the human cerebral cortex. *Hum Brain Mapp*. (2011) 32:872–82. doi: 10.1002/hbm.21075

151. Veldman MP, Zijdewind I, Solnik S, Maffiuletti NA, Berghuis KM, Javet M, et al. Direct and crossed effects of somatosensory electrical stimulation on motor learning and neuronal plasticity in humans. *Eur J Appl Physiol*. (2015) 115:2505–19. doi: 10.1007/s00421-015-3248-z

152. Veldman MP, Zijdewind I, Maffiuletti NA, Hortobágyi T. Motor skill acquisition and retention after somatosensory electrical stimulation in healthy humans. *Front Hum Neurosci*. (2016) 10:115. doi: 10.3389/fnhum.2016.00115

153. Huang S, Liu P, Chen Y, Gao B, Li Y, Chen C, et al. Effectiveness of Contralaterally controlled functional electrical stimulation versus neuromuscular electrical stimulation on upper limb motor functional recovery in subacute stroke patients: a randomized controlled trial. *Neural Plast*. (2021) 2021:1987662. doi: 10.1155/2021/1987662

154. Sentandreu-Mañó T, Tomás JM, Ricardo Salom Terrádez J. A randomised clinical trial comparing 35 Hz versus 50 Hz frequency stimulation effects on hand motor recovery in older adults after stroke. *Sci Rep*. (2021) 11:9131. doi: 10.1038/s41598-021-88607-8

155. Shen Y, Chen L, Zhang L, Hu S, Su B, Qiu H, et al. Effectiveness of a novel Contralaterally controlled neuromuscular electrical stimulation for restoring lower limb motor performance and activities of daily living in stroke survivors: a randomized controlled trial. *Neural Plast*. (2022) 2022:5771634. doi: 10.1155/2022/5771634

156. Yang YR, Mi PL, Huang SF, Chiu SL, Liu YC, Wang RY. Effects of neuromuscular electrical stimulation on gait performance in chronic stroke with inadequate ankle control - a randomized controlled trial. *PLoS One*. (2018) 13:e0208609. doi: 10.1371/journal.pone.0208609

157. Cho HY, In TS, Cho KH, Song CH. A single trial of transcutaneous electrical nerve stimulation (TENS) improves spasticity and balance in patients with chronic stroke. *Tohoku J Exp Med*. (2013) 229:187–93. doi: 10.1620/tjem.229.187

158. Kwong PWH, Chan KL, Choi HY, Guo H, Tam YF, Tao SC, et al. Immediate effects of transcutaneous electrical nerve stimulation on gait patterns in chronic stroke survivors: a single group, pretest-posttest clinical trial. *Hum Mov Sci*. (2022) 83:102948. doi: 10.1016/j.humov.2022.102948

159. Tyson SF, Sadeghi-Demneh E, Nester CJ. The effects of transcutaneous electrical nerve stimulation on strength, proprioception, balance and mobility in people with stroke: a randomized controlled cross-over trial. *Clin Rehabil*. (2013) 27:785–91. doi: 10.1177/0269215513478227

160. Sato A, Torii T, Iwahashi M, Iramina K. Alterations in motor cortical excitability induced by peripheral stimulation with magnetic stimulation. *IEEE Trans Magn*. (2018) 54:1–4. doi: 10.1109/TMAG.2018.2851358

161. Szecsi J, Schiller M, Straube A, Gerling D. A comparison of functional electrical and magnetic stimulation for propelled cycling of paretic patients. *Arch Phys Med Rehabil*. (2009) 90:564–70. doi: 10.1016/j.apmr.2008.09.572

162. Okudera Y, Matsunaga T, Sato M, Chida S, Hatakeyama K, Watanabe M, et al. The impact of high-frequency magnetic stimulation of peripheral nerves: muscle hardness, venous blood flow, and motor function of upper extremity in healthy subjects. *Biomed Res*. (2015) 36:81–7. doi: 10.2220/biomedres.36.81

163. Zschorlich VR, Hillebrecht M, Tanjour T, Qi FX, Behrendt F, Kirschstein T, et al. Repetitive peripheral magnetic nerve stimulation (rPMS) as adjuvant therapy reduces skeletal muscle reflex activity. *Front Neurol*. (2019) 10:8. doi: 10.3389/fneur.2019.00930

164. Flamand VH, Beaulieu L-D, Nadeau L, Schneider C. Peripheral magnetic stimulation to decrease spasticity in cerebral palsy. *Pediatr Neurol*. (2012) 47:345–8. doi: 10.1016/j.pediatrneurol.2012.07.005

165. Krause P, Straube A. Peripheral repetitive magnetic stimulation induces intracortical inhibition in healthy subjects. *Neurol Res*. (2008) 30:690–4. doi: 10.1179/174313208X297959

166. Nielsen JF, Sinkjær T. Long-lasting depression of soleus motoneurons excitability following repetitive magnetic stimuli of the spinal cord in multiple sclerosis patients. *Mult Scler J*. (1997) 3:18–30. doi: 10.1177/135245859700300103

167. Jia Y, Liu X, Wei J, Li D, Liu H. Modulation of the Corticomotor excitability by repetitive peripheral magnetic stimulation on the median nerve in healthy subjects. *Front Neural Circuits*. (2021) 15:616084. doi: 10.3389/fncir.2021.616084

168. Jiang YF, Zhang D, Zhang J, Hai H, Zhao YY, Ma YW. A randomized controlled trial of repetitive peripheral magnetic stimulation applied in early subacute stroke: effects on severe upper-limb impairment. *Clin Rehabil*. (2022) 36:693–702. doi: 10.1177/02692155211072189

169. Obayashi S, Takahashi R. Repetitive peripheral magnetic stimulation improves severe upper limb paresis in early acute phase stroke survivors. *NeuroRehabilitation*. (2020) 46:569–75. doi: 10.3233/NRE-203085

170. Beaulieu LD, Masse-Alarie H, Brouwer B, Schneider C. Noninvasive neurostimulation in chronic stroke: a double-blind randomized sham-controlled testing of clinical and corticomotor effects. *Top Stroke Rehabil*. (2015) 22:8–17. doi: 10.1179/1074935714Z.0000000032

171. Beaulieu LD, Masse-Alarie H, Camire-Bernier S, Ribot-Ciscar E, Schneider C. After-effects of peripheral neurostimulation on brain plasticity and ankle function in chronic stroke: the role of afferents recruited. *Neurophysiol Clin*. (2017) 47:275–91. doi: 10.1016/j.neucli.2017.02.003

172. Chen S, Li Y, Shu X, Wang C, Wang H, Ding L, et al. Electroencephalography mu rhythm changes and decreased spasticity after repetitive peripheral magnetic stimulation in patients following stroke. *Front Neurol*. (2020) 11:546599. doi: 10.3389/fneur.2020.546599

173. Cantarero G, Galea JM, Ajagbe L, Salas R, Willis J, Celnik P. Disrupting the ventral premotor cortex interferes with the contribution of action observation to use-dependent plasticity. *J Cogn Neurosci*. (2011) 23:3757–66. doi: 10.1162/jocn_a_00051

174. Wang L, Nitsche MA, Zschorlich VR, Liu H, Kong Z, Qi F. 20 Hz transcranial alternating current stimulation inhibits observation-execution-related motor cortex excitability. *J Pers Med*. (2021) 11:979. doi: 10.3390/jpm11100979

175. Pollok B, Latz D, Krause V, Butz M, Schnitzler A. Changes of motor-cortical oscillations associated with motor learning. *Neuroscience*. (2014) 275:47–53. doi: 10.1016/j.neuroscience.2014.06.008

176. Yang BI, Ma SR, Song BK. Effects of action observation training with 1 Hz low frequency repeated transcranial magnetic stimulation on cerebral cortex activity and hand function in patients with Ideomotor apraxia after stroke. *J Magn*. (2019) 24:770–5. doi: 10.4283/JMAG.2019.24.4.770

177. Noh JS, Lim JH, Choi TW, Jang SG, Pyun SB. Effects and safety of combined rTMS and action observation for recovery of function in the upper extremities in stroke patients: a randomized controlled trial. *Restor Neurol Neurosci*. (2019) 37:219–30. doi: 10.3233/RNN-180883

178. Bisio A, Avanzino L, Gueugneau N, Pozzo T, Ruggeri P, Bove M. Observing and perceiving: a combined approach to induce plasticity in human motor cortex. *Clin Neurophysiol*. (2015) 126:1212–20. doi: 10.1016/j.clinph.2014.08.024

179. Bisio A, Avanzino L, Lagravinese G, Biggio M, Ruggeri P, Bove M. Spontaneous movement tempo can be influenced by combining action observation and somatosensory stimulation. *Front Behav Neurosci*. (2015) 9:228. doi: 10.3389/fnbeh.2015.00228

180. Rizzo V, Terranova C, Crupi D, Sant'angelo A, Girlanda P, Quartarone A. Increased transcranial direct current stimulation after effects during concurrent peripheral electrical nerve stimulation. *Brain Stimul*. (2014) 7:113–21. doi: 10.1016/j.brs.2013.10.002

181. Schabrun SM, Chipchase LS, Zipf N, Thickbroom GW, Hodges PW. Interaction between simultaneously applied neuromodulatory interventions in humans. *Brain Stimul*. (2013) 6:624–30. doi: 10.1016/j.brs.2012.09.009

182. Tsuiki S, Sasaki R, Miyaguchi S, Kojima S, Saito K, Inukai Y, et al. The effect of combined transcranial direct current stimulation and peripheral nerve electrical stimulation on corticospinal excitability. *PLoS One*. (2019) 14:e0214592. doi: 10.1371/journal.pone.0214592

183. Sattler V, Acket B, Raposo N, Albucher JF, Thalamas C, Loubinoux I, et al. Anodal tDCS combined with radial nerve stimulation promotes hand motor recovery in the acute phase after ischemic stroke. *Neurorehabil Neural Repair*. (2015) 29:743–54. doi: 10.1177/1545968314565465

184. Celnik PA, Paik N-J, Vandermeeren Y, Dimyan MA, Cohen LG. Effects of combined peripheral nerve stimulation and brain polarization on performance of a motor sequence task after chronic stroke. *Stroke*. (2009) 40:1764–71. doi: 10.1161/STROKEAHA.108.540500

185. Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *J Physiol*. (2003) 553:293–301. doi: 10.1113/jphysiol.2003.049916

186. Kaelin-Lang A, Luft AR, Sawaki L, Burstein AH, Sohn YH, Cohen LG, et al. Modulation of human corticomotor excitability by somatosensory input. *J Physiol*. (2002, 2002) 540:623–33. doi: 10.1113/jphysiol.2001.012801

187. Menezes IS, Cohen LG, Mello EA, Machado AG, Peckham PH, Anjos SM, et al. Combined brain and peripheral nerve stimulation in chronic stroke patients with moderate to severe motor impairment. *Neuromodulation*. (2018) 21:176–83. doi: 10.1111/ner.12717

188. Carson RG, Kennedy NC. Modulation of human corticospinal excitability by paired associative stimulation. *Front Hum Neurosci*. (2013) 7:823. doi: 10.3389/fnhum.2013.00823

189. Stefan K. Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain*. (2000) 123:572–84. doi: 10.1093/brain/123.3.572

190. Wolters A. A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. *J Neurophysiol*. (2003) 89:2339–45. doi: 10.1152/jn.00900.2002

191. Rajji TK, Liu SK, Frantseva MV, Mulsant BH, Thoma J, Chen R, et al. Exploring the effect of inducing long-term potentiation in the human motor cortex on motor learning. *Brain Stimul*. (2011) 4:137–44. doi: 10.1016/j.brs.2010.09.007

192. Palmer JA, Wolf SL, Borich MR. Paired associative stimulation modulates corticomotor excitability in chronic stroke: a preliminary investigation. *Restor Neurol Neurosci*. (2018) 36:183–94. doi: 10.3233/RNN-170785

193. Kumru H, Albu S, Rothwell J, Leon D, Flores C, Opisso E, et al. Modulation of motor cortex excitability by paired peripheral and transcranial magnetic stimulation. *Clin Neurophysiol*. (2017) 128:2043–7. doi: 10.1016/j.clinph.2017.06.041

194. Feurra M, Blagovechtchenski E, Nikulin VV, Nazarova M, Lebedeva A, Pozdeeva D, et al. State-dependent effects of transcranial oscillatory currents on the motor system during action observation. *Sci Rep*. (2019) 9:12858. doi: 10.1038/s41598-019-49166-1

195. Kraus D, Naros G, Guggenberger R, Leao MT, Ziemann U, Gharabaghi A. Recruitment of additional corticospinal pathways in the human brain with state-dependent paired associative stimulation. *J Neurosci*. (2018) 38:1396–407. doi: 10.1523/JNEUROSCI.2893-17.2017

196. Mrachacz-Kersting N, Stevenson AJT, Jorgensen HRM, Severinsen KE, Aliakbaryhosseinabadi S, Jiang N, et al. Brain state-dependent stimulation boosts functional recovery following stroke. *Ann Neurol*. (2019) 85:84–95. doi: 10.1002/ana.25375

197. Vergallito A, Varoli E, Pisoni A, Mattavelli G, Mauro LD, Feroldi S, et al. State-dependent effectiveness of cathodal transcranial direct current stimulation on cortical excitability. *NeuroImage*. (2023) 2023:120242. doi: 10.1016/j.neuroimage.2023.120242

frontiers | Frontiers in Neurology

TYPE Study Protocol
PUBLISHED 24 August 2023
DOI 10.3389/fneur.2023.1165145

OPEN ACCESS

EDITED BY
Jean Paul Buu Cuong Nguyen,
Centre Hospitalier Universitaire (CHU) de Nantes, France

REVIEWED BY
Xiechuan Weng,
Chinese Academy of Medical Sciences and Peking Union Medical College, China
Marie-Michele Briand,
Hôpital du Sacré-Cœur de Montréal, Canada

*CORRESPONDENCE
Peijing Rong
✉ drrongpj@163.com
Jianghong He
✉ he_jianghong@sina.cn

†These authors have contributed equally to this work and share first authorship

RECEIVED 15 March 2023
ACCEPTED 08 August 2023
PUBLISHED 24 August 2023

CITATION
Zhuang Y, Zhai W, Li Q, Jiao H, Ge Q, Rong P and He J (2023) Effects of simultaneous transcutaneous auricular vagus nerve stimulation and high-definition transcranial direct current stimulation on disorders of consciousness: a study protocol. *Front. Neurol.* 14:1165145. doi: 10.3389/fneur.2023.1165145

Effects of simultaneous transcutaneous auricular vagus nerve stimulation and high-definition transcranial direct current stimulation on disorders of consciousness: a study protocol

Yutong Zhuang[1,2†], Weihang Zhai[3†], Qinghua Li[4], Haoyang Jiao[5], Qianqian Ge[1], Peijing Rong[3*] and Jianghong He[1*]

[1]Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China, [2]Department of Neurosurgery, The Second Clinical College of Southern Medical University, Guangzhou, China, [3]Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing, China, [4]College of Anesthesiology, Shanxi Medical University, Taiyuan, China, [5]Institute of Documentation, Chinese Academy of Traditional Chinese Medicine, Beijing, China

Background: Non-invasive brain stimulation (NIBS) techniques are now widely used in patients with disorders of consciousness (DOC) for accelerating their recovery of consciousness, especially minimally conscious state (MCS). However, the effectiveness of single NIBS techniques for consciousness rehabilitation needs further improvement. In this regard, we propose to enhance from bottom to top the thalamic–cortical connection by using transcutaneous auricular vagus nerve stimulation (taVNS) and increase from top to bottom cortical-cortical connections using simultaneous high-definition transcranial direct current stimulation (HD-tDCS) to reproduce the network of consciousness.

Methods/design: The study will investigate the effect and safety of simultaneous joint stimulation (SJS) of taVNS and HD-tDCS for the recovery of consciousness. We will enroll 84 MCS patients and randomize them into two groups: a single stimulation group (taVNS and HD-tDCS) and a combined stimulation group (SJS and sham stimulation). All patients will undergo a 4-week treatment. The primary outcome will be assessed using the coma recovery scale-revised (CRS-R) at four time points to quantify the effect of treatment: before treatment (T0), after 1 week of treatment (T1), after 2 weeks of treatment (T2), and after 4 weeks of treatment (T3). At the same time, nociception coma scale-revised (NCS-R) and adverse effects (AEs) will be collected to verify the safety of the treatment. The secondary outcome will involve an analysis of electroencephalogram (EEG) microstates to assess the response mechanisms of dynamic brain networks to SJS. Additionally, CRS-R and AEs will continue to be obtained for a 3-month follow-up (T4) after the end of the treatment.

Discussion: This study protocol aims to innovatively develop a full-time and multi-brain region combined neuromodulation paradigm based on the mesocircuit model to steadily promote consciousness recovery by restoring thalamocortical and cortical-cortical interconnections.

KEYWORDS

disorders of consciousness, high-definition transcranial direct current stimulation, transcutaneous auricular vagus nerve stimulation, simultaneous stimulation, EEG microstate

Introduction

Disorder of consciousness (DOC) is caused mostly by disruption of thalamocortical and cortical-cortical connections due to extensive destruction of long-range white matter fiber tracts after severe brain injury (1). Typically, patients with DOC are classified into two levels of consciousness according to CRS-R: vegetative state/unresponsive wakefulness syndrome (VS/UWS), comprising those who retain only basic brainstem reflexes and sleep-wake cycles but no purposeful behavior, and minimally conscious state (MCS), comprising those who have fluctuating but reproducible signs of consciousness such as movement to command, visual pursuit, and localization to noxious stimulation (2).

In recent years, neuromodulation techniques have played an important role in treating neurological disorders through interventions on key hubs of the brain networks. taVNS is a novel NIBS technique that is safe and easy to use at home. It has been widely used and confirmed to have a good clinical effect on psychiatric disorders such as depression, insomnia, and cognitive disorders (3). In 2017, our team initially applied taVNS to patients with DOC and reported a case of a VS/UWS patient who improved to MCS after treatment (4). Briand et al. (5) further proposed a vagal cortical pathway model and suggested that taVNS might enhance the afferent signals from the auricular branch of the vagal nerve, promoting activity of the tractus solitarius nucleus and spinal trigeminal nucleus. Then, the neural impulses along the ascending reticular activating system (ARAS) strengthened from bottom to top the thalamic-striatal-cortical interaction to promote the recovery of consciousness (Figure 1) (5). Similarly, a subsequent longitudinal case study found another patient had improved from VS/UWS to MCS during taVNS treatment. However, the patient never fully regained consciousness after 6 months of continuous treatment and even had a downward trend in CRS-R after the end of treatment (6). Another study with a larger sample size reported that only 5 out of 14 DOC patients showed improvement in consciousness after treatment with taVNS (7). Similar results reported by Yu et al. (8) showed also that only 50% of patients with DOC had a good outcome after treatment. The fluctuation in the effective rate between study groups demonstrated that taVNS had a poor and unstable therapeutic effect on patients with DOC, which suggested a limited understanding of the underlying mechanism of taVNS for consciousness. That highlighted the urgent need for additional in-depth studies.

Yu et al. (8) further discovered a significant increase in cerebral blood flow in DOC patients with better prognoses after 1 month of taVNS treatment. The affected regions included the right thalamus, right caudate nucleus, left insula, superior temporal gyrus, left prefrontal cortex, precentral gyrus, and left occipital cortex. An EEG study also found that frontal–parietal and frontal-occipital

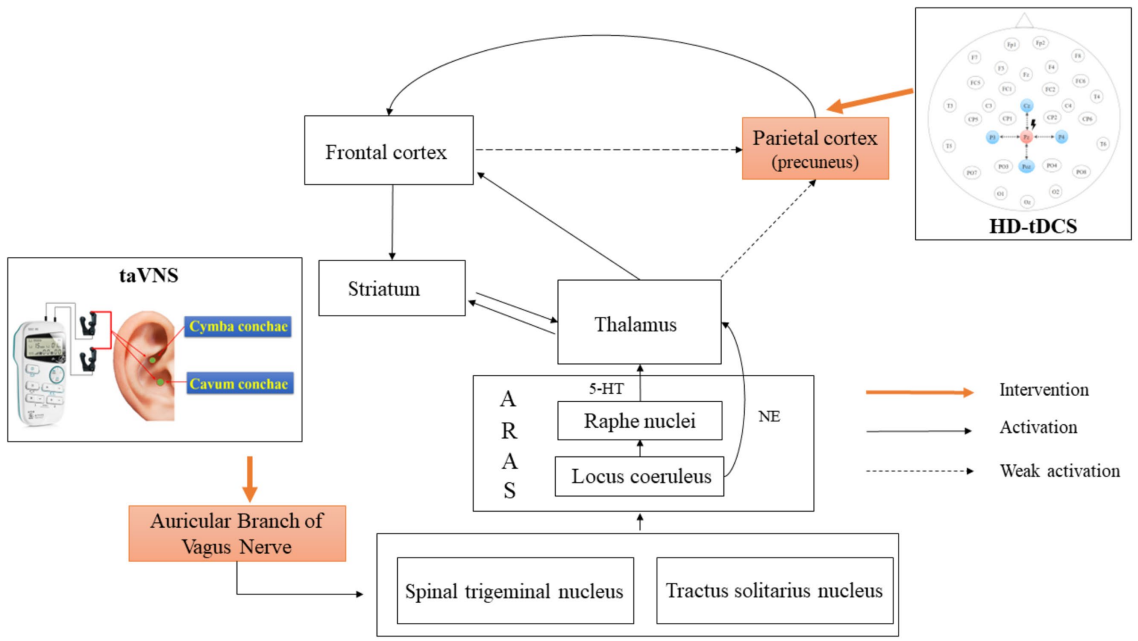


FIGURE 1
Mechanism of action of simultaneous taVNS and HD-tDCS. taVNS, transcutaneous auricular vagus nerve stimulation; HD-tDCS, high-definition transcranial direct current stimulation; 5-HT, 5-hydroxytryptamine pathway; NE, norepinephrine; ARAS, ascending reticular activating system.

connectivities were enhanced in MCS patients after 2 weeks of taVNS treatment (9). For the healthy subjects, a review pointed out that taVNS might commonly activate the thalamus, striatum, medial prefrontal cortex, and postcentral gyrus via the 5-hydroxytryptamine pathway of raphe nucleus and the norepinephrine pathway of locus coeruleus (5). In addition, studies using EEG have found increased power in lower frequency bands in healthy subjects after stimulation of taVNS, especially in the frontal and central regions (10). Based on the above evidence, we hypothesize that taVNS may initially activate the frontal regions at the cortical-cortical level. Then, these signals will disseminate to the parietal and occipital lobes through anatomical connections. However, the indirect weak effects via frontal cortex connectivity may not be enough to completely activate the posterior brain regions (Figure 1). According to the global workspace hypothesis, the formation and maintenance of consciousness required the integration of information from a large-scale frontoparietal network (11). Schiff et al. also proposed the mesocircuit model. They suggested that the initiation of consciousness relied on the interconnection via the thalamus between the frontoparietal network and anterior forebrain mesocircuit, which includes the frontal and prefrontal cortex and the striatopallidal negative feedback loop (1, 12). In conclusion, taVNS may modulate only a single neural circuit or local brain area, which cannot trigger the reconstruction of a complete consciousness network.

Transcranial direct current stimulation (tDCS) is another NIBS technique and is characterized by direct modulation of cortico-cortical connections in a top-down manner (13). Conventional tDCS consists of two electrode pads. The anode increases the excitability of the target area through subthreshold weak stimulation, while the cathode acts as an inhibitor (14). It is generally accepted that the selection of stimulation sites is a critical factor influencing the moderator effect of tDCS on neural networks (15–17). The precuneus and posterior cingulate cortex (PCC) are key nodes of the default mode network (DMN) in the posterior brain region. The precuneus/PCC and the posterior medial cortex were recognized as regions with the highest metabolic activity during the resting state in healthy subjects (18). In addition, the functional diversity and integration of the precuneus and PCC were significantly lower in patients with DOC than in healthy subjects (19). Another study further revealed that an increase in the metabolic ratio of the precuneus to the central thalamus was accompanied by improved levels of consciousness (20). Therefore, the activity of precuneus and PCC was correlated with the level of consciousness. Consequently, it was expected to be a potential stimulation site of tDCS in posterior brain regions to promote restoration of consciousness. A randomized, crossover, controlled trial found that nine patients with DOC showed behavioral recovery after repeated treatments of tDCS targeting the posterior parietal cortex (PPC) for 5 days. But the overall effective rate of the tDCS montages targeting the PPC was lower than the tDCS targeting the dorsolateral prefrontal (15). This disparity in effectiveness might be attributed to the diffuse current of tDCS that could not precisely and effectively stimulate the PPC. In this regard, HD-tDCS with a more focused stimulation current was developed to induce focal neural and specific behavioral changes. Guo et al. (21) used HD-tDCS targeting precuneus to treat patients with DOC and established that 72% (9/11) of patients with DOC had a significant increase in CRS-R scores. Furthermore, the simultaneous EEG results indicated a significant change in central-parietal connectivity, suggesting that HD-tDCS activated a wide range of brain activity outside the target (21). Thus, it seemed that HD-tDCS had a clear modulatory effect on the posterior brain regions of patients with DOC. But the overall effective rate of HD-tDCS for consciousness recovery was still precarious due to different stimulation paradigms in various studies (21–23).

In summary, we propose to enhance from bottom to top the overall activity of the anterior forebrain mesocircuit by using taVNS. Furthermore, HD-tDCS targeting precuneus will be used at the same time to compensatively enhance the frontoparietal network to overcome the issue that single NIBS techniques were insufficient to activate the large-scale consciousness circuit (Figure 1). Ultimately, the thalamocortical and frontoparietal network simultaneously will be maintained at a high level of excitability to restore the integrity of the consciousness network and accelerate the recovery of consciousness in patients with DOC. In the study, we will look into the clinical efficacy and safety of whole-time and multi-brain combined modulation to break the bottleneck of the unstable effect of NIBS techniques and deepen the understanding of the mechanisms of consciousness onset and maintenance in DOC patients.

Methods

Study design

The study is a prospective, randomized, controlled, double-blind clinical trial (Figure 2) that has been registered at the Chinese Clinical Trial Registry (ChiCTR2300069166). The study protocol is designed according to the Declaration of Helsinki and has been approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (NO. KYSQ 2022-347-01). Informed consent will be obtained from a patient-authorized legal representative due to patients' disorders of consciousness.

Participants

The study has initiated in April 2023 and will continue until December 2024. A total of 84 MCS patients will be included in the Neurosurgery Inpatient Department of Beijing Tiantan Hospital. The inclusion and exclusion criteria are presented in Table 1.

Sample size

The sample size was calculated based on the effective rate. An improvement of at least 3 points in the CRS-R was considered an effective treatment. Previous studies found the effective rate of taVNS was 7% ($n = 14$) (7) and of HD-tDCS was 36% ($n = 11$) (21). Assuming the existence of a synergistic effect, the SJS group will have a higher effective rate of 43%, while the sham stimulation group will have no effect. Therefore, the two-sided 2×4 chi-square test in PASS (version 15) was used for the sample size calculation of four groups. The test power (1-β) was 80% and the type I error rate (α) was 5%. The calculated effect size W was 0.436, and then a dropout rate of 20% was considered. Finally, a total of 84 patients will eventually be enrolled, and each group will have 21 patients (Figure 2).

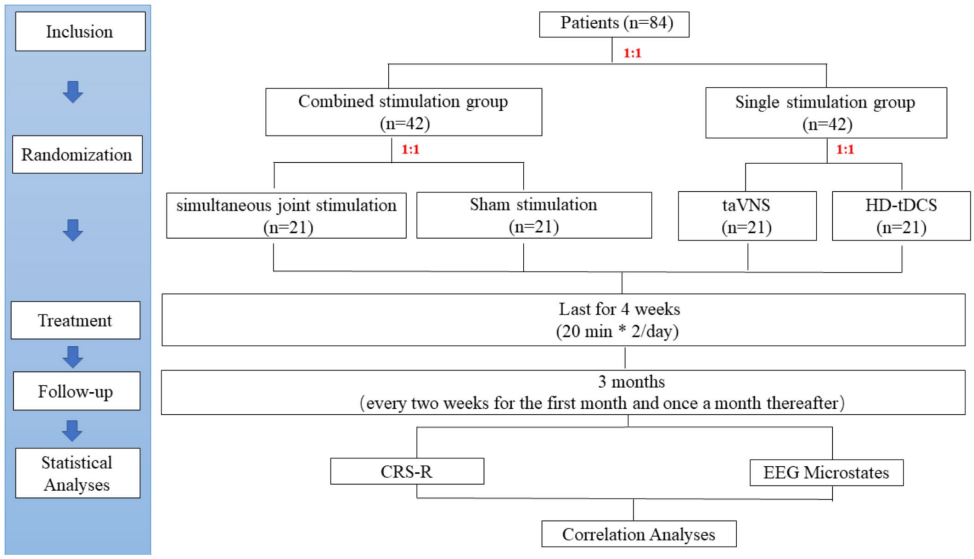


FIGURE 2
Study flow diagram. taVNS, transcutaneous auricular vagus nerve stimulation; HD-tDCS, high-definition transcranial direct current stimulation; NCS-R, nociception coma scale-revised; EEG, Electroencephalogram; CRS-R, coma recovery scale-revised.

Procedures

The randperm function of MATLAB (Version 2020b, MathWorks Inc., Natick, United States) will be used to generate 84 random integers in random order by the study leader. Each patient will be given a random number in the order of enrollment. The first randomization will divide patients into a combined stimulation group (1–42) and a single stimulation group (43–84) based on a 1:1 ratio. Patients in the combined stimulation group will be further randomized in a 1:1 ratio into the SJS group (1–21) and the sham stimulation group (22–42). Similarly, patients in the single stimulation group will also be randomly assigned in a 1:1 ratio to the taVNS group (43–63) and the HD-t DCS group (64–84).

The study protocol is a double-blind design. Each patient will be exposed to identical-looking simultaneous stimulation. Specifically, the SJS group will receive both positive stimulation of taVNS and HD-tDCS. In contrast, the sham stimulation group will receive sham stimulation of taVNS and HD-tDCS to eliminate potential brain effects caused by the physical compression of the instrument. The patients in the single stimulation group will receive one kind of positive stimulation by taVNS or HD-tDCS. They will also receive sham stimulation of another technique at the same time to blind patients/families and therapists/assessors.

All patients will receive treatment twice a day in the morning and afternoon for 4 weeks. There are 2 days' rest every 5 days of treatment. Considering the high current intensity of SJS, the single stimulation time of taVNS, commonly for 30 min (24), will be adjusted downward to 20 min to reduce the burden on the patient's brain.

The Ethics Committee of Beijing Tiantan Hospital will be responsible for independent security monitoring. Adverse events and unintended events will be reported to them when every 10 patients are included. They will further assess the causal relationship between the adverse reaction and treatment. If a serious adverse event is proven to have been caused by the treatment, the trial will be terminated immediately. Appropriate medical emergency and protective measures will be given to patients at the same time.

Stimulations

The stimulation area of the taVNS (SDZ-IIB, Suzhou Medical Supplies Factory) will be bilateral auricles. A pair of clips will be placed on one side of the auricle and another pair of clips will be placed on the opposite side. A clip will have three carbon-impregnated silicone tips. The first tip will serve as the common end of the other two tips to support the posterior surface of the auricle. The second tip will be placed on the lateral scapha. The third tip will be placed on the medial auricular cavity to stimulate targets including cymba conchae and cavum conchae (Figure 1). The stimulator will provide electrical pulses of 1–1.5 mA with an alternate frequency between 4 and 20 Hz and a pulse width of 30 μs. Stimulus intensity will be routinely set at 1.5 mA for each patient. We will turn down the current when the patient's blood oxygen saturation is below 95%, heart rate increases by more than 20%, or the NCS-R score exceeds 3 points and shows a significant increase during stimulation compared to pre-stimulation. The stimulator will have no ramp-up and ramp-off of current during the stimulation. In addition, two identical-looking instruments will be used. One, called number 1, will be capable of normal stimulation as positive stimulation after the switching on. However, the other one, called number 2, will have no current output as a sham stimulation.

The HD-tDCS (4 × 1-C2, Soterix Medical Inc.) stimulation target will be the precuneus. Pz according to an international standard 10–20 EEG system has been proven as a position overlying the medial parietal cortex and the precuneus (25). Therefore, the central electrode of HD-tDCS is placed at Pz, and the four return electrodes are placed at a distance of approximately 3.5 cm from the central electrode at Cz, P3, P4, and POz (Figure 1). The stimulation current is a constant 2 mA with a ramp-up time of 30 s and a ramp-down time of 30 s. According

TABLE 1 Inclusion and exclusion criteria.

Inclusion	
	1. Diagnosed with MCS by coma recovery scale-revised;
	2. Age: from 18 to 60 years;
	3. More than 1 month after the initial brain injury;
	4. Consciousness is in a stable phase (no change in the total score of CRS-R) for at least 2 weeks before admission;
	5. No cranial defect or extensive skull repair;
	6. Precuneus and posterior parietal should be intact on at least one side;
	7. Patient-authorized legal representative agreed to the experimental protocol and signed informed consent.
Exclusion	
	1. Neurodegenerative diseases such as Alzheimer's disease and Lewy body dementia; 2. Disorders of consciousness caused by operation injuries or malignancy;
	3. Time since onset less than 1 month (acute coma);
	4. Patients with seizures that are difficult to control;
	5. Patients are undergoing other clinical trials;
	6. Pregnancy and lactation.
Withdrawal	
	1. Recurrent seizures during treatment;
	2. Life-threatening diseases such as severe lung infection, intracranial infections, and cerebral hernia;
	3. Death;
	4. Patient is lost to follow-up.

to simulation modeling from a realistic volumetric approach to simulate transcranial electric stimulation (ROAST) (26), the HD-tDCS montage can effectively activate the PPC and precuneus of patients with DOC (Figure 3A). In terms of sham stimulation of the HD-tDCS, its parameters will be the same as positive stimulation with the difference that the voltage will rise to 2 mA and decrease immediately to 0 mA when the instrument is turned on. The positive and sham stimulation start buttons will be, respectively, covered by two labels called numbers 3 and 4.

The therapist will be informed of the HD-tDCS button number and the taVNS machine number that should be used for the treatment of each patient by the study leader before treatment. However, the therapist will not know the specific function of each number.

Neuroimaging assessments

T1-weighted brain images will be obtained using a 3.0 T magnetic resonance imaging (MRI) scanner (HD750, GE, United States) to evaluate the resting-state brain structure in each patient before enrollment. Patients with severe damage in the precuneus/PCC will not be included in the study to ensure the effectiveness of HD-tDCS stimulation.

Behavioral assessments

The CRS-R was first proposed by Giacino et al. (2) to assess the level of consciousness in patients. The scale with a total of 23 points included six subscales of auditory, visual, motor, verbal, communication, and arousal levels (2). In the study, patients will be evaluated independently by two trained clinicians. They will perform five repeated CRS-R assessments at least 2 weeks before enrollment to clarify the patient's state of consciousness and clinical diagnosis. Finally, the highest CRS-R score will be taken as the pre-treatment (T0) baseline score. Changes in CRS-R will be assessed at three time points during treatment to reflect the effect of treatment: 1 week (T1), 2 weeks (T2), and 4 weeks (T3) (Figure 4).

Schnakers et al. (27) developed the nociception coma scale (NCS) to assess the nociception of patients with DOC, which included four subscales of motor response, verbal response, visual response, and facial expression (27). Subsequently, Chatelle et al. (28) excluded the visual subscale to propose a more sensitive new version called NCS-R (ranging from 0 to 9 points) for assessment of nociception compared to the NCS. They found that an NCR-R cut-off value of 4 points could differentiate MCS patients' behaviors induced by nociceptive stimulation from behaviors induced by non-noxious stimulation (28). The NCS-R will be used before and during stimulation in the study to adjust the current intensity of taVNS.

EEG recording and microstate analysis

The resting 30-min EEG signal will be recorded at a 1,000 Hz sampling rate by 32 Ag/AgCl electrodes (Nicolet EEG V32, Natus Neurology, United States) according to the international standard 10–20 EEG system (the detailed sites of 32 electrodes can be seen in Figure 1) at each time point. The impedance between the electrode and the patient's skin will always be kept below 5 kΩ. EEG monitoring will be stopped when the patient is tired or asleep, and then the patient will be kept awake by stimulating the patient's earlobe.

The EEG raw data will first be preprocessed offline in MATLAB (Version 2020b, MathWorks Inc., Natick, USA). The preprocessing will mainly consist of 2–20 Hz bandpass filters, 50 Hz notch filters, and down-sampling to 250 Hz. EMG and EEG artifacts will be removed by independent component analysis. Finally, all channels will be re-referenced to the average reference.

After the preprocessing, the 10-min noise-free EEG data will be imported into the Cartool toolbox[1] for microstate analysis. Global Field Power (GFP) was the standard deviation of the amplitude at each point for all channels, which was used to characterize the instantaneous topographic field strength. When GFP was high, the topographic map maintained a relatively steady state and had a high signal-to-noise ratio (29). Therefore, the topographic maps corresponding to the GFP peak will be selected as the original maps for subsequent clustering analysis in this study. The clustering algorithm will be topographic atomize and agglomerative hierarchical clustering (30) with a range of clusters from 1 to 12. The optimal

1 https://sites.google.com/site/cartoolcommunity

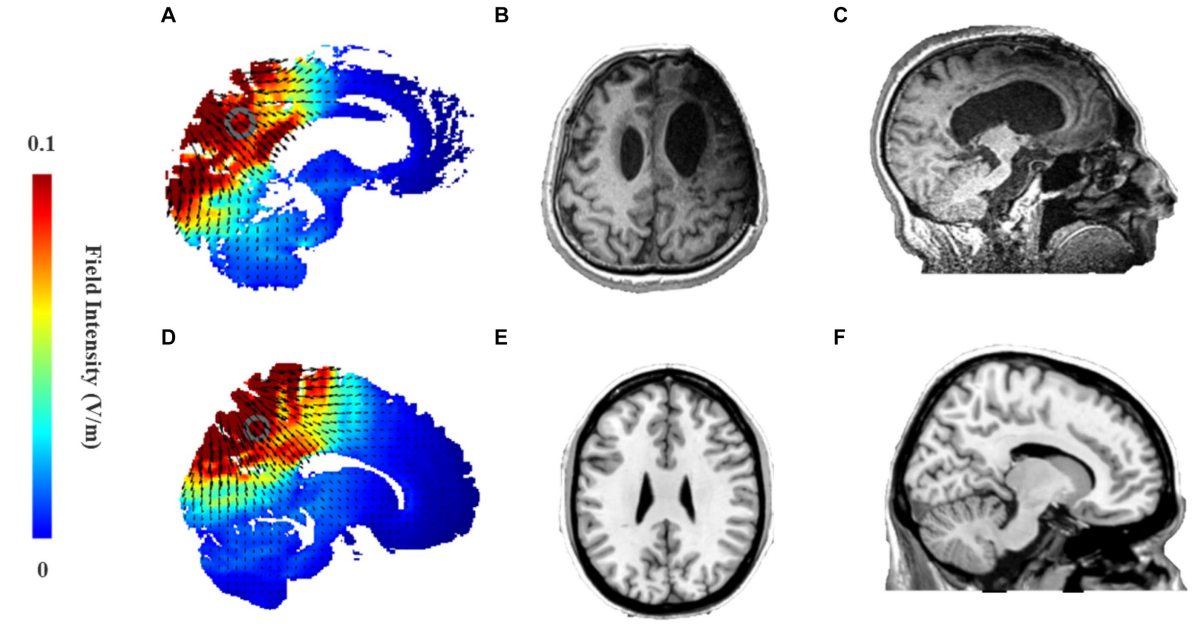


FIGURE 3
(A,D) Electric field intensity map in stimulation model from ROAST of 2.0 mA HD-tDCS that targets precuneus using Pz as the central stimulation electrode and Cz, P3, P4, POz as peripheral return electrodes. **(A)** Sagittal brain activation map of the MCS patient; **(D)** Sagittal brain activation map of Colin27 template; **(B,C)** Head MRI of an MCS patient caused by traumatic brain injury. **(B)** Axis plane; **(C)** Sagittal plan. **(E,F)** Head MRI of Colin27 standard template in the MRIcorn software. **(E)** Axis plane; **(F)** Sagittal plane.

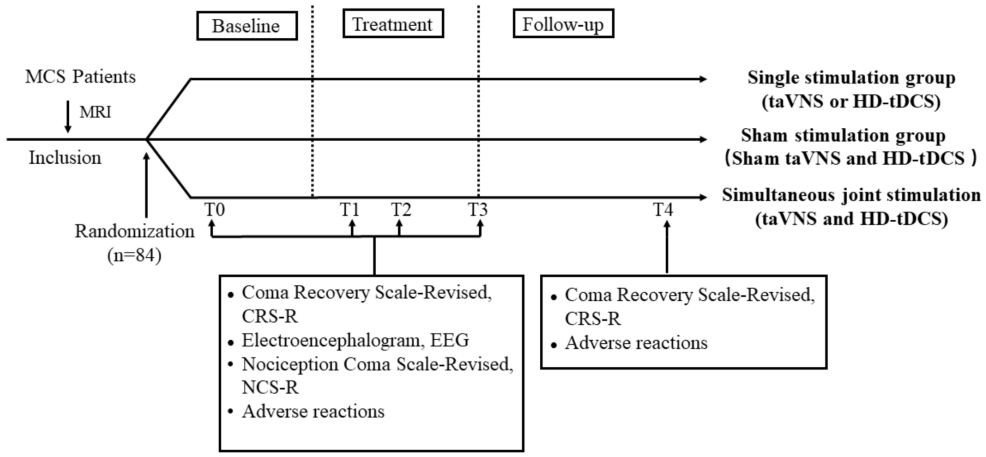


FIGURE 4
Treatment and data collection flow diagram. T0: 2 weeks before treatment; T1: 1 week of treatment; T2: 2 weeks of treatment; T3: 4 weeks of treatment; and T4: 3-month follow-up. MRI, magnetic resonance imaging; taVNS, transcutaneous auricular vagus nerve stimulation; HD-tDCS, high-definition transcranial direct current stimulation.

number of clusters will be determined by the meta-criterion (31). Subsequently, the spatial correlation coefficient between each original map and the microstate template maps will be calculated to determine the microstate category to which the original maps will belong. Then, the microstate time series will be smoothed with time frames set to 8 so that segments that are smaller than 30 ms will be rejected. In the end, four parameters of the EEG microstate will be calculated.

(1) Duration: the average duration for which a microstate remains stable.
(2) Occurrence: the mean occurrences of a microstate per second.
(3) Coverage: the duration of a microstate divided by the total duration of all microstates.
(4) Probability: the probability that a microstate transits to another microstate.

Follow-up period

Each patient will be followed up for 3 months (T4) after the end of treatment to observe residual effects and delayed adverse effects.

Follow-up visits will include outpatient visits, video calls, home visits, and surrogate assessments by other healthcare organizations. The follow-up will include an assessment of CRS-R and a recording of adverse effects. The frequency of follow-up will be every 2 weeks for the first month and once a month thereafter.

Data safety and management

The medical history, demographic data, behavioral data, MRI data, and EEG data of all patients will be stored in the departmental computer database by the study leader. The Ethics Committee of Beijing Tiantan Hospital will regularly check data security.

Statistical analysis

IBM SPSS Statistics 26 software will be used for statistical analysis. The measurement data will be tested for normal distribution by using Kolmogorov-Smirnov tests. Data conforming to a normal distribution will be analyzed by ANOVA or repeated measures ANOVA for differences in each treatment group. Data not conforming to a normal distribution will be analyzed by the Kruskal-Wallis H test or Friedman test. *Post hoc* tests will be carried out with Bonferroni. Count data will be expressed as cases or percentages, and differences between groups for count data with all theoretical frequencies greater than 5 will be tested by the chi-square test, otherwise, Fisher's exact test will be used. $p < 0.05$ will be considered to indicate statistically significant differences.

Discussion

With the advancement of technology, more and more NIBS techniques are being developed and applied in the treatment of patients with DOC, and are divided into two main categories according to the different targets. One is top-down NIBS techniques such as tDCS and repetitive transcranial magnetic stimulation (rTMS). They regulate cortical activity levels via a cortico-thalamo-cortical feedback loop (32). The other is bottom-up NIBS techniques, including taVNS and ultrasound deep brain stimulation. They intervene directly in the thalamus, and signals are further projected along ascending fibers to extensive cortical regions (8, 33). However, these single NIBS techniques of the treatment mechanisms and modulation paradigms are still being explored. Therefore, the overall effective rate is still low (34, 35).

In response, many researchers have begun to experiment with single-technique multi-targeted combined stimulation or multiple-technique combined stimulation modulation paradigms (17, 36). A study reported that an MCS patient showed object recognition, movement to command, and significant non-functional communication after 2 weeks of SJS of tDCS and rTMS targeting inferior parietal lobes (IPL). The patient's CRS-R improved from 9 to 19 at the end of the follow-up. Meanwhile, they found that the improvement in CRS-R was accompanied by increased activities of IPL and PCC and improved connectivity in posterior brain regions (37). In addition, another study in 2021 reported that 30 healthy subjects had significantly stronger activation in the bilateral thalamus, pallidum, parahippocampal gyrus, dorsal raphe nucleus, and substantia nigra after SJS of taVNS and tDCS compared to any single stimulation, suggesting a significant synergistic effect (38). Thus, combined NIBS techniques are expected to break the upper limit of the effect of single modulation techniques.

The frontoparietal network, which is closely related to the recovery of consciousness, is composed mainly of two subnetworks: the executive control network (ECN) and the DMN (1). There is extensive competition between the two networks, which is necessary for flexible switching of attention. The ECN is responsible for external perception tasks. In contrast, the DMN is mainly involved in internal attention-directed cognitive processing such as autobiographical recall, imagining the future, and planning. Key nodes of DMN are divided into the medial prefrontal cortex in the anterior brain region and the precuneus/PCC and the inferior parietal lobe in the posterior brain region. It was reported that internal connectivity in DMN was significantly lower in VS/UWS than in MCS (39). Further study of the transient analysis found that disrupted functional connectivity in the alpha band of the anterior state between PCC and medial prefrontal cortex was accompanied by decreased level of consciousness, while high functional connectivity between the two regions indicated a positive prognosis in the distant future (40, 41). Thus, the interconnection of the two key anterior and posterior nodes within the DMN plays a key role in the generation of consciousness.

The precuneus is part of the superior parietal lobe and is located in the medial cerebral hemisphere. As mentioned in the introduction, it is hard for tDCS with low spatial resolution to focus current into the deep cortex. A recent study showed that HD-tDCS over Pz was able to activate the precuneus/PCC to improve memory retrieval performance in healthy subjects (42). As for patients with DOC, severe brain injuries often led to extensive damage and deformation of brain structures. The anterior forebrain mesocircuit was shown to be vulnerable to multifocal brain injuries due to widespread anatomical connections, while the posterior brain regions were shown to be more likely to be well-preserved (1, 21). To clarify the depth of stimulation of HD-tDCS over Pz in patients with DOC, we enrolled an MCS patient. His left frontotemporal lobe was severely damaged (Figure 3B), but there was only slight atrophy in the posterior brain regions compared to healthy subjects (Figures 3C,F). Then, his simulation modeling from ROAST demonstrated that 2 mA HD-tDCS could still effectively activate the less damaged PPC and precuneus (Figure 3A). Most studies have also generally found that HD-tDCS over Pz can effectively enhance information processing in posterior brain regions to promote recovery of consciousness (43, 44).

Based on the aforementioned theories and evidence from previous clinical studies, we propose to use taVNS to increase the excitability of the anterior forebrain mesocircuit and utilize HD-tDCS to strengthen the activities in the precuneus to facilitate the reconstruction of the frontoparietal network. Finally, SJS of taVNS and HD-tDCS will help the cortical and subcortical networks interconnect with the thalamus as the hub to reproduce the complete consciousness network.

The protocol will include only MCS patients because they have better neural plasticity and benefit more from taVNS and HD-tDCS compared to VS/UWS (9, 44). In addition, the duration of treatment is a key factor influencing the outcome. A meta-analysis summarized eight clinical studies of tDCS for DOC and found better outcomes in patients who received more than five repeated tDCS sessions than

those who received only a single stimulation session (45). Wang et al. (9) used taVNS in 12 patients with DOC and none of them showed behavioral improvement after 2 weeks of treatment (9). In contrast, another study using a similar stimulation protocol but a longer stimulation time found that five patients regained consciousness, which might be due to the long-term potentiation of taVNS to increase excitatory synaptic connections (8). Therefore, 1 month was set as the treatment cycle in the study. For the primary outcome, we hypothesize that the SJS group will show a significant CRS-R increase after 2 weeks of treatment. This increase will be expected to reach its peak at 4 weeks post-treatment and remain during the 3-month follow-up. In contrast, the single stimulation group will show a significant increase in CRS-R only after 4 weeks of treatment compared to baseline. As for AEs, although tDCS and taVNS caused some mild or transient AEs, neither of them induced serious AEs. A review pointed out that the most common AEs of tDCS in patients with stroke were itching, burning sensation, headache, tingling, sleepiness, difficulty in concentration, mild fatigue, skin redness, and dizziness. Likewise, the most common AEs of taVNS were ear pain, headache, tingling, dizziness, skin redness, fatigue, prickling, pressure, itching, and unpleasant feeling (46–48). In this study, we will judge pain AEs by the NCS-R and observe bedside changes in patients' ears, scalp, expressions, and levels of arousal and sleep to detect their discomfort and fatigue because patients will be unable to subjectively report their symptoms. In addition, if patients exhibit great residual motor function (motor subscale of CRS-R $\geq$ 3), we will determine the areas of pain induced by stimulation according to the patient's performance on localization to noxious stimulation.

EEG was particularly suitable for bedside assessment of NIBS techniques in DOC because of its high temporal resolution and simplicity of operation. Microstate was a reliable method to assess dynamical changes of large-scale organized brain activity by clustering EEG topography (49). Most studies reported that four typical microstates (A–D) were sufficient to explain EEG resting activity. A microstate always remained relatively stable for 80–120 ms, and then it rapidly switched to another. The activity characteristic of the microstate was similar to the transient and metastable brain activation pattern of conscious activity (50). In the diagnosis of consciousness, microstate D was the best to classify VS/UWS and MCS patients among multiple quantitative indicators of resting-state EEG (51). Similarly, a study found that microstate D was more frequent in MCS compared to VS/UWS and was positively correlated with CRS-R. Further treatment of DOC by HD-tDCS for 2 weeks increased the frequency, duration, and coverage of microstate D in responders, while the duration and coverage of microstate C decreased (22) compared to the baseline. The latest study combined microstate C related to the salient networks and DMN (52) and microstate D related to the ECN as the L-R diagram. On the contrary, microstate A was related to the auditory network, and microstate B was related to the visual network, and both microstates were combined as the A-P diagram. It was found that the shorter duration of L-R diagrams and the higher incidence of A-P diagrams might reflect the higher-level language processing capacity of the brain in MCS (53). Therefore, microstate temporal dynamics features were reliable metrics to reflect the residual dynamic conscious activity of patients with DOC at the whole brain level. Microstates C and D might be associated with higher cognitive processing activities.

In conclusion, we intend to utilize combined stimulation to activate the intact consciousness loop and investigate the efficacy and safety of the new stimulation paradigm for speeding up the recovery of consciousness in patients with DOC. The protocol will additionally use EEG microstates that reflect global transient neural activity to evaluate the intervention mechanism of SJS on the dynamic activity of thalamocortical and cortical-cortical neural networks. These findings, in combination with clinical outcomes, will guide the subsequent development and optimization of the stimulation paradigm of combined modulation for multiple brain regions. The ultimate goal will be to achieve stable improvement in consciousness and confirm the importance of frontoparietal high-level connectivity for the formation and recovery of consciousness.

Ethics statement

The study protocol involving humans was approved by The Ethics Committee of Beijing Tiantan Hospital. The protocol will be conducted in accordance with the local legislation and institutional requirements. The patient-authorized legal representative will provide their written informed consent to participate in this study.

Author contributions

JH: conceptualization. JH and PR: funding acquisition. YZ and WZ: methodology and writing. QL: validation. HJ and QG: visualization and revision. All authors contributed to the article and approved the submitted version.

Funding

The work was supported by the National Natural Science Foundation of China [No. 82272118 and 81771128] and the CACMS Innovation Fund [No. CI2021A03305].

Acknowledgments

All authors express their gratitude to Yanjun Wang for the literature search and to Guangxiao Ni for the sample size calculation.

Conflict of interest

The authors declare that the research will be conducted in the absence of any commercial or financial relationships that will be construed as a potential conflict of interest.

Publisher's note

References

1. Edlow BL, Claassen J, Schiff ND, Greer DM. Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies. *Nat Rev Neurol*. (2021) 17:135–56. doi: 10.1038/s41582-020-00428-x

2. Giacino JT, Kalmar K, Whyte J. The JFK coma recovery scale-revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil*. (2004) 85:2020–9. doi: 10.1016/j.apmr.2004.02.033

3. Wang L, Wang Y, Wang Y, Wang F, Zhang J, Li S, et al. Transcutaneous auricular vagus nerve stimulators: a review of past, present, and future devices. *Expert Rev Med Devices*. (2022) 19:43–61. doi: 10.1080/17434440.2022.2020095

4. Yu Y, Yang Y, Wang L, Fang J, Chen Y, He JH, et al. Transcutaneous auricular vagus nerve stimulation in disorders of consciousness monitored by fMRI: the first case report. *Brain Stimul*. (2017) 10:328–30. doi: 10.1016/j.brs.2016.12.004

5. Briand M-M, Gosseries O, Staumont B, Laureys S, Thibaut A. Transcutaneous auricular vagal nerve stimulation and disorders of consciousness: a hypothesis for mechanisms of action. *Front Neurol*. (2020) 11:933. doi: 10.3389/fneur.2020.00933

6. Osińska A, Rynkiewicz A, Binder M, Komendziński T, Borowicz A, Leszczyński A. Non-invasive Vagus nerve stimulation in treatment of disorders of consciousness – longitudinal case study. *Front Neurosci*. (2022) 16:834507. doi: 10.3389/fnins.2022.834507

7. Noé E, Ferri J, Colomer C, Moliner B, O'Valle M, Ugart P, et al. Feasibility, safety and efficacy of transauricular vagus nerve stimulation in a cohort of patients with disorders of consciousness. *Brain Stimul*. (2020) 13:427–9. doi: 10.1016/j.brs.2019.12.005

8. Yu Y, Yang Y, Gan S, Guo S, Fang J, Wang S, et al. Cerebral hemodynamic correlates of transcutaneous auricular vagal nerve stimulation in consciousness restoration: an open-label pilot study. *Front Neurol*. (2021) 12:684791. doi: 10.3389/fneur.2021.684791

9. Wang Y, Yang Y, Wang Y, Zhang J. Transcutaneous auricular vague nerve stimulation improved brain connection activity on patients of disorders of consciousness: a pilot study. *J Tradit Chin Med*. (2022) 42:463–71. doi: 10.19852/j.cnki.jtcm.2022.03.012

10. Gianlorenco ACL, de Melo PS, Marduy A, Kim AY, Kim CK, Choi H, et al. Electroencephalographic patterns in taVNS: a systematic review. *Biomedicine*. (2022) 10:2208. doi: 10.3390/biomedicines10092208

11. Mashour GA, Roelfsema P, Changeux J-P, Dehaene S. Conscious processing and the global neuronal workspace hypothesis. *Neuron*. (2020) 105:776–98. doi: 10.1016/j.neuron.2020.01.026

12. Schiff N. Mesocircuit mechanisms in the diagnosis and treatment of disorders of consciousness. *Presse Med*. (2022) 52:104161. doi: 10.1016/j.lpm.2022.104161

13. Xia X, Yang Y, Guo Y, Bai Y, Dang Y, Xu R, et al. Current status of Neuromodulatory therapies for disorders of consciousness. *Neurosci Bull*. (2018) 34:615–25. doi: 10.1007/s12264-018-0244-4

14. Rahman A, Reato D, Arlotti M, Gasca F, Datta A, Parra LC, et al. Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects: somatic and terminal origin of DCS effects. *J Physiol*. (2013) 591:2563–78. doi: 10.1113/jphysiol.2012.247171

15. Huang W, Wannez S, Fregni F, Hu X, Jing S, Martens G, et al. Repeated stimulation of the posterior parietal cortex in patients in minimally conscious state: a sham-controlled randomized clinical trial. *Brain Stimul*. (2017) 10:718–20. doi: 10.1016/j.brs.2017.02.001

16. Santos Ferreira I, Teixeira Costa B, Lima Ramos C, Lucena P, Thibaut A, Fregni F. Searching for the optimal tDCS target for motor rehabilitation. *J NeuroEng Rehabil*. (2019) 16:90. doi: 10.1186/s12984-019-0561-5

17. Zhang X, Liu B, Li Y, Duan G, Hou J, Wu D. Multi-target and multi-session transcranial direct current stimulation in patients with prolonged disorders of consciousness: a controlled study. *Front Neurosci*. (2021) 15:641951. doi: 10.3389/fnins.2021.641951

18. Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci*. (2001) 2:685–94. doi: 10.1038/35094500

19. Luppi AI, Craig MM, Pappas I, Finoia P, Williams GB, Allanson J, et al. Consciousness-specific dynamic interactions of brain integration and functional diversity. *Nat Commun*. (2019) 10:4616. doi: 10.1038/s41467-019-12658-9

20. Fridman EA, Beattie BJ, Broft A, Laureys S, Schiff ND. Regional cerebral metabolic patterns demonstrate the role of anterior forebrain mesocircuit dysfunction in the severely injured brain. *Proc Natl Acad Sci U S A*. (2014) 111:6473–8. doi: 10.1073/pnas.1320969111

21. Guo Y, Bai Y, Xia X, Li J, Wang X, Dai Y, et al. Effects of long-lasting high-definition transcranial direct current stimulation in chronic disorders of consciousness: a pilot study. *Front Neurosci*. (2019) 13:412. doi: 10.3389/fnins.2019.00412

22. Guo Y, Li R, Zhang R, Liu C, Zhang L, Zhao D, et al. Dynamic changes of brain activity in patients with disorders of consciousness during recovery of consciousness. *Front Neurosci*. (2022) 16:878203. doi: 10.3389/fnins.2022.878203

23. Han J, Chen C, Zheng S, Zhou T, Hu S, Yan X, et al. Functional connectivity increases in response to high-definition transcranial direct current stimulation in patients with chronic disorder of consciousness. *Brain Sci*. (2022) 12:1095. doi: 10.3390/brainsci12081095

24. Jang SH, Cho MJ. Transcutaneous auricular vagus nerve stimulation in disorders of consciousness: a mini-narrative review. *Medicine*. (2022) 101:e31808. doi: 10.1097/MD.0000000000031808

25. Ashizuka A, Mima T, Sawamoto N, Aso T, Oishi N, Sugihara G, et al. Functional relevance of the precuneus in verbal politeness. *Neurosci Res*. (2015) 91:48–56. doi: 10.1016/j.neures.2014.10.009

26. Huang Y, Datta A, Bikson M, Parra LC. (2018). ROAST: an open-source, fully-automated, realistic volumetric-approach-based simulator for TES. In: 40th annual international conference of the IEEE engineering in medicine and biology society (EMBC). Honolulu, HI: IEEE (2018). p. 3072–3075.

27. Schnakers C, Chatelle C, Vanhaudenhuyse A, Majerus S, Ledoux D, Boly M, et al. The nociception coma scale: a new tool to assess nociception in disorders of consciousness. *Pain*. (2010) 148:215–9. doi: 10.1016/j.pain.2009.09.028

28. Chatelle C, Majerus S, Whyte J, Laureys S, Schnakers C. A sensitive scale to assess nociceptive pain in patients with disorders of consciousness. *J Neurol Neurosurg Psychiatry*. (2012) 83:1233–7. doi: 10.1136/jnnp-2012-302987

29. Lehmann D, Skrandies W. Reference-free identification of components of checkerboard-evoked multichannel potential fields. *Electroencephalogr Clin Neurophysiol*. (1980) 48:609–21. doi: 10.1016/0013-4694(80)90419-8

30. Murray MM, Brunet D, Michel CM. Topographic ERP analyses: a step-by-step tutorial review. *Brain Topogr*. (2008) 20:249–64. doi: 10.1007/s10548-008-0054-5

31. Custo A, Van De Ville D, Wells WM, Tomescu MI, Brunet D, Michel CM. Electroencephalographic resting-state networks: source localization of microstates. *Brain Connect*. (2017) 7:671–82. doi: 10.1089/brain.2016.0476

32. Krone L, Frase L, Piosczyk H, Selhausen P, Zittel S, Jahn F, et al. Top-down control of arousal and sleep: fundamentals and clinical implications. *Sleep Med Rev*. (2017) 31:17–24. doi: 10.1016/j.smrv.2015.12.005

33. Cain JA, Spivak NM, Coetzee JP, Crone JS, Johnson MA, Lutkenhoff ES, et al. Ultrasonic deep brain neuromodulation in acute disorders of consciousness: a proof-of-concept. *Brain Sci*. (2022) 12:428. doi: 10.3390/brainsci12040428

34. Thibaut A, Schiff N, Giacino J, Laureys S, Gosseries O. Therapeutic interventions in patients with prolonged disorders of consciousness. *Lancet Neurol*. (2019) 18:600–14. doi: 10.1016/S1474-4422(19)30031-6

35. Feng Y, Zhang J, Zhou Y, Bai Z, Yin Y. Noninvasive brain stimulation for patients with a disorder of consciousness: a systematic review and meta-analysis. *Rev Neurosci*. (2020) 31:905–14. doi: 10.1515/revneuro-2020-0033

36. Bender Pape TL, Herrold AA, Livengood SL, Guernon A, Weaver JA, Higgins JP, et al. A pilot trial examining the merits of combining amantadine and repetitive transcranial magnetic stimulation as an intervention for persons with disordered consciousness after TBI. *J Head Trauma Rehabil*. (2020) 35:371–87. doi: 10.1097/HTR.0000000000000634

37. Lin Y, Liu T, Huang Q, Su Y, Chen W, Gao D, et al. Electroencephalography and functional magnetic resonance imaging-guided simultaneous transcranial direct current stimulation and repetitive transcranial magnetic stimulation in a patient with minimally conscious state. *Front Neurosci*. (2019) 13:746. doi: 10.3389/fnins.2019.00746

38. Sun JB, Tian QQ, Yang XJ, Deng H, Li N, Meng LX, et al. Synergistic effects of simultaneous transcranial direct current stimulation (tDCS) and transcutaneous auricular vagus nerve stimulation (taVNS) on the brain responses. *Brain Stimul*. (2021) 14:417–9. doi: 10.1016/j.brs.2021.02.010

39. Amiri M, Fisher PM, Raimondo F, Sidaros A, Cacic Hribljan M, Othman MH, et al. Multimodal prediction of residual consciousness in the intensive care unit: the CONNECT-ME study. *Brain*. (2023) 146:50–64. doi: 10.1093/brain/awac335

40. Bai Y, He J, Xia X, Wang Y, Yang Y, di H, et al. Spontaneous transient brain states in EEG source space in disorders of consciousness. *NeuroImage*. (2021) 240:118407. doi: 10.1016/j.neuroimage.2021.118407

41. Lemaire JJ, Pontier B, Chaix R, El Ouadih Y, Khalil T, Sinardet D, et al. Neural correlates of consciousness and related disorders: from phenotypic descriptors of behavioral and relative consciousness to cortico-subcortical circuitry. *Neurochirurgie*. (2022) 68:212–22. doi: 10.1016/j.neuchi.2021.05.003

42. Huang Y, Mohan A, McLeod SL, Luckey AM, Hart J, Vanneste S. Polarity-specific high-definition transcranial direct current stimulation of the anterior and posterior default mode network improves remote memory retrieval. *Brain Stimul*. (2021) 14:1005–14. doi: 10.1016/j.brs.2021.06.007

43. Zhang C, Han S, Li Z, Wang X, Lv C, Zou X, et al. Multidimensional assessment of electroencephalography in the neuromodulation of disorders of consciousness. *Front Neurosci*. (2022) 16:903703. doi: 10.3389/fnins.2022.903703

44. Zhang R, Zhang L, Guo Y, Shi L, Gao J, Wang X, et al. Effects of high-definition transcranial direct-current stimulation on resting-state functional connectivity in patients with disorders of consciousness. *Front Hum Neurosci*. (2020) 14:560586. doi: 10.3389/fnhum.2020.560586

45. Xu Z, Zheng R, Xia T, Qi Z, Zang D, Wang Z, et al. Behavioral effects in disorders of consciousness following transcranial direct current stimulation: a systematic review

and individual patient data meta-analysis of randomized clinical trials. *Front Neurol*. (2022) 13:940361. doi: 10.3389/fneur.2022.940361

46. Russo C, Souza Carneiro MI, Bolognini N, Fregni F. Safety review of transcranial direct current stimulation in stroke. Neuromodulation: Technology at the Neural. *Interface*. (2017) 20:215–22. doi: 10.1111/ner.12574

47. Kim AY, Marduy A, De Melo PS, Gianlorenco AC, Kim CK, Choi H, et al. Safety of transcutaneous auricular vagus nerve stimulation (taVNS): a systematic review and meta-analysis. *Sci Rep*. (2022) 12:22055. doi: 10.1038/s41598-022-25864-1

48. Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al. Safety of transcranial direct current stimulation: Evidence based update. *Brain Stimul*. (2016) 9:641–61. doi: 10.1016/j.brs.2016.06.004

49. Liu Z, Si L, Xu W, Zhang K, Wang Q, Chen B, et al. Characteristics of EEG microstate sequences during propofol-induced alterations of brain consciousness states. *IEEE Trans Neural Syst Rehabil Eng*. (2022) 30:1631–41. doi: 10.1109/TNSRE.2022.3182705

50. Michel CM, Koenig T. EEG microstates as a tool for studying the temporal dynamics of whole-brain neuronal networks: a review. *NeuroImage*. (2018) 180:577–93. doi: 10.1016/j.neuroimage.2017.11.062

51. Stefan S, Schorr B, Lopez-Rolon A, Kolassa I-T, Shock JP, Rosenfelder M, et al. Consciousness indexing and outcome prediction with resting-state EEG in severe disorders of consciousness. *Brain Topogr*. (2018) 31:848–62. doi: 10.1007/s10548-018-0643-x

52. Xu J, Pan Y, Zhou S, Zou G, Liu J, Su Z, et al. EEG microstates are correlated with brain functional networks during slow-wave sleep. *NeuroImage*. (2020) 215:116786. doi: 10.1016/j.neuroimage.2020.116786

53. Gui P, Jiang Y, Zang D, Qi Z, Tan J, Tanigawa H, et al. Assessing the depth of language processing in patients with disorders of consciousness. *Nat Neurosci*. (2020) 23:761–70. doi: 10.1038/s41593-020-0639-1

Glossary

DOC	Disorders of consciousness
NIBS	Non-invasive brain stimulation
MCS	Minimally conscious state
taVNS	Transcutaneous auricular vagus nerve stimulation
HD-tDCS	High-definition transcranial direct current stimulation
CRS-R	Coma recovery scale-revised
NCS	Nociception coma scale
NCS-R	Nociception coma scale-revised
EEG	Electroencephalogram
SJS	Simultaneous joint stimulation
ARAS	Ascending reticular activating system
VS/UWS	Vegetative state/unresponsive wakefulness syndrome
MRI	Magnetic resonance imaging
ECN	Executive control network
DMN	Default mode network
rTMS	Repetitive transcranial magnetic stimulation
PPC	Posterior parietal cortex
PCC	Posterior cingulate gyrus
ROAST	Realistic volumetric approach to simulate transcranial electric stimulation

frontiers | Frontiers in Neurology

TYPE Study Protocol
PUBLISHED 02 October 2023
DOI 10.3389/fneur.2023.1243857

OPEN ACCESS

EDITED BY
Helena Knotkova,
MJHS Institute for Innovation in Palliative Care, United States

REVIEWED BY
Mariagiovanna Cantone,
Gaspare Rodolico Hospital, Italy
Pedro Jesús Serrano-Castro,
University of Malaga, Spain

*CORRESPONDENCE
Leonardo Boccuni
✉ boccunileonardo@gmail.com

RECEIVED 21 June 2023
ACCEPTED 04 September 2023
PUBLISHED 02 October 2023

CITATION
Boccuni L, Abellaneda-Pérez K, Martín-Fernández J, Leno-Colorado D, Roca-Ventura A, Prats Bisbe A, Buloz-Osorio EA, Bartrés-Faz D, Bargalló N, Cabello-Toscano M, Pariente JC, Muñoz-Moreno E, Trompetto C, Marinelli L, Villalba-Martinez G, Duffau H, Pascual-Leone Á and Tormos Muñoz JM (2023) Neuromodulation-induced prehabilitation to leverage neuroplasticity before brain tumor surgery: a single-cohort feasibility trial protocol. *Front. Neurol.* 14:1243857. doi: 10.3389/fneur.2023.1243857

Neuromodulation-induced prehabilitation to leverage neuroplasticity before brain tumor surgery: a single-cohort feasibility trial protocol

Leonardo Boccuni[1,2,3]*, Kilian Abellaneda-Pérez[1,2,3], Jesús Martín-Fernández[4,5,6], David Leno-Colorado[1,2,3], Alba Roca-Ventura[1,3,7], Alba Prats Bisbe[1,2,3], Edgar Antonio Buloz-Osorio[1,2,3,8], David Bartrés-Faz[1,7,9], Nuria Bargalló[9,10], María Cabello-Toscano[1,7,9], José Carlos Pariente[9], Emma Muñoz-Moreno[11], Carlo Trompetto[12,13], Lucio Marinelli[12,14], Gloria Villalba-Martinez[15], Hugues Duffau[4,16], Álvaro Pascual-Leone[17,18] and Josep María Tormos Muñoz[1,19] on behalf of the Neuromodulation-Induced Prehabilitation in Brain Tumour Surgery Group

[1]Institut Guttmann, Institut Universitari de Neurorehabilitació adscrit a la UAB, Badalona, Barcelona, Spain, [2]Universitat Autònoma de Barcelona, Bellaterra, Barcelona, Spain, [3]Fundació Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol, Badalona, Barcelona, Spain, [4]Department of Neurosurgery, Hôpital Gui de Chauliac, Montpellier, France, [5]Department of Neurosurgery, Hospital Universitario Nuestra Señora de Candelaria, Tenerife, Spain, [6]Department of Basic Medical Sciences, Universidad de La Laguna, Tenerife, Spain, [7]Department of Medicine, Faculty of Medicine and Health Sciences, Institute of Neurosciences, University of Barcelona, Barcelona, Spain, [8]Department of Morphological Sciences (Human Anatomy and Embriology Unit), Faculty of Medicine, Universitat Autònoma de Barcelona, Bellaterra, Barcelona, Spain, [9]Institut de Recerca Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain, [10]Centre de Diagnòstic per la Imatge Clínic, Hospital Clínic de Barcelona, Barcelona, Spain, [11]Experimental 7T MRI Unit, Magnetic Resonance Imaging Core Facility, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, [12]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genova, Italy, [13]Department of Neuroscience, Division of Neurorehabilitation, IRCCS Ospedale Policlinico San Martino, Genova, Italy, [14]Department of Neuroscience, Division of Clinical Neurophysiology, IRCCS Ospedale Policlinico San Martino, Genova, Italy, [15]Department of Neurosurgery, Hospital del Mar, Barcelona, Spain, [16]Institute of Functional Genomics, University of Montpellier, CNRS, INSERM, Montpellier, France, [17]Hinda and Arthur Marcus Institute for Aging Research and Deanna and Sidney Wolk Center for Memory Health, Hebrew Senior Life, Boston, MA, United States, [18]Department of Neurology, Harvard Medical School, Boston, MA, United States, [19]Centro de Investigación Traslacional San Alberto Magno, Facultad de Medicina y Ciencias de la Salud, Universidad Católica de Valencia San Vicente Mártir, Valencia, Spain

Introduction: Neurosurgery for brain tumors needs to find a complex balance between the effective removal of targeted tissue and the preservation of surrounding brain areas. Neuromodulation-induced cortical prehabilitation (NICP) is a promising strategy that combines temporary inhibition of critical areas (virtual lesion) with intensive behavioral training to foster the activation of alternative brain resources. By progressively reducing the functional relevance of targeted areas, the goal is to facilitate resection with reduced risks of neurological sequelae. However, it is still unclear which modality (invasive vs. non-invasive neuromodulation) and volume of therapy (behavioral training) may be optimal in terms of feasibility and efficacy.

Methods and analysis: Patients undertake between 10 and 20 daily sessions consisting of neuromodulation coupled with intensive task training, individualized based on the target site and neurological functions at risk of being compromised. The primary outcome of the proposed pilot, single-cohort trial is to investigate the feasibility and potential effectiveness of a non-invasive NICP protocol on neuroplasticity and post-surgical outcomes. Secondary outcomes investigating longitudinal changes (neuroimaging, neurophysiology, and clinical) are measured pre-NICP, post-NICP, and post-surgery.

Ethics and dissemination: Ethics approval was obtained from the Research Ethical Committee of *Fundació Unió Catalana d'Hospitals* (approval number: CEI 21/65, version 1, 13/07/2021). The results of the study will be submitted to a peer-reviewed journal and presented at scientific congresses.

Clinical trial registration: ClinicalTrials.gov, identifier NCT05844605.

KEYWORDS

brain tumor, neuro-oncology, prehabilitation, neuromodulation, neurorehabilitation, neurosurgery, neuroplasticity, clinical trial

Introduction

Neurosurgeons performing surgery for brain tumors face a complex dilemma: On the one hand, they must achieve the complete eradication of the tumor; on the other hand, they must preserve the healthy brain tissue surrounding the tumor (1). In fact, radical approaches have the advantage of removing a higher percentage of the tumor, but at the cost of increased risk for post-surgery functional impairments; more conservative approaches have less risks of functional deficits but expose patients to an increased likelihood of developing secondarities. In the last few years, it has been proposed to apply a conditioning intervention before surgery (prehabilitation) to modulate neuroplasticity (2, 3), called neuromodulation-induced cortical prehabilitation (NICP) (4). The objective was to reduce the functional relevance of brain areas close to the tumor (critical areas) in favor of a more distributed brain network, functionally associated with the targeted area but anatomically distant from the tumor. This way, neurosurgeons may apply a more radical approach without the associated risk of functional impairments; from this perspective, it is argued that NICP could represent the optimal therapeutic intervention before intraoperative cortical–subcortical mapping to tailor the resection up to the functional boundaries (hopefully widened by previous neuroplastic changes induced with NICP) (3).

Pioneering efforts have been made in the field, with the publication of four articles (three case reports and one case series) where NICP was undertaken by a total of seven patients with brain tumor (2, 5–7). A common element was neuromodulation coupled with behavioral training: Neuromodulation provokes temporary inhibition (virtual lesion) of eloquent areas, while behavioral training (cognitive/speech or motor training) promotes the activation of alternative brain resources. By performing several sessions of intensive neuromodulation and task-specific training, long-term depression and long-term potentiation mechanisms determine the consolidation of neuroplastic changes before surgery (4, 8).

Notably, NICP by means of *non-invasive* neuromodulation was applied in only one patient, the first case report of NICP published by Barcia et al. (5). The patient (a 59-year-old woman) presented with dysnomia and was diagnosed with left-sided precentral oligodendroglioma (WHO II); during the first brain surgery, the tumor could not be completely removed because of the presence of active language areas. Nine months later, symptoms worsened because of tumor progression. Therefore, before a second surgery, the patient received 13 daily sessions of NICP, consisting of continuous repetitive transcranial magnetic stimulation (rTMS) over Broca's area immediately followed by 10 min of intensive speech training. MEG showed greater bilateralization during speech production, while fMRI with a similar paradigm did not show any change. Language function was temporarily affected after each rTMS session and improved over basal values after each speech training session; along the experiment language function improved, with rTMS having a progressively lower impact. Transient language deficits were present after the second surgery, recovered after 3 weeks, but did not achieve preoperative scores. Surgery was not performed with radical intent, given that an intraoperative biopsy indicated radiation necrosis. Afterward, the patient developed secondarities and died 3 months later.

Since this first case report, it has been inferred that NICP could promote neuroplastic and behavioral changes, but also that higher dosages or different modalities of intervention may have been required (5). In line with these hypotheses, subsequent studies applied radically different NICP protocols, where *invasive* neuromodulation (extraoperative direct cortical stimulation) was applied continuously (24 h a day) at maximal tolerable intensity, with the goal of inhibiting eloquent areas within or near the tumor. In a case series of five patients, Rivera et al. (2) performed first brain surgery, followed by NICP over 15–25 days of therapy, and finally a second surgery (2). During the first surgery, neurosurgeons removed as much tumor mass as possible based on results from cortical and subcortical intraoperative stimulation mapping, while at the same time implanting a grid

of subdural electrodes for intracranial electrical stimulation. The subsequent NICP protocol consisted of continuous intracranial stimulation over eloquent areas to inhibit their functionality (virtual lesion), while at the same time providing intensive behavioral training (several hours a day) to patients, to foster the activation of associated functional networks. After several weeks of prehabilitation, a second surgery was performed, where neurosurgeons removed the grid of electrodes and sought to eradicate an additional tumor mass. Results were promising: there was a marked reduction in the functional relevance of eloquent areas, so that during the second surgery, neurosurgeons could remove an additional percentage of tumor mass, without any permanent deficit. However, the main limitations were the need to perform two surgeries and the relatively high rate of adverse events (focal seizure, osteomyelitis, epidural abscess, intermittent myoclonus, and subdural hematoma) caused by surgery and by the presence of intracranial electrodes. More recently, Serrano-Castro et al. (7) published a case report of a 17-year-old patient with a neuroepithelial dysembryoblastic tumor in the left temporo-parietal region provoking refractory focal motor seizures (7), who undertook a similar protocol as described by Rivera-Rivera et al. (2) (first surgery, placement of intracranial electrodes for invasive neuromodulation during subsequent prehabilitation, and second definitive surgery to remove the tumor and the electrodes). However, the first craniotomy was intended specifically for placing electrodes, and NICP was performed for only 6 days, during which language training was provided very intensively (6 h a day). The outcomes were the development of functional activation in the homologous right Wernicke's area and no residual motor language function over the tumor region. Such neuroplastic changes made possible to perform complete tumor eradication, and the patient has since then (at least 1 year) been seizure-free, with no neurological symptoms.

To summarize, seminal results from previous studies indicate that NICP is capable of clinically meaningful neuroplastic changes, although the optimal modality and dosage of therapy remain to be elucidated (4). On the one hand, invasive modalities allow intensive and prolonged inhibition of cortical activity over targeted areas, resulting in meaningful neuroplastic changes, but at the cost of additional surgery and an increased rate of adverse events (2). On the other hand, non-invasive neuromodulation is relatively safe and feasible but has shown less convincing results regarding neuroplasticity (5). However, non-invasive NICP was investigated in only one patient receiving a small, and perhaps insufficient, volume of intervention; further cohort studies exploring different neuromodulation modalities and higher volumes of therapy are needed to determine the feasibility and effectiveness of non-invasive NICP (3, 4).

Therefore, the objectives of the present single-cohort, pilot feasibility trial were to investigate the feasibility (primary outcome) and effectiveness (secondary outcome) of a NICP protocol before brain surgery, consisting of daily sessions of non-invasive neuromodulation over critical areas, followed by intensive behavioral training. We include patients with brain tumors requiring elective neurosurgery. By performing non-invasive neuromodulation within safety guidelines (9), we hypothesize that the protocol is safe and well-tolerated by subjects, with no adverse events and high adherence to the treatment. Second, by comparing neural correlates pre- vs. post-prehabilitation, we will determine whether the intervention is effective in promoting a functional reorganization of the brain, similar to what has already been demonstrated for therapeutic applications of neuromodulation in stroke and other neurological disorders (10). Finally, we will report outcomes post-surgery and the individual's evolution in the long-term recovery phase. The main results will be disseminated by publishing an open-access original research article on the feasibility and effectiveness of non-invasive prehabilitation in neuro-oncology. Furthermore, we will create an online database of case reports with detailed information regarding prehabilitation, surgery, post-surgery rehabilitation, and the long-term evolution of each patient to inform the international community of neurosurgeons and other clinicians in the neurological field.

Methods and analysis

A schematic of the study protocol is outlined in Figure 1. The whole protocol has been developed according to the SPIRIT 2013 guidelines for protocols of clinical trials (11, 12).

Study settings

Patients on the waiting list for brain surgery are referred by neurosurgeons involved in the study. The principal investigator (JMTM) obtains written informed consent from patients wishing to be enrolled. Participants undertake an articulated, multidisciplinary protocol consisting of clinical, neurophysiological, and neuroimaging assessment, non-invasive brain stimulation, and intensive neurorehabilitation before surgery, neurosurgery, and neurorehabilitation post-surgery. Clinical assessments, neurophysiological investigations, and the whole prehabilitation program are performed at the *Guttmann Institute (Guttmann Barcelona – Brain Health and Neurorehabilitation, Barcelona, Spain)*. Neuroimaging assessment is performed at the *Unitat d'Imatge per Ressonància Magnètica IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer) at Hospital Clínic de Barcelona, Barcelona*. Neurosurgery is performed at the hospitals where the neurosurgeons involved in the study operate. Post-surgery neurorehabilitation is provided at the *Guttmann Institute (Institut Guttmann, Badalona, Spain)*.

Eligibility

Inclusion criteria are as follows: adults (age $\geq$ 18 years old) with a diagnosis of brain tumor requiring neurosurgery; ability to undertake at least 10 sessions of the prehabilitation protocol; tumor location posing the patient at risk of developing post-operative neurological deficits, for instance at the level of upper limb motor function and speech production; ability to understand the general purpose of the prehabilitation program and understand simple instructions; being willing to participate and sign the informed consent; being able to sit unassisted for 1 h.

Patients are excluded in cases of any contraindication for magnetic resonance imaging or transcranial magnetic stimulation (9); unstable medical conditions; musculoskeletal disorders

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
INTERVENTIONS:								
Prehabilitation				←	→			
Surgery							X	
ASSESSMENTS:								
Baseline:								
Not modifiable variables (birth date, gender, diagnosis etc.)	X	X						
Mobility, independency, quality of life			X			X		X
fMRI		X				X		X
TMS mapping		X				X		X
Clinical outcomes related to the intervention			X			X		X
Feasibility	X	X	X	X	X	X		
Surgical outcomes							X	

FIGURE 1
Schedule of enrollment, interventions, and assessments. Interventions at each time point of the study period: -t1 (enrollment): eligibility screen, informed consent, and baseline evaluation. t0 (allocation): fMRI and TMS mapping to determine whether to allocate patients in the prehabilitation program for upper limb or language training; baseline evaluation, if not performed at -t1; assessment of mobility, independency, and quality of life. t1: assessment before starting the prehabilitation protocol; assessment of clinical outcomes related to upper limb or language/cognitive function. t2: first session of prehabilitation. t3: last session of prehabilitation. t4: assessment after the end of the prehabilitation protocol; assessment of clinical outcomes related to the intervention, mobility, independency, quality of life, fMRI, and TMS mapping. t5: surgery. t6: surgical outcomes: intraoperative brain mapping, amount of tumor removed, adverse events, and post-surgery symptoms.

that may significantly affect functional training; severe speech and/or cognitive impairment; pain, depression, and fatigue that may significantly affect functional training; and a history of alcohol/drug abuse.

Primary and secondary outcomes

The primary outcome is the feasibility of the whole intervention, defined by the following parameters:

- Adherence to treatment: to define that the patient completed the protocol, at least 75% of the planned sessions should be performed.
- Retention: successful retention rate is reached if at least 75% of enrolled participants complete the prehabilitation program.
- Adverse events: absence of any adverse event attributable to the prehabilitation program, except for expected transient mild symptoms previously reported for neuromodulation (headache, syncope, and skin irritation) or motor training (mild pain and fatigue).
- Patient's satisfaction: At the end of the protocol, participants fill out questionnaires evaluating the patient's satisfaction with the treatments received (13).

Secondary outcomes are related to exploratory analyses of the effectiveness and potential mechanisms of action of the proposed intervention. We investigate changes from baseline regarding clinical outcomes, fMRI, and TMS mapping. Notably, the goal of the intervention is to reduce the functional relevance of targeted areas because of compensatory activation of other brain resources within the same functional network. Slow-growing tumors already demonstrated that similar neuroplastic changes may occur, with the tumor mass progressively interfering with the functionality of critical areas, while remote brain areas increase their activation; such compensatory mechanisms may explain why these types of tumors are asymptomatic and without any functional deficits in the initial phases (14, 15). From this perspective, the prehabilitation program could be considered a method to artificially optimize and accelerate this neuroplastic adaptation for therapeutic purposes (3). Therefore, we do not expect significant changes regarding clinical outcomes, whereas we consider changes in neuroimaging and neurophysiology outcomes as indicators for the effectiveness of the prehabilitation program.

Brain tumor classification and surgical outcomes

For oncological patients, tumor classification is based on the 2021 WHO Classification of Tumors of the Central Nervous System, which represents the most updated taxonomy of brain tumors, and the first classification system considering molecular profiling together with histology (16). Surgical outcomes consider results from intraoperative brain mapping, the absolute and relative amount of tumor removed, adverse events, and neurological status post-surgery.

Measurement of motor function, independency, and quality of life

Clinical assessments of upper limb motor function include the following measurements:

- Nine-Hole Peg Test (9HPT) evaluates manual dexterity (17, 18). A dedicated platform is placed in front of the patient, with nine pegs inside a container on the side to be evaluated, and nine holes on the other side. The patient is asked to place pegs into the holes and then put them back in the container, as fast as possible; they are allowed to perform a practice trial before the test trial. The therapist has a stopwatch to measure the time to complete the task and instructs the patient in case of errors (more than one peg picked up at the same time, pegs dropped on the table/floor, etc.). Excellent inter-rater and intra-rater reliability (19, 20) and sensitivity to change have been reported for patients with multiple sclerosis and other neurological disorders (20, 21).
- Fugl–Meyer upper extremity (FM-UE) evaluates upper limb motor impairment, from reflex activity to voluntary motor control out of synergies (22). There are four separate sections, for the assessment of motor function at the level of the arm, the wrist, the hand, and speed–tremor coordination during a finger-to-nose task. Each item is scored as 0, 1, or 2, with a total score ranging from 0 to 66, with lower scores indicating more severe motor impairment. Excellent intra- and inter-rater reliability has been established (23), together with other psychometric measures related to validity, sensitivity, and responsiveness to change (24–26).
- Shoulder abduction finger extension (SAFE) is a quick clinical assessment of upper limb strength, defined as the ability to perform abduction of the shoulder and extension of the index finger; it has potentially high prognostic value for neurological disorders, such as stroke (22). Scoring is usually based on the Medical Research Council scale, ranging from 0 (no visible muscle contraction) to 5 (normal). For the present study, we consider the corresponding items from FM-UE (27).
- To quantify the strength of the hand grip, we use an electronic hand dynamometer. According to the standardized setup, patients are holding the dynamometer while sitting, shoulder adducted and neutrally rotated, elbow at 90-degree flexion, and forearm halfway between pronation and supination (28). They are asked to perform a maximal grip strength effort for 3 s, rest for 60 s, and then repeat the measurement two more times; the average of the three trials is used as the most reliable test result (29). Excellent test–retest reliability has been established (30).
- Reaction time tasks are useful to measure the efficiency of basic processes for perception and response execution. For the present study, we use the Deary–Liewald reaction time task, a freely available program with established validity and reliability (31). In the simple reaction task paradigm, the patient is facing a blue computer screen with one white window in the center, and the index finger of the hand that is being evaluated over the space bar. The instruction is to click on the space bar as soon as an 'X' appears on the white window; practice trials are allowed before the test trial, which consists of 20 stimuli with a random interval (1–3 s) in between. In the choice reaction task paradigm, there is a similar setup; this time there are four white windows aligned in the center of the screen, and the patient is holding the fingers over the four corresponding letters of the keyboard. Every stimulus consists of an "X" appearing randomly in one of the four windows; patients are instructed to click the corresponding letter as soon as possible. Practice trials are allowed before the formal test trial. For the present study, we adapted the program of reaction time tasks to evaluate one hand at a time without stringent time constraints.

For lower limb motor function, balance, mobility, independency, and quality of life, we consider the following measurements:

- Fugl–Meyer lower extremity: assessment of lower limb motor impairment (22). Each item is scored 0, 1, or 2, with a total score ranging from 0 to 34; low scores are indicative of more severe motor impairment. Excellent reliability has been established for the assessment of motor function after stroke (32).
- Brunel balance assessment: assessment of balance based on 12-item hierarchical tasks, from sitting with arm support to stepping over a step, with excellent reliability and responsiveness to change (33).
- Six-min walking test: submaximal test of aerobic capacity (34, 35). The patient is instructed to walk along a straight path for 6 min, with the goal of covering the longest distance possible within 6 min. Patients are allowed to walk, independently or with the use of assistive devices, and to take rests while standing. Running, sitting, or receiving physical assistance from the therapist (other than help for balance) is not allowed. For the present study, we use a 25-meter path, with visible turning points at the beginning and the end.
- Dual-task assessment is performed, to investigate the interference between cognitive and motor tasks, in particular counting backward three by three during standing balance and gait.
- Neurologic Assessment in Neuro-Oncology (NANO) scale, for the evaluation of neurological functional status in patients with brain tumor (36);
- Karnofsky Performance Status (KPS), for the classification of oncological patients based on the severity of symptoms and their impact on functional independency (37).
- EORTC-QLQ-C30: questionnaire of quality of life for oncological patients (38, 39).
- BN20: EORTC brain cancer module, assessing quality of life specifically for patients with brain tumor (40).
- FA12: EORTC module assessing the impact of fatigue on quality of life for oncological patients (41).

Measurement of language/cognitive function

For the clinical evaluation of language and the rest of higher cognitive functions, subtests from the following batteries and neuropsychological tests are used:

- Revised Barcelona Test (TB-R) (42): battery of neuropsychological tests with the aim of assessing high cognitive functions.
- WAIS-III Wechsler Adult Intelligence Scale (43): global intelligence scale for adults that allows for obtaining verbal, manipulative, and total intelligence quotients, as well as indicators of verbal comprehension, perceptual organization, working memory, and processing speed.
- Trail Making Test (44): test used to assess visual attention, sequencing, flexibility, and graphomotor ability. It consists of two parts. In the first part, the subject must place numbers in order along a line; in the second part, the task is to place numbers and letters alternately, in an orderly way.
- Continuous Performance Test-III (CPT-III) (45): computerized test that assesses sustained attention. The subject must press a key whenever a non-target letter appears (if the target is the letter "x," it should not be pressed).
- Rey Auditory Verbal Learning Test (46): test assessing auditory verbal memory. Fifteen words are read aloud to the subject, who is then asked to repeat as many words as they remember. The procedure is repeated four more times. After some time, a delayed recall of the list is made, and finally, a recognition test is carried out.
- WMS-IV Wechsler Memory Scale (47): scale to assess memory functions.
- Symbol Digit Modalities Test (46): test of attention and visual tracking, concentration, and psychomotor speed. An answer sheet divided into boxes is presented, in which the stimuli are made up of a sequence of geometric figures with a number assigned to each one. The subject must write the number corresponding to each figure in the relevant box, as quickly as possible.
- PMR verbal fluency by letter (48): test assessing lexical access and verbal fluency, in which the subject is asked to say as many words beginning with "P" as they can, within 1 min. The same instructions are given for the letters "M" and "R".
- Hayling test (49): test that evaluates behavioral regulation, initiation speed, and response inhibition. In the first part, the subject is asked to complete a series of sentences as quickly as possible. In the second part, the subject must complete the sentence with a non-obvious word based on the context.
- Wisconsin Card Sorting Test (50): test evaluating executive function, in particular mental flexibility and abstract reasoning. Four stimulus cards are presented, with different shapes, colors, and number of figures (categories). The subject must match each card in the deck with one of the four key cards (without being told how to do this). The participant only receives feedback on whether the match is correct or incorrect.

Bilingualism is tested by means of a questionnaire (51). Each participant is going to be self-rated on a 4-point scale on the abilities of comprehension, Reading, writing, fluency, and pronunciation for each language (1 = poor, 2 = regular, 3 = good, and 4 = perfect). In addition, a laterality test is included, the Edinburgh Handedness Inventory (52), as well as a questionnaire to assess anxiety and depression, the Hospital Anxiety and Depression Scale (53).

Neuroimaging

Magnetic resonance imaging (MRI) is acquired to assess anatomical and functional (fMRI activation maps) brain changes due to intervention and surgery. For instance, the development of novel activation sites distant from the surgical target may indicate that NICP was effective in promoting a reduction of functional relevance for targeted areas, in favor of a more distributed network. Therefore, all patients undergo three identical MRI sessions: (1) before NICP, (2) after NICP but before surgery, and (3) after surgery. Each session consists of MRI data acquisition using a 3 Tesla Siemens PRISMA scanner and a 32-channel head coil. The protocol includes accelerated multiband sequences adapted from the Human Connectome Project and provided by the

Center of Magnetic Resonance Research (CMRR) at the University of Minnesota.

Regarding anatomical acquisitions, a high-resolution T1-weighted structural image is obtained with a magnetization-prepared rapid acquisition gradient-echo (MPRAGE) three-dimensional protocol, in which in an ascending fashion a total of 208 contiguous axial slices are obtained [repetition time (TR) = 2400 ms, echo time (TE) = 2.22 ms, inversion time = 1000 ms, flip angle = 8°, field of view (FOV) = 256 mm and 0.8 mm isotropic voxel]. In the same session, a high-resolution multishell diffusion-weighted MRI scan is obtained. This scan consists of two multiband acquisitions (anterior–posterior; acceleration factor = 4), sensitized in 99 monopolar directions with a b-value of 3000 s/mm2 in an echo-planar imaging sequence [TR = 3230 ms, TE = 89.20 ms, section thickness = 1.5 mm, voxel size = 1.5 × 1.5 × 1.5 mm, FOV = 210 mm].

In terms of quantifying brain function, resting-state and task functional MRI (fMRI) are acquired. Both consist of high-resolution multiband (anterior–posterior phase-encoding, acceleration factor = 8) interleaved acquisitions [T2*-weighted EPI scans, TR = 800 ms, TE = 37 ms, 750 volumes, 72 slices, slice thickness = 2 mm, FOV = 208 mm]. First, resting-state fMRI is acquired while the patient is instructed to keep his eyes closed and remain still without falling asleep.

Then, task fMRI is acquired during three language and three motor paradigms, which adhere to the following procedures:

- Word generation task: Block paradigm consisting of five cycles. Each cycle comprises 30 s of rest followed by 30 s during which the participant must mention words starting with a certain letter. These letters are "F", "A", "S", "M", and "E", in this same order.
- Semantic decision task: Block paradigm consisting of five cycles. Each cycle comprises 30 s of rest followed by 30 s during which the participant must mention objects from certain places: school, kitchen, car, house, and hospital.
- Comprehensive auditory task: Block paradigm consisting of three cycles. Each cycle comprises a 30 s block, in which a story is narrated in a made-up language (inactive/rest block/condition), followed by another 30 s block, in which a story is narrated in Spanish (active block/condition).
- Finger tapping task: Block paradigm consisting of three cycles. Each cycle comprises a 30 s block, in which the patient is asked to do a fingering exercise (tap each finger with the thumb) in the corresponding hand, followed by another 30 s of rest.
- Ankle flexion task: Block paradigm consisting of three cycles. Each cycle comprises a 30 s block, in which the patient is asked to move the corresponding foot up and down slowly, followed by another 30 s of rest.
- Tongue movement task: Block paradigm consisting of three cycles. Each cycle comprises a 30 s block, in which the patient is asked to move the tongue in circles without opening the mouth, followed by another 30 s of rest.

TMS for assessment and modulation of brain function

Neuromodulation by means of TMS is used for assessment and therapeutic purposes, to both non-invasively estimate the excitability and modulate the plasticity of the cerebral cortex (Figure 2).

Typical assessments are single-pulse and paired-pulse protocols (54, 55). With single-pulse, it is possible to determine the resting motor threshold (RMT) and then measure contralateral peripheral response to suprathreshold motor evoked potentials (MEPs) during motor mapping of the upper limb, lower limb, and facial muscles. When a suprathreshold MEP is delivered over contralateral M1 during an isotonic muscle contraction, a cortical silent period (transient disruption of EMG activity) is visible immediately after the stimulus and is a measure of intracortical inhibitory circuitry. Other assessments of intracortical inhibition are investigated by paired-pulse protocols, such as short-interval and long-interval paradigms where the inter-stimulus interval is between 1–5 ms and 50–200 ms, respectively. By contrast, paired-pulse at intervals between 8 and 30 ms cause intracortical facilitation.

There are several paradigms of repeated TMS (rTMS) to promote neuroplastic changes (9, 56). Conventional rTMS has inhibitory effect at low frequency (≤1 Hertz) and excitatory effect at high frequency (>1 Hertz). For patterned (theta-burst stimulation, TBS) rTMS, inhibitory and excitatory effects result from continuous TBS and intermittent TBS, respectively. Stimulation parameters (stimulation intensity, number of pulses) and external factors (medications, drugs, mental status) may significantly alter or even reverse the effect of the neuromodulation (57, 58); therefore, treatment sessions should be performed in standard conditions and following specific protocol parameters.

Neurophysiological assessment

By performing neuronavigated TMS mapping, we compare the anatomical distribution of active targets pre- vs. post-intervention. The same targets and intensity of stimulation defined at baseline are used at the end of the intervention, to allow comparisons. A figure of 8 coil (MagPro Cool B65-AP-RO Coil) connected to a transcranial magnetic stimulator (MagVenture MagPro x100) is driven by a robotic arm (Axilum Robotics TMS-Cobot) controlled manually or through a dedicated neuronavigation software (Brainsight TMS neuronavigation). We apply biphasic current with an anterior–posterior followed by a posterior–anterior current direction in the brain; the TMS coil is held tangential to the scalp, the handle pointing backward with a 45-degree deviation from the sagittal plane. For curvilinear 3D brain reconstruction (MNI coordinates), participant's structural and functional MRI data are uploaded. Grids of targets (inter-target distance: 10 mm) are defined based on anatomical landmarks for the subsequent motor/language mapping protocol and to determine the hotspot for neuromodulation. Grids are placed in correspondence with the primary sensorimotor and premotor areas (motor mapping) and over the pars triangularis and the gyrus supramarginalis (language mapping).

The procedure for motor and language mapping (at baseline and at the end of the prehabilitation program) is as follows:

Set up. The patient is seated on an electromechanics treatment chair to ensure comfort and stability during the assessment. An optic tracker (Polaris Vicra) detects trackers for 3D localization of the Cobot, the patient (a Brainsight Adhesive Subject Tracker

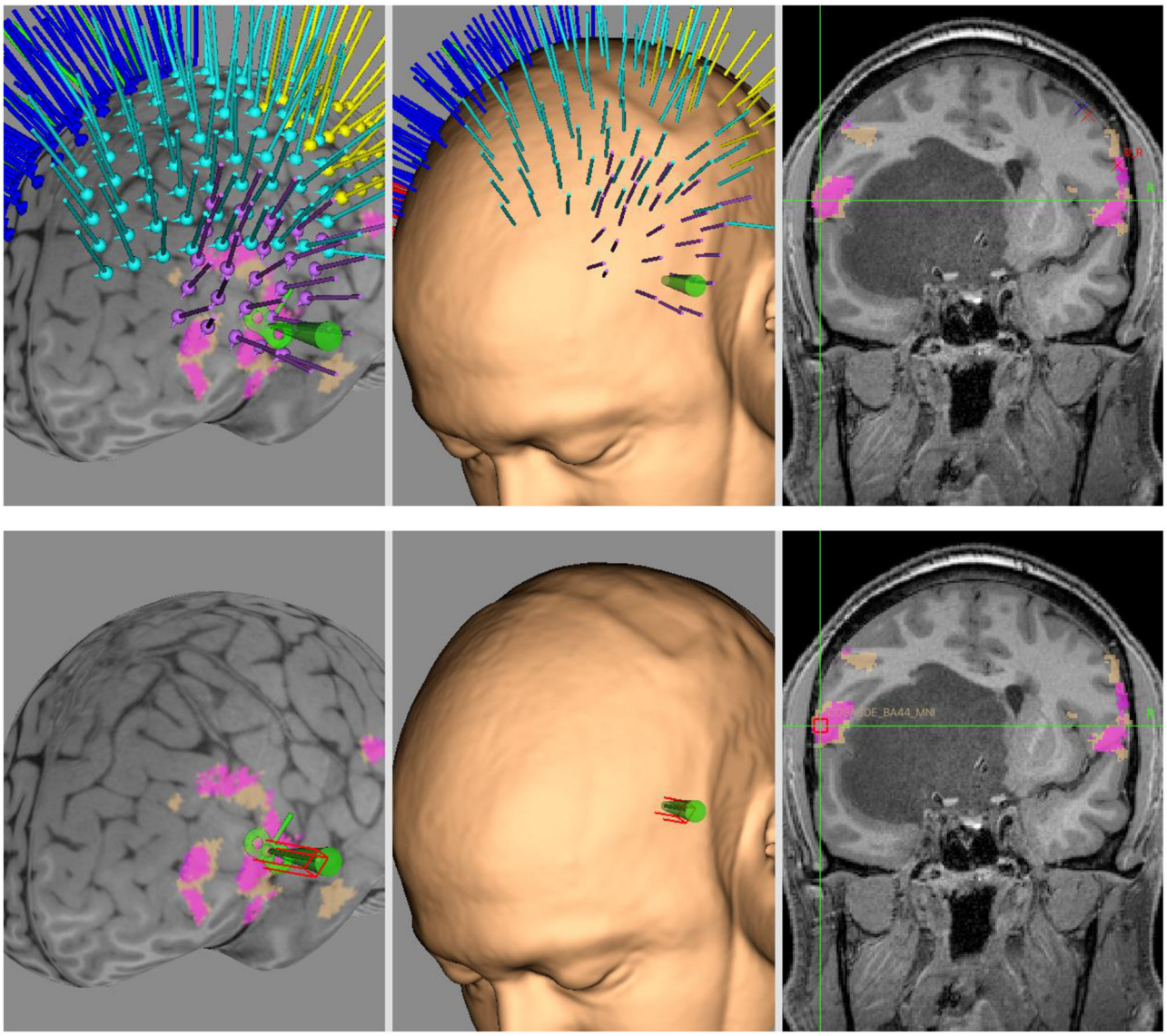


FIGURE 2
Neuronavigated TMS mapping and neuromodulation. Example of Brainsight project developed for neuronavigated TMS mapping of motor and language functions (upper row) and for subsequent neuromodulation by means of low-frequency rTMS (lower row). In this case, a patient with subcortical frontotemporal tumor undertook NICP for language function, with the target of stimulation based on MNI coordinates of peak fMRI activity for ipsilesional semantic decision task. The overlays in fuchsia and beige are clusters of fMRI for word generation task and semantic decision task, respectively.

is attached to the patient's forehead), and the pointer (Brainsight P-970, for the registration of anatomical landmarks). After skin preparation (alcohol swab), self-adhesive electrodes for EMG recording are attached bilaterally to the olecranon (ground), the muscle belly of the first dorsal interosseus (FDI, negative electrode), and the muscle tendon of the FDI (positive electrode). A pillow is placed underneath the forearm of the side being assessed, to ensure that muscles are completely at rest during the protocol. PowerLab 8/35 and Quad Bio Amp (ADInstruments, data acquisition hardware devices) register the EMG response and send data to the dedicated software (ADInstruments, LabChart, data analysis software). Every time a TMS pulse is delivered, a trigger signal is sent automatically from the MagPro x100 to the PowerLab through a D-type 26-BNC interface cable, to initiate the recording of the EMG response. For language mapping, a screen for image presentation is placed in front of the patient. One computer runs Brainsight, while another computer runs LabChart and a dedicated MATLAB script for language mapping.

Mapping protocol. The whole protocol is performed for both the affected and unaffected sides. For motor mapping, the entire session is recorded in LabChart. A preliminary search of the hotspot is performed around the hand knob of the precentral gyrus, starting from an intensity of 35–40% and rising progressively up the intensity until stable MEPs (here defined as signals with peak-to-peak amplitude larger than 500 μV) are produced. Then, a formal hotspot search is performed, by applying five stimuli to

each selected target; the target showing the largest average MEPs is considered the hotspot to determine the RMT, defined as the lowest intensity capable of eliciting three MEPs (signals with peak-to-peak amplitude larger than 50 μV) out of six consecutive stimuli (5- to 10-s interval). Once RMT has been determined, motor mapping is performed by applying five stimuli for each target (120% RMT intensity, 5- to 10-s interval) as far as positive MEPs (signals with peak-to-peak amplitude larger than 50 μV) are detectable.

For language mapping, a speech disruption protocol is applied. Initially, patients are familiarized with pictures and instructed to name them as soon as they appear on a screen in front of them. Once it is verified that the patient can name pictures correctly, we start language mapping. rTMS (five pulses at 5 Hertz, 90% RMT) is delivered to each target, together with presenting a picture on the screen (picture presentation time: 500 ms; delay picture-rTMS: 0 ms). The order of target stimulations and picture presentations is pseudo-randomized. An audio/video recording of the patient's response (from 0 to 3000 ms after the first rTMS stimulus) is evaluated offline by a neuropsychologist unaware of the target that has been stimulated to determine whether there was an episode of speech arrest, anomia, or other speech disruption phenomena. The language protocol is repeated until each target receives rTMS three times. A dedicated MATLAB script is developed to automatically synchronize rTMS with picture presentation and audio–video recording.

Interventions

Patients are scheduled for a minimum of 10 and a maximum of 20 treatment sessions, distributed as one/two sessions each weekday. Each session consists of 30 min of neuromodulation (rTMS or tDCS) coupled with 60 min of intensive motor or language training. The decision on whether to provide rTMS or tDCS is individualized based on specific patient and lesion characteristics.

Notably, the coupling between neuromodulation and task training represents a therapeutic application of the concept of metaplasticity. In fact, metaplasticity has been defined as any change in the direction or degree of synaptic plasticity based on prior neural activity (59). A typical study design investigating metaplasticity applies multiple rTMS sessions within the same day (accelerated rTMS), with minutes/hours between sessions (60). Compared to single rTMS, it has been demonstrated that accelerated rTMS may produce additive strengthening of neuroplastic changes, both for excitatory (60) and inhibitory (61) paradigms. Another way of exploiting the therapeutic potential of metaplasticity is through the combination of rTMS with task training. Previous systematic reviews and randomized controlled trials have already demonstrated the beneficial effect of rTMS delivered before therapy for aphasia, lower limb, and upper limb motor function in stroke patients (62–64). In this perspective, for the present study, neuromodulation is the metaplastic 'primer' setting the direction and degree for subsequent neuroplastic changes promoted by intensive task training.

Neuromodulation – Navigated rTMS

rTMS is applied with the following parameters: waveform: monophasic; intensity: 90% resting motor threshold (RMT); pulse frequency: 1 Hertz; total number of pulses: 1800. The choice of the target is determined based on anatomical considerations and results from neurophysiological and neuroimaging assessments; hence, the area of highest activity among those structures anatomically located near the tumor is considered the target. For instance, by performing motor and language mapping, we could identify active targets at the level of targeted areas, such as the hand knob or sites where speech arrest was detected. We also consider the center of mass of fMRI mapping related to hand movement and speech production as potential hotspots for neuromodulation.

Neuromodulation – tDCS

In those cases of subcortical tumors potentially affecting a wider area and more than one function, tDCS is performed with the aim of inhibiting (cathodal stimulation) distributed areas related to functions potentially at risk of being compromised, while at the same time promoting the activation (anodal stimulation) of safer areas within the same functional network.

Training of functions at risk of being compromised

Training is performed immediately after inducing a virtual lesion, focusing on functions related to structures targeted by neuromodulation. Motor, language, and/or cognitive functions are selected at the beginning of the protocol, considering the anatomical location of the tumor, medical condition, and pattern of activation by each of the assessed functions in the fMRI.

Detailed design and monitoring of training sessions are gathered, including goals pursued in any session, assigned activity, number of repetitions, and performance.

Prehabilitation motor training

Patients undertake intensive motor training sessions soon after (TMS) or during (tDCS) neuromodulation, i.e., in the condition of a virtual brain lesion (targeted area temporarily inhibited). This way, the brain must recruit alternative resources, which cumulatively determine neuroplastic changes and a stable shift of functional activation patterns away from critical areas.

There is a potentially infinite range of activities that could be trained; to be systematic, we defined a taxonomy of exercises based on anatomical and functional domains. Considering, for instance, the upper limb, we decided to prioritize tasks based on proximal (reaching and hand orientation) or distal (finger individuation and manipulation) components of upper limb movements. Within each component, we consider the integration between upper limb motor function and other body segments and/or task domains. For instance, some tasks may be accomplished by using one arm or hand (unimanual), while others may require the cooperation of both limbs (bimanual coordination) or additional balance and/or cognitive challenges (sequence learning, motor memory, and dual task). The goal is to cover all aspects of upper limb functionality and possibly to promote network

connectivity of cortical–subcortical–cerebellar structures related to motor control and executive function, beyond the predominant activation of motor–premotor areas of the affected side (65–68).

Other important concepts of motor learning that we consider are task difficulty, task intensity, and task variability (69). Task difficulty refers to the type of challenge that we impose; for instance, speed, accuracy, the ability to isolate or integrate different motor, and/or cognitive tasks. Task intensity refers to the necessity of a high number of repetitions to promote neuroplastic changes associated with motor learning. Task variability is necessary to avoid patient boredom and generalize the benefits of the training; in fact, training always on the same task makes you proficient specifically on that task, while varying training conditions foster retention and generalization of learning to new tasks (70).

Finally, we should point out that most patients are relatively young adults with limited to no symptoms of motor/cognitive impairments before surgery. Therefore, we consider challenging activities that resemble sports and playful games, such as hitting targets, playing ball games, playing the Piano, and manipulating objects. Two common elements of all interventions are (1) that task performance is made up of discrete repetitions and (2) that outcomes are quantitatively measurable. For instance, preparing a meal, dressing, or tidying the table are motor tasks that cannot be easily divided into repetitions or whose outcome is quantitatively defined. By contrast, hitting targets or playing the piano are made of discrete individual repetitions, require specific spatial and temporal accuracy, the success/error rate can be easily measured, and progression can be monitored over time. To summarize, we prioritize goal-oriented, challenging tasks for their positive impact on neuroplasticity (network activation and connectivity), motor learning (difficulty, intensity, and variability), and motivation (constant monitoring of performance).

Virtual reality is also used to promote the activation of non-canonical pathways related to function (71). Any user can effectively distinguish immersive virtual reality from the real world, evidencing different enough recruited networks. However, training in a virtual environment transfers to real-environment learning (72, 73). This well-documented phenomenon enables virtual reality training to promote the recruitment of alternative pathways in the context of preferential ones.

Prehabilitation language and cognitive training

Similar to motor training, sessions are performed soon after TMS or during concomitant tDCS. Patients undertake computerized cognitive training sessions on the online rehabilitation platform "Guttmann NeuroPersonalTrainer"® (GNPT) (74), with a duration of ∼60 min per session. Tasks aim at language training (60% of the tasks) and other cognitive functions (40%), consisting of a set of personalized cognitive exercises based on the initial neuropsychological assessment that allows for establishing the profile of cognitive impairment. These tasks are adequately parameterized. To this end, neuropsychologists may define a set of input parameters for every task, such as presentation speed, latency time, or number of images, allowing personalization based on different difficulty levels. Regarding language, tasks are planned and supervised in a personalized way by a neuropsychologist, readjusting their planning if necessary.

Language tasks are oriented to naming and generating words, although other tasks oriented to language expression (grammar, semantics, and writing) and language comprehension (reading, comprehension of words, sentences, texts, and listening) could be contemplated.

For the rest of the cognitive functions, GNPT platform allows programming the following functions: (1) temporospatial orientation; (2) attention (selective, sustained, and divided); (3) memory (visual, verbal, and working memory); (4) executive functions (planning, inhibition, flexibility, sequencing, and categorization); (5) visual gnosis; (6) mental calculation; and (7) constructive praxis.

Furthermore, cognitive training is complemented by the telerehabilitation platform of the Barcelona Brain Health Initiative (BBHI) (75).

Finally, we apply specific tasks to train bilingualism. The objective is to achieve the disturbance of linguistic tasks through the temporary inhibition of the critical areas near the lesion (peritumoral), so that the brain can find alternative resources and facilitate neuroplasticity processes. This linguistic disturbance is made according to the representation of the tumor area (areas of higher functional compromise), to later realize language tasks, such as naming, comprehension, and fluency tasks in two languages (Spanish/Catalan), to enhance residual activities and promote a reorganization of functions during the disturbance. Prior to these procedures, a bilingualism questionnaire is administered to assess the dominant language of each participant.

Discontinuation, adherence, permission for concomitant care, ancillary, and post-trial care

Intervention is discontinued at the participant's request or in case of adverse events attributable to neuromodulation (seizure). Adherence to treatment is monitored by recording the rate of sessions attended over the total number of planned sessions.

Patients are allowed to undertake any concomitant care during the intervention if it does not interfere with the schedule of the prehabilitation program. However, we also recommend patients avoid other neuromodulation or motor skill training approaches, as they may be counterproductive to the desired outcome of the intervention. For instance, undertaking additional upper limb training sessions outside the prehabilitation protocol may reinforce the activation of peritumoral areas, as the inhibitory effect of neuromodulation might not be present anymore.

In case of post-surgery cognitive and/or neurological deficits, neurorehabilitation (usually 10 to 30 sessions) will be provided by the Guttmann Institute as a service offered to patients who have participated in the research study.

TABLE 1 SPIRIT WHO trial registration data set.

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov (NCT05844605)
Date of registration in primary registry	04/05/2023
Secondary identifying numbers	Protocol ID 2020330
Source(s) of monetary or material support	Fundación Joan Ribas Araquistain (reference project 2020.330) Fundació La Marató De TV3 (reference project 201735.10) Fundació Bancària La Caixa (reference project LCF/PR/PR16/11110004)
Primary sponsor	Institut Guttmann, Institut Universitari de Neurorehabilitació adscrit a la UAB, Badalona, Spain
Contact for public or scientific queries	Name: José María Tormos Muñoz Email address: jmtormos@guttmann.com Telephone: 934 977 700 Postal address: Camí de Can Ruti, s/n 08916 Badalona, Spain
Title	Neuromodulation-Induced Prehabilitation to leverage neuroplasticity before surgery for brain tumors: protocol for a single-cohort feasibility trial.
Countries of recruitment	Spain
Health condition(s) or problem(s) studied	Primary brain tumor
Intervention(s)	Neuromodulation, behavioral training, neurosurgery
Key inclusion and exclusion criteria	Inclusion: diagnosis of primary brain tumor requiring neurosurgery Exclusion: contraindications to TMS or MRI
Study type	Single-arm pilot feasibility trial
Date of first enrollment	21 June 2021
Target sample size	20
Recruitment status	Recruiting
Primary outcome(s)	Feasibility
Key secondary outcomes	Changes pre-/post-intervention on clinical, neurophysiology, and neuroimaging outcomes

Dissemination

A summarized version of the study protocol has been published online with ClinicalTrials.gov Identifier NCT05844605 (more information of the SPIRIT WHO trial registration data set are reported in Table 1).

Study data are collected and managed using REDCap electronic data capture tools hosted at Guttmann Institute (76, 77). To ensure confidentiality, each study participant is identified with an alphanumerical code. Data from neurophysiology and neuroimaging are anonymized and stored on online cloud platforms. Accessibility to data files is granted by the principal investigator only to researchers involved in data management. The hard copy of informed consent forms and other data collected on paper is stored in a locked closet at the Guttmann Institute, accessible only by the principal investigator.

Anonymized data supporting study findings are available from the corresponding author, upon reasonable request. Alternatively, an online data repository named "Joan Ribas Araquistain Dataset on Brain Tumor Prehabilitation" is created and made accessible upon reasonable request to accredited clinicians, researchers, and institutions in the field of neuro-oncology. Furthermore, we sought to establish collaboration agreements with international oncology databases, such as the Georgetown Database of Cancer (G-DOC), REMBRANDT (Repository of Molecular Brain Neoplasia Data), and the Cancer Imaging Archive.

The results of the study will be submitted to a peer-reviewed journal and presented at scientific congresses.

Statistical analysis

We use R software for statistical analysis and graphics (78). Given the small sample size (20 patients, based on a realistic estimate of the recruitment rate) and the use of ordinal scales, we perform non-parametric statistics. For descriptive reporting of continuous/ordinal variables, median and interquartile range (IQR) are used to indicate measures of central tendency and dispersion, respectively; frequencies are reported by indicating the absolute value, followed by the relative value (percentage) in brackets; in case of binary variables (such as gender), only one of the two variables is reported. For the primary analysis (feasibility), we report descriptively whether we met the criteria for recruitment, retention, and adverse events; adherence to treatment (both neuromodulation and behavioral training) is reported as the median (IQR). An exploratory analysis of effectiveness is conducted by performing a repeated-measure comparison (pre- vs. post-prehabilitation). Together with reporting the estimates of treatment effect, we indicate the actual level of significance (two-sided p-value) and 95% confidence interval (79). For quantitative and ordinal variables, we use Wilcoxon signed-rank test. For dichotomous variables, we use McNemar's test. For correlations between quantitative/ordinal variables measured at the same time point, we use Kendall's tau rank correlation coefficient. To explore prediction models, we use simple and multiple linear regression analyses for continuous/ordinal outcomes and simple and multiple logistic regression for binary outcomes. In case of missing data, we perform pairwise deletion. Further explorative analysis may include big data analysis of neuroimaging/neurophysiology data.

Ethics statement

All procedures from the present study were performed in accordance with the Helsinki Declaration. Ethics approval was obtained for the present experimental protocol by the Research Ethical Committee of Fundació Unió Catalana d'Hospitals (approval number: CEI 21/65, version 1, 13/07/2021). Patients provide written informed consent before being enrolled in the study.

Author contributions

LB, ÁP-L, and JT conceived the manuscript. LB, DB-F, NB, and MC-T initiated the study design. KA-P, JM-F, DL-C, JP, and EM-M helped with implementation. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Neuromodulation-induced prehabilitation in the brain tumour surgery group

Andreu Gabarrós Canals (Hospital de Bellvitge), Alberto Di Somma, Joaquim Enseñat, Jordi Rumià Arboix, José Poblete Carrizo, and Ramón Torné Torné (Hospital Clínic de Barcelona), Carlos Domínguez Alonso, Ferran Brugada Bellsolà, and Pilar Teixidor Rodríguez (Hospital Germans Trias i Pujol), Cristóbal Perla y Perla, Estela Lladó Carbó, Mireia Illueca Moreno (Hospital HM Nou Delfos), Cristian de Quintana, Fernando Muñoz Hernández, and Gloria Villalba Martinez [Hospital del Mar y Hospital de la Santa Creu i Sant Pau (Servicio de Neurocirugía mancomunado)], Mònica Buxeda Rodríguez (Hospital Mutúa de Tarrasa), Fabián Romero Chala (Hospital Parc Taulí), Fran Martinez Ricarte (Hospital Vall d'Hebron).

Funding

This study was funded by the Fundación Joan Ribas Araquistain (reference project 2020.330), Fundaciò La Maratò De TV3 (reference project 201735.10), and Fundaciò Bancària La Caixa (reference project LCF/PR/PR16/11110004). The primary sponsor is responsible for the design and overall conduct of the study. Funding entities had no role in the design of this study and will not have any role in its execution, analyses, interpretation of data, or decision to submit results.

Conflict of interest

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.

Publisher's note

References

1. Duffau H. Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. *Lancet Neurol.* (2005) 4:476–86. doi: 10.1016/S1474-4422(05)70140-X

2. Rivera-Rivera PA, Rios-Lago M, Sanchez-Casarrubios S, Salazar O, Yus M, González-Hidalgo M, et al. Cortical plasticity catalyzed by prehabilitation enables extensive resection of brain tumors in eloquent areas. *J Neurosurg.* (2017) 126:1323–33. doi: 10.3171/2016.2.JNS152485

3. Duffau H. Can non-invasive brain stimulation be considered to facilitate reoperation for low-grade glioma relapse by eliciting neuroplasticity? *Front Neurol.* (2020) 11:582489. doi: 10.3389/fneur.2020.582489

4. Hamer RP, Yeo TT. Current status of neuromodulation-induced cortical prehabilitation and considerations for treatment pathways in lower-grade glioma surgery. *Life.* (2022) 12:466. doi: 10.3390/life12040466

5. Barcia JA, Sanz A, González-Hidalgo M, de las Heras C, Alonso-Lera P, Díaz P. rTMS stimulation to induce plastic changes at the language motor area in a patient with a left recidivant brain tumor affecting Broca's area. *Neurocase.* (2012) 18:132–8. doi: 10.1080/13554794.2011.568500

6. Barcia JA, Sanz A, Balugo P, Alonso-Lera P, Brin JR, Yus M, et al. High-frequency cortical subdural stimulation enhanced plasticity in surgery of a tumor in Broca's area. *Neuroreport.* (2012) 23:304–9. doi: 10.1097/WNR.0b013e3283513307

7. Serrano-Castro PJ, Ros-López B, Fernández-Sánchez VE, García-Casares N, Muñoz-Becerra L, Cabezudo-Garcia P, et al. Neuroplasticity and epilepsy surgery in brain eloquent areas: case report. *Front Neurol.* (2020) 11:698. doi: 10.3389/fneur.2020.00698

8. Hoogendam JM, Ramakers GMJ, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimul.* (2010) 3:95–118. doi: 10.1016/j.brs.2009.10.005

9. Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clin Neurophysiol.* (2021) 132:269–306. doi: 10.1016/j.clinph.2020.10.003

10. Lefaucheur J-P, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014-2018). *Clin Neurophysiol.* (2020) 131:474–528. doi: 10.1016/j.clinph.2020.02.003

11. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, KrleŽa-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med.* (2013) 158:200–7. doi: 10.7326/0003-4819-158-3-201302050-00583

12. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ.* (2013) 346:e7586. doi: 10.1136/bmj.e7586

13. Brédart A, Anota A, Young T, Tomaszewski KA, Arraras JI, Moura De Albuquerque Melo H. Phase III study of the European Organisation for Research and Treatment of Cancer satisfaction with cancer care core questionnaire (EORTC PATSAT-C33) and specific complementary outpatient module (EORTC OUT-PATSAT7). *Eur J Cancer Care.* (2018) 27:786. doi: 10.1111/ecc.12786

14. Desmurget M, Bonnetblanc F, Duffau H. Contrasting acute and slow-growing lesions: a new door to brain plasticity. *Brain.* (2007) 130:898–914. doi: 10.1093/brain/awl300

15. Duffau H. Functional mapping before and after low-grade glioma surgery: a new way to decipher various spatiotemporal patterns of individual neuroplastic potential in brain tumor patients. *Cancers.* (2020) 12:2611. doi: 10.3390/cancers12092611

16. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol.* (2021) 23:1231–51. doi: 10.1093/neuonc/noab106

17. Kellor M, Frost J, Silberberg N, Iversen I, Cummings R. Hand strength and dexterity. *Am J Occup Ther.* (1971) 25:77–83.

18. Feys P, Lamers I, Francis G, Benedict R, Phillips G, LaRocca N, et al. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. *Mult Scler.* (2017) 23:711–20. doi: 10.1177/1352458517690824

19. Rosti-Otajärvi E, Hämäläinen P, Koivisto K, Hokkanen L. The reliability of the MSFC and its components. *Acta Neurol Scand.* (2008) 117:421–7. doi: 10.1111/j.1600-0404.2007.00972.x

20. Hervault M, Balto JM, Hubbard EA, Motl RW. Reliability, precision, and clinically important change of the Nine-Hole Peg Test in individuals with multiple sclerosis. *Int J Rehabil Res.* (2017) 40:91–3. doi: 10.1097/MRR.0000000000000209

21. Lamers I, Cattaneo D, Chen CC, Bertoni R, Van Wijmeersch B, Feys P. Associations of upper limb disability measures on different levels of the international classification of functioning, disability and health in people with multiple sclerosis. *Phys Ther.* (2015) 95:65–75. doi: 10.2522/ptj.20130588

22. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1 a method for evaluation of physical performance. *Scand J Rehabil Med.* (1975) 7:13–31. doi: 10.2340/1650197771331

23. See J, Dodakian L, Chou C, Chan V, McKenzie A, Reinkensmeyer DJ, et al. Standardized approach to the fugl-meyer assessment and its implications for clinical trials. *Neurorehabil Neural Repair.* (2013) 27:732–41. doi: 10.1177/1545968313491000

24. Kim H, Her J, Ko J, Park D, Woo J-H, You Y, et al. Reliability, concurrent validity, and responsiveness of the Fugl-Meyer assessment (FMA) for hemiplegic patients. *J Phys Ther Sci.* (2012) 24:893–9. doi: 10.1589/jpts.24.893

25. Wagner JM, Rhodes JA, Patten C. Reproducibility and minimal detectable change of three-dimensional kinematic analysis of reaching tasks in people with hemiparesis after stroke. *Phys Ther.* (2008) 88:652–63. doi: 10.2522/ptj.20070255

26. Lin JH, Hsu MJ, Sheu CF, Wu TS, Lin RT, Chen CH, et al. Psychometric comparisons of 4 measures for assessing upper-extremity function in people with stroke. *Phys Ther.* (2009) 89:840–50. doi: 10.2522/ptj.20080285

27. Plantin J, Verneau M, Godbolt AK, Pennati GV, Laurencikas E, Johansson B, et al. Recovery and prediction of bimanual hand use after stroke. *Neurology.* (2021) 97:e706–19. doi: 10.1212/WNL.0000000000012366

28. Bertrand AM, Fournier K, Wick Brasey M-G, Kaiser M-L, Frischknecht R, Diserens K. Reliability of maximal grip strength measurements and grip strength recovery following a stroke. *J Hand Ther.* (2015) 28:356–62. doi: 10.1016/j.jht.2015.04.004

29. Mathiowetz V, Weber K, Volland G, Kashman N. Reliability and validity of grip and pinch strength evaluations. *J Hand Surg Am.* (1984) 9:222–6. doi: 10.1016/S0363-5023(84)80146-X

30. Mani P. Test-retest reliability of electronic hand dynamometer in healthy adults. *Int J Adv Res.* (2019) 7:325–31. doi: 10.21474/IJAR01/9042

31. Deary IJ, Liewald D, Nissan J, A. free, easy-to-use, computer-based simple and four-choice reaction time programme: the Deary-Liewald reaction time task. *Behav Res.* (2011) 43:258–68. doi: 10.3758/s13428-010-0024-1

32. Sullivan KJ, Tilson JK, Cen SY, Rose DK, Hershberg J, Correa A, et al. Fugl-Meyer assessment of sensorimotor function after stroke: standardized training procedure for clinical practice and clinical trials. *Stroke.* (2011) 42:427–32. doi: 10.1161/STROKEAHA.110.592766

33. Tyson SF, DeSouza LH. Development of the Brunel Balance Assessment: a new measure of balance disability post stroke. *Clin Rehabil.* (2004) 18:801–10. doi: 10.1191/0269215504cr744oa

34. Cuenca-Garcia M, Marin-Jimenez N, Perez-Bey A, Sánchez-Oliva D, Camiletti-Moiron D, Alvarez-Gallardo IC. Reliability of field-based fitness tests in adults: a systematic review. *Sports Med.* (2022) 2:1–14. doi: 10.1007/s40279-021-01635-2

35. Ruden E, Reardon DA, Coan AD, Herndon JE, Hornsby WE, West M, et al. Exercise behavior, functional capacity, and survival in adults with malignant recurrent glioma. *J Clin Oncol.* (2011) 29:2918–23. doi: 10.1200/JCO.2011.34.9852

36. Nayak L, DeAngelis LM, Brandes AA, Peereboom DM, Galanis E, Lin NU, et al. The neurologic assessment in neuro-oncology (NANO) scale: a tool to assess neurologic function for integration into the response assessment in neuro-oncology (RANO) criteria. *Neuro Oncol.* (2017) 19:625–35. doi: 10.1093/neuonc/nox029

37. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. *J Clin Oncol.* (1984) 2:187–93. doi: 10.1200/JCO.1984.2.3.187

38. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* (1993) 85:365–76. doi: 10.1093/jnci/85.5.365

39. Nolte S, Liegl G, Petersen MA, Aaronson NK, Costantini A, Fayers PM, et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. *Eur J Cancer.* (2019) 107:153–63. doi: 10.1016/j.ejca.2018.11.024

40. Taphoorn MJB, Claassens L, Aaronson NK, Coens C, Mauer M, Osoba D, et al. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. *Eur J Cancer.* (2010) 46:1033–40. doi: 10.1016/j.ejca.2010.01.012

41. Weis J, Tomaszewski KA, Hammerlid E, Ignacio Arraras J, Conroy T, Lanceley A. International psychometric validation of an eortc quality of life module measuring cancer related fatigue (EORTC QLQ-FA12). *J Natl Cancer Inst.* (2017) 109:273. doi: 10.1093/jnci/djw273

42. Peña-Casanova J, Esparcia AJJ, Saladié DG, Olmos JG. Normalidad, semiología y patología neuropsicológicas: programa integrado de exploración neuropsicológica "Test Barcelona." *Masson.* (1991) 24:1–7. doi: 10.1016/S0214-4603(91)75507-1

43. Cubero NS, Wechsler D. *WAIS-III: Escala de Inteligencia de Wechsler para Adultos III.* Madrid: Manual técnico TEA Ediciones. (1999).

44. Reed JC, Reed HBC. The Halstead—Reitan Neuropsychological Battery. In: Goldstein G, Incagnoli TM, editors. *Contemporary Approaches to Neuropsychological Assessment. Critical Issues in Neuropsychology.* (Boston, MA: Springer US), (1997). p. 93–129.

45. Conners CK, Epstein JN, Angold A, Klaric J. Continuous performance test performance in a normative epidemiological sample. *J Abnorm Child Psychol.* (2003) 31:555–62. doi: 10.1023/A:1025457300409

46. Schmidt M. *Rey Auditory Verbal Learning Test: RAVLT : A Handbook.* Los Angeles, CA: Western Psychological Services. (1996).

47. Dzikon C. "The Wechsler Memory Scale (WMS-IV)," In: Carducci BJ, Nave CS, Di Fabio A, editors. *The Wiley Encyclopedia of Personality and Individual Differences.* London: John Wiley & Sons, Ltd (2020). p. 529–532.

48. Artiola I. Fortuny L, Romo DH, Heaton RK, Pardee Iii RE. *Manual de Normas y Procedimientos Para la Bateria Neuropsicologia. London:* Psychology Press. (1999).

49. Pérez-Pérez A, Matias-Guiu JA, Cáceres-Guillén I, Rognoni T, Valles-Salgado M, Fernández-Matarrubia M, et al. The hayling test: development and normalization of the Spanish version. *Arch Clin Neuropsychol.* (2016) 31:411–9. doi: 10.1093/arclin/acw027

50. Miles S, Howlett CA, Berryman C, Nedeljkovic M, Moseley GL, Phillipou A. Considerations for using the Wisconsin card sorting test to assess cognitive flexibility. *Behav Res Methods.* (2021) 53:2083–91. doi: 10.3758/s13428-021-01551-3

51. Cattaneo G, Calabria M, Marne P, Gironell A, Abutalebi J, Costa A. The role of executive control in bilingual language production: a study with Parkinson's disease individuals. *Neuropsychologia.* (2015) 66:99–110. doi: 10.1016/j.neuropsychologia.2014.11.006

52. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia.* (1971) 9:97–113. doi: 10.1016/0028-3932(71)90067-4

53. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* (1983) 67:361–70. doi: 10.1111/j.1600-0447.1983.tb09716.x

54. Groppa S, Oliviero A, Eisen A, Quartarone A, Cohen LG, Mall V, et al. A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. *Clin Neurophysiol.* (2012) 123:858–82. doi: 10.1016/j.clinph.2012.01.010

55. Di Pino G, Pellegrino G, Assenza G, Capone F, Ferreri F, Formica D, et al. Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nat Rev Neurol.* (2014) 10:597–608. doi: 10.1038/nrneurol.2014.162

56. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology.* (2009) 120:2008–39. doi: 10.1016/j.clinph.2009.08.016

57. Huang Y-Z, Lu M-K, Antal A, Classen J, Nitsche M, Ziemann U, et al. Plasticity induced by non-invasive transcranial brain stimulation: A position paper. *Clin Neurophysiol.* (2017) 128:2318–29. doi: 10.1016/j.clinph.2017.09.007

58. Gamboa OL, Antal A, Moliadze V, Paulus W. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. *Exp Brain Res.* (2010) 204:181–7. doi: 10.1007/s00221-010-2293-4

59. Abraham WC, Bear MF. Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci.* (1996) 19:126–30. doi: 10.1016/S0166-2236(96)80018-X

60. Thomson AC, Sack AT. How to design optimal accelerated rTMS Protocols capable of promoting therapeutically beneficial metaplasticity. *Front Neurol.* (2020) 11:599918. doi: 10.3389/fneur.2020.599918

61. Goldsworthy MR, Pitcher JB, Ridding MC. Spaced noninvasive brain stimulation: prospects for inducing long-lasting human cortical plasticity. *Neurorehabil Neural Repair.* (2015) 29:714–21. doi: 10.1177/1545968314562649

62. Elsner B, Kugler J, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving aphasia after stroke: a systematic review with network meta-analysis of randomized controlled trials. *J Neuroeng Rehabil.* (2020) 17:88. doi: 10.1186/s12984-020-00708-z

63. Bressi F, Cinnera AM, Morone G, Campagnola B, Cricenti L, Santacaterina F, et al. Combining robot-assisted gait training and non-invasive brain stimulation in chronic stroke patients: a systematic review. *Front Neurol.* (2022) 13:795788. doi: 10.3389/fneur.2022.795788

64. Vabalaite B, Petruseviciene L, Savickas R, Kubilius R, Ignatavicius P, Lendraitiene E. Effects of high-frequency (HF) repetitive transcranial magnetic stimulation (rTMS) on upper extremity motor function in stroke patients: a systematic review. *Medicina.* (2021) 57:1215. doi: 10.3390/medicina57111215

65. Gerloff C, Andres FG. Bimanual coordination and interhemispheric interaction. *Acta Psychol.* (2002) 110:161–86. doi: 10.1016/S0001-6918(02)00032-X

66. Walsh RR, Small SL, Chen EE, Solodkin A. Network activation during bimanual movements in humans. *Neuroimage.* (2008) 43:540–53. doi: 10.1016/j.neuroimage.2008.07.019

67. Wu T, Liu J, Hallett M, Zheng Z, Chan P. Cerebellum and integration of neural networks in dual-task processing. *Neuroimage.* (2013) 65:466–75. doi: 10.1016/j.neuroimage.2012.10.004

68. Rietschel JC, Miller MW, Gentili RJ, Goodman RN, McDonald CG, Hatfield BD. Cerebral-cortical networking and activation increase as a function of cognitive-motor task difficulty. *Biol Psychol.* (2012) 90:127–33. doi: 10.1016/j.biopsycho.2012.02.022

69. Maier M, Ballester BR, Verschure PFMJ. Principles of neurorehabilitation after stroke based on motor learning and brain plasticity mechanisms. *Front Syst Neurosci.* (2019) 13:74. doi: 10.3389/fnsys.2019.00074

70. Krakauer JW. Motor learning: its relevance to stroke recovery and neurorehabilitation. *Curr Opin Neurol.* (2006) 19:84–90. doi: 10.1097/01.wco.0000200544.29915.cc

71. Kober SE, Settgast V, Brunnhofer M, Augsdörfer U, Wood G. Move your virtual body: differences and similarities in brain activation patterns during hand movements in real world and virtual reality. *Virtual Real.* (2022) 26:501–11. doi: 10.1007/s10055-021-00588-1

72. Feitosa JA, Fernandes CA, Casseb RF, Castellano G. Effects of virtual reality-based motor rehabilitation: a systematic review of fMRI studies. *J Neural Eng.* (2022) 19:456. doi: 10.1088/1741-2552/ac456e

73. Hao J, Xie H, Harp K, Chen Z, Siu K-C. Effects of virtual reality intervention on neural plasticity in stroke rehabilitation: a systematic review. *Arch Phys Med Rehabil.* (2022) 103:523–41. doi: 10.1016/j.apmr.2021.06.024

74. Solana J, Cáceres C, García-Molina A, Opisso E, Roig T, Tormos JM, et al. Improving brain injury cognitive rehabilitation by personalized telerehabilitation services: guttmann neuropersonal trainer. *IEEE J Biomed Health Inf.* (2015) 19:124–31. doi: 10.1109/JBHI.2014.2354537

75. Cattaneo G, Bartrés-Faz D, Morris TP, Sánchez JS, Macià D, Tarrero C, et al. The Barcelona brain health initiative: a cohort study to define and promote determinants of brain health. *Front Aging Neurosci.* (2018) 10:321. doi: 10.3389/fnagi.2018.00321

76. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* (2009) 42:377–81. doi: 10.1016/j.jbi.2008.08.010

77. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform.* (2019) 95:103208. doi: 10.1016/j.jbi.2019.103208

78. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Core Team (2021).

79. Pocock SJ, McMurray JJV, Collier TJ. Making sense of statistics in clinical trial reports: part 1 of a 4-part series on statistics for clinical trials. *J Am Coll Cardiol.* (2015) 66:2536–49. doi: 10.1016/j.jacc.2015.10.014

frontiers | Frontiers in Neurology

TYPE Case Report
PUBLISHED 07 November 2023
DOI 10.3389/fneur.2023.1195513

OPEN ACCESS

EDITED BY
Giorgio Sandrini,
Fondazione Cirna Onlus, Italy

REVIEWED BY
Mustafa Q. Hameed,
Boston Children's Hospital and Harvard Medical School, United States
Shankar Tumati,
University of Toronto, Canada

*CORRESPONDENCE
Jean-Paul Nguyen
✉ jeanpaul.nguye@gmail.com
Tiphanie Caloc'h
✉ tiphanie.caloch@laposte.net
Estelle Le Saout
✉ estelle.lesaout@clinique-breteche.fr
Séverine Litaneur
✉ severine.litaneur@clinique-breteche.fr
Alcira Suarez
✉ alcirasum@yahoo.fr
Sylvain Durand
✉ loaldesy@orange.fr
Jean-Pascal Lefaucheur
✉ jean-pascal.lefaucheur@aphp.fr

RECEIVED 28 March 2023
ACCEPTED 23 October 2023
PUBLISHED 07 November 2023

CITATION
Caloc'h T, Le Saout E, Litaneur S, Suarez A, Durand S, Lefaucheur J-P and Nguyen J-P (2023) Treatment of cognitive and mood disorders secondary to traumatic brain injury by the association of bilateral occipital nerve stimulation and a combined protocol of multisite repetitive transcranial magnetic stimulation and cognitive training: A case report. *Front. Neurol.* 14:1195513. doi: 10.3389/fneur.2023.1195513

Treatment of cognitive and mood disorders secondary to traumatic brain injury by the association of bilateral occipital nerve stimulation and a combined protocol of multisite repetitive transcranial magnetic stimulation and cognitive training: A case report

Tiphanie Caloc'h[1]*, Estelle Le Saout[1]*, Séverine Litaneur[1]*, Alcira Suarez[1]*, Sylvain Durand[1]*, Jean-Pascal Lefaucheur[2,3]* and Jean-Paul Nguyen[1]*

[1]Unité de stimulation transcrânienne, Clinique Bretéché, Groupe Elsan, Nantes, France, [2]EA 4391, équipe ENT (Excitabilité Nerveuse et Thérapeutique), Université Paris-Est Créteil, Créteil, France, [3]Unité de Neurophysiologie Clinique, Hôpital Henri Mondor, Assistance Publique - Hôpitaux de Paris, Créteil, France

Purpose: Cognitive impairment secondary to traumatic brain injury (TBI) is difficult to treat and usually results in severe disability.

Method: A 48-year-old man presented with chronic refractory headaches and persistent disabling cognitive impairment after TBI. He was first treated with occipital nerve stimulation (ONS) implanted bilaterally to relieve headaches (8 years after the head trauma). Two years later, he was treated with a 6-week protocol combining repetitive transcranial magnetic stimulation (rTMS) delivered to multiple cortical sites (prefrontal cortex, language areas, and areas involved in visuo-spatial functions) and computerized cognitive training (CogT) (targeting memory, language, and visuo-spatial functions) to improve cognitive performance.

Results: Executive and cognitive functions (attention, ability to perform calculations, and verbal fluency) improved in association with pain relief after ONS (33–42% improvement) and then improved even more after the rTMS-CogT protocol with an additional improvement of 36–40% on apathy, depression, and anxiety, leading to a significant reduction in caregiver burden. The functional improvement persisted and even increased at 6 months after the end of the rTMS-CogT procedure (10 years after the onset of TBI and 2 years after ONS implantation).

Conclusion: This is the first observation describing sustained improvement in post-TBI refractory headache, depression, and cognitive impairment by the

association of bilaterally implanted ONS and a combined procedure of multisite rTMS and CogT to target various brain functions.

KEYWORDS

traumatic brain injury, refractory headache, occipital nerve stimulation, repetitive transcranial magnetic simulation, cognitive training, combined strategy

Introduction

Cognitive impairment is one of the most common sequelae of traumatic brain injury (TBI) (1). Their number tends to increase with the increase in the number of survivors, linked to better management of severe head injuries in the acute phase (2). Cognitive sequelae are considered more disabling than motor sequelae (3–7). They play an important role in hindering the possibility of reintegration into working life. The most frequent disorders concern memory (8), attention (9), and executive functions (10). Classic treatment consists of cognitive rehabilitation combined with drug treatments used in the cognitive disorders of Alzheimer's disease, such as cholinesterase inhibitors (Donezepil, Rivastigmine) (11). However, these treatments have side effects and only act inconsistently (12).

The efficacy of cognitive rehabilitation depends above all on the patient's participation, which may be disrupted by stress, a depressive state or other symptoms encountered in the context of post-TBI syndrome, such as headaches. These different factors must be taken into account before starting cognitive rehabilitation (11).

Recovery from a cognitive deficit can also be hampered by other factors, such as arousal and attention disorders. These disorders are common when trauma causes shear damage to the white matter responsible for a disconnection between the thalamus and the neocortex (13–15). Thus, interventions that can stimulate the thalamus directly [thalamic stimulation (16)] or indirectly [stimulation of the vagus nerve or peripheral nerves (17)] have been proposed in this context.

Currently, it is considered that the goal of cognitive rehabilitation is to develop neuroplasticity that will make the neural circuits involved in cognition more efficient (18). The outcome could be optimized by combining cognitive rehabilitation with a technique of non-invasive stimulation of the cerebral cortex such as repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) (19), which are known to promote synaptic plasticity.

We report the case of a patient who suffered a head injury responsible for a post-TBI syndrome with disabling headaches and cognitive disorders. A first treatment with surgically implanted occipital nerve stimulation (ONS) was effective on headaches and clearly led to a cognitive improvement. Subsequently, a treatment combining multisite rTMS with computerized cognitive training (CogT) (20–22) further improved cognitive performance and acted on depression, anxiety, and apathy.

Case report

This is a 48-year-old patient who in 2012 had severe head injury related to a serious quad bike accident. On the initial CT scan, there was a fracture of the temporal and petrous bones on the left side, a diffuse subarachnoid hemorrhage and an edematous parenchymal contusion predominating on the right side, accompanied by a right temporal subdural hematoma (3 mm thick). A follow-up CT scan performed 72 h later showed a small intracerebral hemorrhage localized in the right temporal region, with increased edema in the right temporoparietal region leading to a mass effect with displacement of midline structures and the effacement of some cortical sulci, but without signs of cerebral herniation. The patient initially presented with an intermediate disorder of consciousness (Glasgow score 12) which lasted 5 days. Afterwards, the patient rapidly complained of headaches, followed by memory and attention disturbances and verbal expression difficulties. He also became irritable and had sleep disorders with difficulty falling asleep and frequent waking up. Daily headaches affected the entire head, suggesting a diagnosis of tension headache. The patient was discharged from the intensive care unit after 10 days. Despite several drug trials, the headaches persisted. The same was true for cognitive impairment, despite cognitive rehabilitation with weekly speech therapy sessions. The patient was unable to resume his professional activity as a telephone network administrator at the national level. He was on occupational disability, living at home with a very good family environment.

He was referred to our center at the beginning of 2018 mainly due to permanent headaches that had become increasingly debilitating. A treatment with non-invasive transcutaneous electrical neurostimulation (TENS) applied to the both occipital nerves was initiated in February 2018 and proved to be remarkably effective. In July 2019, the neuropsychological assessment (initial evaluation) reported a total score of 19/30 on the Mini-Mental State Examination (MMSE) (23) (Table 1; Figure 1). Subsequently, the headaches gradually worsened as the patient used TENS less and less, which he considered too restrictive in daily life. At the same time, cognitive problems also increased, suggesting a link between the two symptoms. This led us to decide to implant an ONS device. The preoperative cognitive assessment performed at the end of May 2020 (pre-ONS baseline) confirmed the worsening of cognitive problems with a MMSE total score of 14/30. Cognitive disorders consisted of impaired executive functions, with a total score of 9/18 on the Frontal Assessment Battery (FAB) (24) (Table 1). In addition, psychomotor slowing was observed during visual attention and word reading tests. The patient also had great difficulty concentrating due to headaches.

TABLE 1 Clinical assessment performed initially after 18 months of transcutaneous electrical neurostimulation of the occipital nerves (ON-TENS), before bilateral implantation of occipital nerve stimulation (ONS), 18 months after ONS implantation, at the end of a subsequent 6-week therapy combining multisite repetitive transcranial magnetic stimulation and computerized cognitive training (rTMS-CogT), and finally 6 months after the end of the rTMS-CogT protocol.

	Initial evaluation after 18 months of ON-TENS (July 2019)	Pre-ONS baseline (May 2020)	18-month follow-up post-ONS (pre-rTMS-CogT baseline) (March 2022)	Immediate evaluation after rTMS-CogT protocol (May 2022)	6-month follow- up after rTMS-CogT protocol (November 2022)
Mini-mental state examination (MMSE) score/30	19	14	20	23	23
1. Orientation score/10	5	5	6	9	9
2. Registration score/3	3	3	3	3	3
3. Attention and calculation score/5	5	1	4	4	4
4. Recall score/3	0	0	0	0	0
5. Language score/8	5	4	6	6	6
6. Copying score/1	1	1	1	1	1
Frontal assessment battery (FAB) score/18	11	9	12	12	11
Phonemic fluency score/15*	11	11	13	14	11
Semantic fluency score/22*	5	4	4	7	8
Hospital anxiety and depression scale (HADS) anxiety subscore/21	-	11	15	9	5
Hospital anxiety and depression scale (HADS) depression subscore/21	-	17	15	9	6
Apathy inventory (AI) score/36	8	15	11	7	2
Disability assessment for dementia (DAD) score/100%	55	55	82.5	70	86.5
Zarit score/7	6	7	6	4.5	2
Alzheimer's disease assessment scale-cognitive subscale (ADASCog) score/70			24.75	18.05	18
1. Spoken language ability score/5			1	0	0
2. Comprehension score/5			1	0	0
3. Word finding difficulty score/5			3	1	1
4. Word recall task score/10			8	8.3	9
5. Naming objects and fingers score/5			2	0	1
6. Orientation score/8			5	2	1
7. Commands score/5			2	3	2
8. Ideational praxis score/5			0	1	0
9. Constructional praxis score/5			0	0	0
10. Word recognition task score/12			2.75	2.75	4
11. Remembering test instructions score/5			0	0	0

*Mean number of correct words recorded during 1 min in a healthy population (25, 26).

10.3389/fneur.2023.1195513

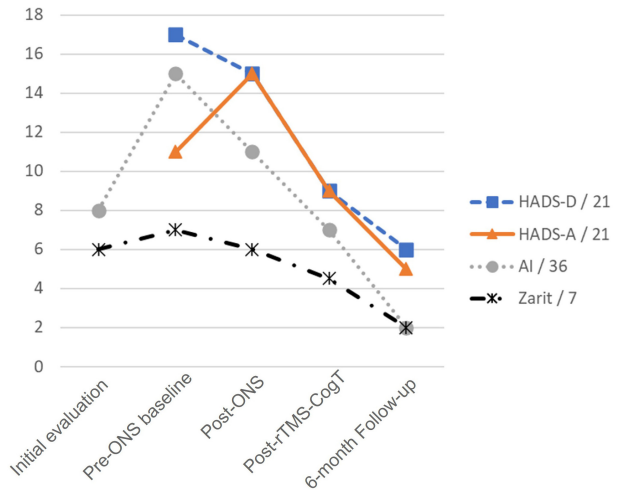


FIGURE 1
Evolution of clinical scores over time. Evolution of the Hospital Anxiety and Depression scale Depression (HADS-D) and Anxiety (HADS-A) subscores, the Apathy Inventory (AI) and the Zarit scores, at the following timepoints: (i) after 18 months of transcutaneous electrical neurostimulation of the occipital nerves: Initial evaluation; (ii) before bilateral implantation of occipital nerve stimulation (ONS): Pre-ONS baseline; (iii) 18 months after ONS implantation: Post-ONS; (iv) at the end of a subsequent 6-week therapy combining multisite repetitive transcranial magnetic stimulation and computerized cognitive training (rTMS-CogT): Post-rTMS-CogT; (v) 6 months after the end of the rTMS-CogT protocol: 6-month Follow-up.

The surgical implantation of the ONS device (electrodes and pulse generator) was performed in September 2020. The continuous stimulation of the occipital nerves allowed headaches to be relieved very efficaciously. Additionally, cognitive performance gradually improved over a period of time and then stabilized after 1 year. In March 2022 (18 months after ONS implantation), the MMSE total score was 20/30, corresponding to a 43% improvement from pre-ONS implantation baseline, including increased attention and ability to perform calculations as well as in language functions (Table 1). At the same time, the FAB score was 12/18, corresponding to a 33% improvement of executive functions from pre-ONS implantation baseline. This resulted in greater autonomy [Disability Assessment for Dementia (DAD) (27) score: 82.5 vs. 55% at baseline, 33% improvement], but with only a slightly lower load for caregivers [Zarit score (28): 6/7 vs. 7/7 at baseline].

As the improvement produced by ONS did not seem sufficient and no longer progressing, we decided to perform an additional therapeutic approach, based on rTMS applied to multiple cortical sites combined with CogT. Such a combined protocol has been developed under the name NeuroAD® therapy for the treatment of cognitive disorders, mainly apathy in the context of Alzheimer's disease (AD) (20–22). The detailed protocol we applied, similar to that used for patients with AD, has been described elsewhere (22). Briefly, this consisted of a daily session of rTMS-CogT for 5 consecutive days per week for a period of 6 weeks (30 sessions in total). Regarding rTMS, six different cortical regions were targeted, identified by a neuronavigation system (NeuroAD, Neuronix Ltd., Yoqnea'm, Israel) on the patient's brain magnetic resonance imaging (MRI): the right and left dorsolateral prefrontal cortices (DLPFC), the Broca's and Wernicke's language areas, and the right and left posterior parietal areas. On each region, 20 trains of 20 rTMS pulses were delivered at 10 Hz (2-s train duration and 40-s intertrain interval) for a total of 400 pulses over a period of 14 min. The intensity of stimulation was set at 100% of the rest motor threshold. During each intertrain interval of 40 s of rTMS interruption, the patient was asked to perform a cognitive task corresponding to the function of the stimulated cortical area: (i) naming of actions or objects, word recall, or spatial memory tasks for the DLPFC; (ii) syntax or grammar tasks for language areas; (iii) visuospatial attention tasks for parietal areas. Each task had six levels of gradual difficulty and the patients were allowed to progress to the next level of difficulty based on their performance in the previous session. During each daily session, three different cortical regions were treated by combining rTMS and corresponding CogT and the three other regions were treated the following day. Overall, each daily rTMS-CogT session lasted ~1 h.

The rTMS-CogT protocol was initiated in March 2022 and was completed without any adverse event or side effect. An initial assessment was performed just at the end of the 6 weeks of treatment (Table 1; Figure 1), including the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADASCog) (29) score. Unlike the MMSE, a lower ADASCog score reveals a better cognitive level. Following rTMS-CogT, the ADASCog score decreased by almost 7 points (27% improvement from pre-rTMS-CogT assessment), mainly in the naming objects, word finding, and orientation subscores. The orientation subscore of the MMSE also improved (from 6/10 to 9/10), leading to a 3-point increase in total MMSE score, as well as in semantic verbal fluency score. The rTMS-CogT therapy also produced beneficial effects on apathy [Apathy Inventory (AI) (30) score: 7/36 vs. 11/36 before rTMS-CogT, 36% improvement] and on depression and anxiety [Hospital Anxiety and Depression scale (HADS) (31) total score: 18/42 vs. 30/42 before rTMS-CogT, 40% improvement]. Finally, the caregiver burden was reduced (Zarit score: 4.5/7 vs. 6/7 before rTMS-CogT).

A follow-up assessment was performed 6 months after the end of the rTMS-CogT protocol (Table 1). At this time point, apathy, as well as depression and anxiety, further improved compared to the assessment performed just after the rTMS-CogT protocol (AI score: 2/36 vs. 7/36, 71% improvement; HADS total score: 11/42 vs. 18/42, 39% improvement). The caregiver burden was also greatly reduced (Zarit score: 2/7 vs. 4.5/7).

Discussion

In this observation, a significant and lasting improvement in cognition and mood was achieved in a patient with a severe TBI after a sequence of two neuromodulation treatments including (1) bilateral implantation of ONS and (2) multisite rTMS performed in combination with CogT. The latter approach is generally dedicated to the treatment of cognitive disorders associated with AD (20–22). Our study is, to our knowledge, the first to have used this procedure to treat cognitive impairment secondary to head trauma. This therapeutic solution was justified in this patient who presented with memory, language and orientation disorders, such as those encountered in AD (32).

Cognitive disorders secondary to head trauma are related to complex biochemical processes, resulting in particular from damage to the blood-brain barrier in the white matter, later responsible for diffuse axonal damage (13–15). Depending on whether these lesions are located at the superficial cortical, subcortical or deep brain level close to the basal ganglia, quite different clinical sequelae can result. Superficial lesions are more likely to disrupt the functioning of different cortical areas and the connections between them, resulting in a picture of cognitive impairment similar to that observed in AD. Deep lesions are more responsible for disorders of consciousness, alertness and attention that are encountered in more or less severe vegetative states. In the case presented here, brain imaging showed that there was a left temporal impact, marked by the fracture of the temporal bone and its petrous part, and also lesions on the opposite side, marked by an acute subdural hematoma and a right temporoparietal contusion. These findings suggest traumatic lesions secondary to a rotation mechanism in the coronal plane (33) theoretically responsible for axonal lesions of moderate severity but affecting both the subcortical and deep brain regions (34).

However, cognitive impairment following head trauma is not solely determined by white matter lesions. The homeostatic balance between inhibition and excitation is also disrupted in the brain's neural networks following TBI (35). Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter and glutamate the major excitatory neurotransmitter in the central nervous system. There is evidence for the occurrence of an immediate rise in glutamate levels following severe TBI in humans (36). A disruption in GABAergic signaling may lead to a further increase in glutamate excitotoxicity, which can worsen the impact of neuronal damage (37). By being able to modulate the GABA/glutamate balance and producing long-lasting effects on synaptic transmission (38–40), non-invasive brain stimulation techniques, such as rTMS, have a certain interest in this clinical context (41). However, it is difficult to have preconceptions regarding the type of rTMS pattern to apply to modulate the GABA/glutamate balance after TBI, particularly according to the influence of metaplasticity processes (42). Indeed, while rTMS tonically applied at low frequency ($\leq$1 Hz) is known to be able to depress long-term synaptic transmission and is therefore potentially neuroprotective, high-frequency rTMS (as applied in our patient), although considered excitatory, has also shown neuroprotective or pro-GABAergic effects in various experimental models (43–45) or clinical conditions (46–48). Furthermore, the situation is more complex than a dual mechanism of increased vs. decreased excitability, because cognitive recovery after TBI depends on various neural repair processes, including restoration and synchronization of neuronal network connectivity for cognitive performance, in which the modulation of tonic and phasic GABA levels plays a complex interaction role.

Our results show that combined rTMS-CogT therapy may be a well-suited approach to promote post-TBI cognitive recovery. However, performing such a protocol requires good attentional and psychomotor capacities to complete the cognitive tasks quickly within the time imposed by the rTMS protocol. Our patient initially presented with great difficulty concentrating, mainly due to disabling headaches, which could have initially prevented him from complying with the rTMS-CogT protocol. This is the reason why it appeared to us that the priority was to treat his headaches first, which led us to propose the treatment by ONS. High analgesic efficacy of this neuromodulation technique has been reported in various types of non-migrainous chronic headaches (49) and was therefore confirmed in our patient. To our knowledge, implanted ONS has never been proposed before to relieve refractory headaches secondary to TBI, but clearly appears to be an interesting therapeutic solution in this context.

The ONS probably made it possible to take a first step in cognitive improvement in our patient, but indirectly, thanks to the reduction of pain. However, a cognitive improvement more directly produced by ONS was also possible, as suggested by a previous study showing the increase in memory performance thanks to the application of tDCS to stimulate the greater occipital nerve (50), possibly via the activation of the locus coeruleus (51). Other authors have suggested that ONS may also improve attention by acting on the thalamus or basal ganglia (52, 53). Thus, our patient improved his attentional and executive functions following ONS therapy, but this proved insufficient to restore quality daily life and the rTMS-CogT protocol seemed to us to be a good approach to further improve the cognitive performance and reduce mood disorders to a clinically satisfactory level.

Various rTMS protocols have already been proposed to treat the clinical symptoms associated with concussion (mild TBI) or more severe TBI and this has been the subject of about 40 publications since 2006, including three recent reviews (54–56) and three meta-analyses (57–59). Symptoms intended to be treated by rTMS, primarily targeted to the left DLPFC at high frequency (or more rarely to the right DLPFC at low frequency), were disorders of consciousness, dizziness, auditory disorders, motor dysfunction, pain, headache, depression, or cognitive impairment, including post-concussion syndrome after mild TBI.

All recent reviews and meta-analyses (54–59) have concluded that there is significant evidence for the efficacy of rTMS of the DLPFC as a therapeutic intervention for depression, headache or pain associated with TBI. In contrast, the effects were more moderate and variable with respect to the improvement of cognitive performance, including executive functions, attentional abilities, and memory, except perhaps for visuospatial memory tasks, whereas the level of evidence was very low for disorders of consciousness.

For example, in a series of 21 patients with refractory post-TBI headache, 4 sessions of 10 Hz rTMS administered to the left DLPFC showed a small but significant improvement in depressive symptoms on the Hamilton Rating Scale for Depression score (3-point reduction, 15% from baseline) after active but not sham rTMS, beyond major analgesic effects on headaches (60). However, other studies have shown less significant effects of rTMS on depression associated with TBI. First, in a series of 30 patients, only small and very variable beneficial effects were observed on depression following a protocol of 20 sessions of 1 Hz rTMS delivered to the right DLPFC (61). Second, in a series of 21 patients, no differences were observed between active and sham protocols of 20 sessions of sequential bilateral rTMS to the right and left DLPFC (62). Furthermore, in these studies, rTMS therapy improved post-concussion subjective symptoms (61) or cognitive performance regarding executive functions and working memory (62).

Thus, given the results of these previous studies, one can question the relevance of delivering rTMS at low (1 Hz) or high (10–20 Hz) frequency of stimulation to the DLPFC target depending on its laterality (right or left) and also the method to determine the optimal location of this DLPFC target (using cranial landmarks or image-guided navigation). On the one hand, in our case, rTMS trains were applied at high frequency on the DLPFC, whatever the hemisphere. On the other hand, one group targeted the DLPFC with individualized resting-state network brain mapping of the functional connectivity between the subgenual anterior cingulate cortex (sgACC) and the default-mode network using functional magnetic resonance imaging (63, 64). After 20 sequential bilateral rTMS sessions on this individualized target (low-frequency stimulation on the right side and high-frequency stimulation on the left side), TBI-associated depression was improved twice by active stimulation than by sham stimulation on the Montgomery-Asberg Depression Rating Scale score.

However, beyond depression, our study mainly showed rTMS-induced improvement on various cognitive symptoms. In the literature, at least six studies have evaluated the effects of rTMS delivered at high frequency over the left DLPFC on cognitive impairment associated with TBI (65–70). First, in 12 patients with mild TBI, 20 sessions of 10 Hz-rTMS delivered to the left DLPFC improved post-concussion symptoms, including cognitive deficits (mainly memory disturbances), for <3 months (65). Second, in 26 patients with cognitive complaints and a history of mild-to-moderate TBI, 5 sessions of 10 Hz-rTMS delivered to the left DLPFC improved executive functions and subjective measures of cognitive dysfunction related to a post-concussion syndrome, up to 2-week follow-up (66). In contrast, no effect of treatment was observed on cognitive test performance assessing selective attention control and verbal learning or fluency. Third, in 18 patients with persistent post-concussion syndrome, 13 sessions of 20 Hz rTMS delivered to the left DLPFC produced significant cognitive improvement up to 2 months after the intervention, but only in patients with recent TBI (<12 months) (67). In contrast, our patient benefited from rTMS therapy 10 years after the initial trauma. Finally, in two studies of patients with TBI, the overall effect of 10 Hz rTMS delivered to the left DLPFC produced either cognitive improvement below clinically meaningful thresholds (69) or no significant changes in executive function evaluated using the Trail Making Test Part B or other neuropsychological tests for attention, learning and visuospatial memory (70).

Concerning low-frequency (1 Hz) rTMS delivered to the right DLPFC, a protocol of 30 sessions twice-daily applied to 15 patients with mild TBI showed significant improvement in different post-concussion symptoms, such as pain, depression and anxiety, as well as in cognitive tasks assessing verbal fluency, working memory, selective attention, and cognitive processing speed (71). In contrast, there were no significant changes in executive functioning, fatigue severity, or apathy.

In all these studies, rTMS was applied in isolation, mainly targeting the left DLPFC and not associated with CogT at the same time. Only one study has previously evaluated the benefit of treating TBI-associated cognitive impairment by combining rTMS and CogT (72). In this retrospective study of 166 patients, half received rTMS and CogT and the other half (control group) various usual methods of treatment (72). The protocol was not well described but was based on 1 Hz-rTMS delivered to the DLPFC (likely to the right hemisphere) once a day, 5 days a week for 3 months, in combination with CogT (but not performed during the rTMS protocol), including various tasks to improve concentration, visuospatial memory, visual perception, judgment and reasoning. Cognitive improvement was significantly better in the rTMS-CogT group than in the control group.

Our case highlights several original elements likely to improve the therapeutic management of patients with TBI.

First, the benefit of using ONS to treat chronic refractory headaches secondary to TBI, even several years after the head trauma, must be emphasized, as this is the first case reported here. Our case broadens the spectrum of indications for this technique. It is important to point out that it is possible to perform this neuromodulation strategy non-invasively, using a TENS technique. ONS-TENS can be a temporary solution, but if this technique is effective but insufficient to control headaches over time, then this efficacy can be predictive of a good outcome provided by implanted ONS (73, 74).

Second, our case shows that the implantation of ONS can be well tolerated in patients who have previously had a head trauma, and that this implanted neuromodulation technique does not prohibit the subsequent performance of rTMS sessions, even on different cortical sites such as the posterior parietal areas.

Third, our case also shows that the treatment of headaches associated with TBI is a therapeutic priority, making it possible to trigger a virtuous circle of management of other post-concussion symptoms. Perhaps also the ONS could have direct beneficial effects on certain central dysfunctions, for example in the cognitive domain.

Fourth, the clinical results obtained in this patient may also suggest that the prior ONS could have set the stage for a significant and lasting improvement in cognitive performance and mood produced by the subsequent rTMS-CogT protocol. Persistent cognitive disorders may be responsible for anxiety and depression (75), possibly by alteration of dopaminergic circuits in the context of TBI, mainly concerning the striatum and the frontal/prefrontal cortex (76–78). It is therefore conceivable that the combination of techniques capable of modulating deep brain structures such as the basal ganglia on the one hand (ONS) and the cortical brain networks on the other hand (rTMS) could have a synergistic interest in reactivating dopaminergic circuits in order to improve various post-concussion symptoms in the context of TBI. This hypothesis could be tested in the future, in particular by functional brain imaging techniques.

Finally, our results support a likely greater efficacy (in terms of magnitude and duration) on improving cognitive performance and mood by means of a combined treatment with multisite rTMS and CogT compared to the rTMS strategy usually applied in isolation in the context of TBI, which is the stimulation of the DLPFC only (usually at high frequency on the left hemisphere). However, it is difficult to distinguish between (i) a potential beneficial effect of multisite stimulation related to the total stimulation dose or the modulation of cerebral connectivity, (ii) the specific effect of CogT, or (iii) the possible synergy between both approaches.

Of course, a single case does not justify unqualified approval of the techniques used. Additionally, given that most clinical measures improved linearly over time, this may suggest that the entire treatment received regularly may have benefited the patient rather than a specific technique (ONS or rTMS-CogT). It is also clear as we have repeatedly pointed out that the remission of the headaches contributed greatly to the overall improvement of the patient. Finally, it is obvious that this case does not eliminate a placebo effect of the different neuromodulation techniques used, and that the simple fact of being included in an innovative therapeutic program could have improved his symptoms, regarding mood for example. It must, however, be emphasized that the beneficial therapeutic effects were obtained very far from the initial traumatic episode and over a prolonged period of several years, which supports the real efficacy of the neuromodulation techniques that were added. In any case, this original observation opens the prospect of a controlled study on a larger sample, evaluating the effects on the various post-concussion symptoms that can be produced by means of an active multisite rTMS protocol compared to a sham condition and associated or not with a CogT protocol.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

TC and J-PN: conceived and designed the study. J-PL and AS: provided supervision. EL, SL, and SD: collected the data. All authors contributed to manuscript revision and read and approved the final version.

Conflict of interest

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.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. McCullagh S, Oucherlony D, Protzner A, Blair N, Feinstein A. Prediction of neuropsychiatric outcome following mild trauma brain injury: an examination of the Glasgow Coma Scale. *Brain Inj.* (2001) 15:489–97. doi: 10.1080/02699050010007353

2. Bigler ED. Neuropsychology and clinical neuroscience of persistent post-concussive syndrome. *J Int Neuropsychol Soc.* (2008) 14:1–22. doi: 10.1017/S135561770808017X

3. Brooks N, McKinlay W, Symington C, Beattie A, Campsie L. Return to work within the first seven years of severe head injury. *Brain Inj.* (1987) 1:5–19. doi: 10.3109/02699058709034439

4. Prigatano GP. Personality disturbances associated with traumatic brain injury. *J Consult Clin Psychol.* (1992) 60:360–8. doi: 10.1037/0022-006X.60.3.360

5. Riggio S. Traumatic brain injury and its neurobehavioral sequelae. *Neurol Clin.* (2011) 29:35–47. doi: 10.1016/j.ncl.2010.10.008

6. Arciniegas DB, Wortzel HS. Emotional and behavioral dyscontrol after traumatic brain injury. *Psychiatr Clin North Am.* (2014) 37:31–53. doi: 10.1016/j.psc.2013.12.001

7. Walker WC, Pickett TC. Motor impairment after severe traumatic brain injury: a longitudinal multicenter study. *J Rehabil Res Dev.* (2007) 44:975–82. doi: 10.1682/JRRD.2006.12.0158

8. Wiegner S, Donders J. Performance on the California Verbal Learning Test after traumatic brain injury. *J Clin Exp Neuropsychol.* (1999) 21:159–70. doi: 10.1076/jcen.21.2.159.925

9. Slovarp L, Azuma T, Lapointe L. The effect of traumatic brain injury on sustained attention and working memory. *Brain Inj.* (2012) 26:48–57. doi: 10.3109/02699052.2011.635355

10. Brooks J, Fos LA, Greve KW, Hammond JS. Assessment of executive function in patients with mild traumatic brain injury. *J Trauma.* (1999) 46:159–63. doi: 10.1097/00005373-199901000-00027

11. Wortzel HS, Arciniegas DB. Treatment of post-traumatic cognitive impairments. *Curr Treat Options Neurol.* (2012) 14:493–508. doi: 10.1007/s11940-012-0193-6

12. Arciniegas DB, Silver JM. Pharmacotherapy of posttraumatic cognitive impairments. *Behav Neurol.* (2006) 17:25–42. doi: 10.1155/2006/460592

13. Felmingham KL, Baguley IJ, Green AM. Effects of diffuse axonal injury on speed of information processing following severe traumatic brain injury. *Neuropsychology.* (2004) 18:564–71. doi: 10.1037/0894-4105.18.3.564

14. Scheid R, Walther K, Guthke T, Preul C, von Cramon DY. Cognitive sequelae of diffuse axonal injury. *Arch Neurol.* (2006) 63:418–24. doi: 10.1001/archneur.63.3.418

15. Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature.* (2007) 448:600–3. doi: 10.1038/nature06041

16. Munivenkatappa A, Devi BI, Shukla DP, Rajeswaran J. Role of the thalamus in natural recovery of cognitive impairment in patients with mild traumatic brain injury. *Brain Inj.* (2016) 30:388–92. doi: 10.3109/02699052.2015.1089599

17. Shirvalkar P, Seth M, Schiff ND, Herrera DG. Cognitive enhancement with central thalamic electrical stimulation. *Proc Natl Acad Sci USA.* (2006) 103:17007–12. doi: 10.1073/pnas.0604811103

18. Galetto V, Sacco K. Neuroplastic changes induced by cognitive rehabilitation in traumatic brain injury: a review. *Neurorehabil Neural Repair.* (2017) 31:800–13. doi: 10.1177/1545968317723748

19. Rochon E, Eskes GA, Skidmore ER, Winstein CJ. Editorial: combined therapeutic approaches to neurological rehabilitation. *Front Rehabil Sci.* (2022) 3:918005. doi: 10.3389/978-2-88976-469-3

20. Bentwich J, Dobronevsky E, Aichenbaum S, Shorer R, Peretz R, Khaigrekht M, et al. Beneficial effect of repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease: a proof of concept study. *J Neural Transm.* (2011) 118:463–71. doi: 10.1007/s00702-010-0578-1

21. Lee J, Choi BH, Oh E, Sohn EH, Lee AY. Treatment of Alzheimer's disease with repetitive transcranial magnetic stimulation combined with cognitive training: a prospective, randomized, double-blind, placebo-controlled study. *J Clin Neurol.* (2016) 12:57–64. doi: 10.3988/jcn.2016.12.1.57

22. Nguyen JP, Suarez A, Kemoun G, Meignier M, Le Saout E, Damier P, et al. Repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease. *Neurophysiol Clin.* (2017) 47:47–53. doi: 10.1016/j.neucli.2017.01.001

23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* (1975) 12:189–98. doi: 10.1016/0022-3956(75)90026-6

24. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a frontal assessment battery at bedside. *Neurology.* (2000) 55:1621–6. doi: 10.1212/WNL.55.11.1621

25. Obeso I, Casabona E, Bringas ML, Alvarez L, Jahanshahi M. Semantic and phonemic verbal fluency in Parkinson's disease: Influence of clinical and demographic variables. *Behav Neurol.* (2012) 25:111–8. doi: 10.3233/BEN-2011-0354

26. Shao Z, Janse E, Visser K, Meyer AS. What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Front Psychol.* (2014) 5:772. doi: 10.3389/fpsyg.2014.00772

27. Gélinas I, Gauthier L, McIntyre M, Gauthier S. Development of a functional measure for persons with Alzheimer's disease: the disability assessment for dementia. *Am J Occup Ther.* (1999) 53:471–81. doi: 10.5014/ajot.53.5.471

28. Bédard M, Molloy DW, Squire L, Dubois S, Lever JA, O'Donnell M. The Zarit Burden Interview: a new short version and screening version. *Gerontologist.* (2001) 41:652–7. doi: 10.1093/geront/41.5.652

29. Cano SJ, Posner HB, Moline ML, Hurt SW, Swartz J, Hsu T, et al. The ADAS-cog in Alzheimer's disease clinical trials: psychometric evaluation of the sum and its parts. *J Neurol Neurosurg Psychiatry.* (2010) 81:1363–8. doi: 10.1136/jnnp.2009.204008

30. Robert PH, Clairet S, Benoit M, Koutaich J, Bertogliati C, Tible O, et al. The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. *Int J Geriatr Psychiatry.* (2002) 17:1099–105. doi: 10.1002/gps.755

31. Mykletun A, Stordal E, Dahl AA. Hospital anxiety and depression (HAD) scale: factor structure, item analyses and internal consistency in a large population. *Br J Psychiatry.* (2001) 179:540–4. doi: 10.1192/bjp.179.6.540

32. Morris JC. Revised criteria for mild cognitive impairment may compromise the diagnosis of Alzheimer disease dementia. *Arch Neurol.* (2012) 69:700–8. doi: 10.1001/archneurol.2011.3152

33. Browne KD, Chen XH, Meaney DF, Smith DH. Mild traumatic brain injury and diffuse axonal injury in swine. *J Neurotrauma.* (2011) 28:1747–55. doi: 10.1089/neu.2011.1913

34. Laskowski RA, Creed JA, Raghupathi R. Pathophysiology of mild TBI: implications for altered signaling pathways. In: Kobeissy FH, editor. *Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects*. Boca Raton, FL: CRC Press/Taylor & Francis (2015).

35. Guerriero RM, Giza CC, Rotenberg A. Glutamate and GABA imbalance following traumatic brain injury. *Curr Neurol Neurosci Rep.* (2015) 15:27. doi: 10.1007/s11910-015-0545-1

36. Chamoun R, Suki D, Gopinath SP, Goodman JC, Robertson C. Role of extracellular glutamate measured by cerebral microdialysis in severe traumatic brain injury. *J Neurosurg.* (2010) 113:564–70. doi: 10.3171/2009.12.JNS09689

37. Cantu D, Walker K, Andresen L, Taylor-Weiner A, Hampton D, Tesco G, et al. Traumatic brain injury increases cortical glutamate network activity by compromising GABAergic control. *Cereb Cortex.* (2015) 25:2306–20. doi: 10.1093/cercor/bhu041

38. Lefaucheur JP. Principles of therapeutic use of transcranial and epidural cortical stimulation. *Clin Neurophysiol.* (2008) 119:2179–84. doi: 10.1016/j.clinph.2008.07.007

39. Lefaucheur JP. Methods of therapeutic cortical stimulation. *Neurophysiol Clin.* (2009) 39:1–14. doi: 10.1016/j.neucli.2008.11.001

40. Hoogendam JM, Ramakers GM, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimul.* (2010) 3:95–118. doi: 10.1016/j.brs.2009.10.005

41. Galimberti A, Tik M, Pellegrino G, Schuler AL. Effectiveness of rTMS and tDCS treatment for chronic TBI symptoms: a systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry.* (2023) 128:110863. doi: 10.1016/j.pnpbp.2023.110863

42. Abraham WC, Bear MF. Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci.* (1996) 19:126–30. doi: 10.1016/S0166-2236(96)80018-X

43. Wang F, Zhang Y, Wang L, Sun P, Luo X, Ishigaki Y, et al. Improvement of spatial learning by facilitating large-conductance calcium-activated potassium channel with transcranial magnetic stimulation in Alzheimer's disease model mice. *Neuropharmacology.* (2015) 97:210–9. doi: 10.1016/j.neuropharm.2015.05.027

44. Cao H, Zuo C, Gu Z, Huang Y, Yang Y, Zhu L, et al. High frequency repetitive transcranial magnetic stimulation alleviates cognitive deficits in 3xTg-AD mice by modulating the PI3K/Akt/GLT-1 axis. *Redox Biol.* (2022) 54:102354. doi: 10.1016/j.redox.2022.102354

45. Wang N, Jia Y, Zhou X, Wang X, Zhou H, Xiao N. Effects of repetitive transcranial magnetic stimulation on pallidum GABAergic neurons and motor function in rat models of kernicterus. *Brain Sci.* (2023) 13:1252. doi: 10.3390/brainsci13091252

46. Lefaucheur JP, Drouot X, Ménard-Lefaucheur I, Keravel Y, Nguyen JP. Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. *Neurology.* (2006) 67:1568–74. doi: 10.1212/01.wnl.0000242731.10074.3c

47. Fierro B, Brighina F, D'Amelio M, Daniele O, Lupo I, Ragonese P, et al. Motor intracortical inhibition in PD: L-DOPA modulation of high-frequency rTMS effects. *Exp Brain Res.* (2008) 184:521–8. doi: 10.1007/s00221-007-1121-y

48. Sun H, Gan C, Wang L, Ji M, Cao X, Yuan Y, et al. Cortical disinhibition drives freezing of gait in Parkinson's disease and an exploratory repetitive transcranial magnetic stimulation study. *Mov Disord.* (2023). in press. doi: 10.1002/mds.29595

49. Carrondo Cottin S, Gallani N, Cantin L, Prud'Homme M. Occipital nerve stimulation for non-migrainous chronic headaches: a systematic review protocol. *Syst Rev.* (2019) 8:181. doi: 10.1186/s13643-019-1101-x

50. Vanneste S, Mohan A, Yoo HB, Huang Y, Luckey AM, McLeod SL, et al. The peripheral effect of direct current stimulation on brain circuits involving memory. *Sci Adv.* (2020) 6:eaax9538. doi: 10.1126/sciadv.aax9538

51. Luckey AM, McLeod SL, Robertson IH, To WT, Vanneste S. Greater occipital nerve stimulation boosts associative memory in older individuals: a randomized trial. *Neurorehabil Neural Repair.* (2020) 34:1020–9. doi: 10.1177/1545968320943573

52. Walling I, Smith H, Gee LE, Kaszuba B, Chockalingam A, Barborica A, et al. Occipital nerve stimulation attenuates neuronal firing response to mechanical stimuli in the ventral posteromedial thalamus of a rodent model of chronic migraine. *Neurosurgery.* (2017) 81:696–701. doi: 10.1093/neuros/nyx135

53. Kovacs S, Peeters R, De Ridder D, Plazier M, Menovsky T, Sunaert S. Central effects of occipital nerve electrical stimulation studied by functional magnetic resonance imaging. *Neuromodulation.* (2011) 14:46–55; discussion 56–7. doi: 10.1111/j.1525-1403.2010.00312.x

54. Nardone R, Sebastianelli L, Versace V, Brigo F, Golaszewski S, Manganotti P, et al. Repetitive transcranial magnetic stimulation in traumatic brain injury: evidence from animal and human studies. *Brain Res Bull.* (2020) 159:44–52. doi: 10.1016/j.brainresbull.2020.03.016

55. Pink AE, Williams C, Alderman N, Stoffels M. The use of repetitive transcranial magnetic stimulation (rTMS) following traumatic brain injury (TBI): a scoping review. *Neuropsychol Rehabil.* (2021) 31:479–505. doi: 10.1080/09602011.2019.1706585

56. Mollica A, Greben R, Oriuwa C, Siddiqi SH, Burke MJ. Neuromodulation treatments for mild traumatic brain injury and post-concussive symptoms. *Curr Neurol Neurosci Rep.* (2022) 22:171–81. doi: 10.1007/s11910-022-01183-w

57. Ahorsu DK, Adjaottor ES, Lam BYH. Intervention effect of non-invasive brain stimulation on cognitive functions among people with traumatic brain injury: a systematic review and meta-analysis. *Brain Sci.* (2021) 11:840. doi: 10.3390/brainsci11070840

58. Tsai PY, Chen YC, Wang JY, Chung KH, Lai CH. Effect of repetitive transcranial magnetic stimulation on depression and cognition in individuals with traumatic brain injury: a systematic review and meta-analysis. *Sci Rep.* (2021) 11:16940. doi: 10.1038/s41598-021-95838-2

59. Li X, Lu T, Yu H, Shen J, Chen Z, Yang X, et al. Repetitive transcranial magnetic stimulation for neuropathic pain and neuropsychiatric symptoms in traumatic brain injury: a systematic review and meta-analysis. *Neural Plast.* (2022) 2022:2036736. doi: 10.1155/2022/2036736

60. Leung A, Metzger-Smith V, He Y, Cordero J, Ehlert B, Song D, et al. Left dorsolateral prefrontal cortex rTMS in alleviating MTBI related headaches and depressive symptoms. *Neuromodulation.* (2018) 21:390–401. doi: 10.1111/ner.12615

61. Rao V, Bechtold K, McCann U, Roy D, Peters M, Vaishnavi S, et al. Low-frequency right repetitive transcranial magnetic stimulation for the treatment of depression after traumatic brain injury: a randomized sham-controlled pilot study. *J Neuropsychiatry Clin Neurosci.* (2019) 31:306–18. doi: 10.1176/appi.neuropsych.17110338

62. Hoy KE, McQueen S, Elliot D, Herring SE, Maller JJ, Fitzgerald PB, et al. Pilot investigation of repetitive transcranial magnetic stimulation for post-traumatic brain injury depression: safety, tolerability, and efficacy. *J Neurotrauma.* (2019) 36:2092–8. doi: 10.1089/neu.2018.6097

63. Siddiqi SH, Trapp NT, Hacker CD, Laumann TO, Kandala S, Hong X, et al. Repetitive transcranial magnetic stimulation with resting-state network targeting for treatment-resistant depression in traumatic brain injury: a randomized, controlled, double-blinded pilot study. *J Neurotrauma.* (2019) 36:1361–74. doi: 10.1089/neu.2018.5889

64. Siddiqi SH, Kandala S, Hacker CD, Trapp NT, Leuthardt EC, Carter AR, et al. Individualized precision targeting of dorsal attention and default mode networks with rTMS in traumatic brain injury-associated depression. *Sci Rep.* (2023) 13:4052. doi: 10.1038/s41598-022-21905-x

65. Koski L, Kolivakis T, Yu C, Chen JK, Delaney S, Ptito A. Noninvasive brainstimulation for persistent postconcussion symptoms in mild traumatic braininjury. *J Neurotrauma.* (2015) 32:38–44. doi: 10.1089/neu.2014.3449

66. Franke LM, Gitchel GT, Perera RA, Hadimani RL, Holloway KL, Walker WC. Randomized trial of rTMS in traumatic brain injury: improved subjective neurobehavioral symptoms and increases in EEG delta activity. *Brain Inj.* (2022) 36:683–92. doi: 10.1080/02699052.2022.2033845

67. Moussavi Z, Suleiman A, Rutherford G, Ranjbar Pouya O, Dastgheib Z, Zhang W, et al. A pilot randomised double-blind study of the tolerability and efficacy of repetitive transcranial magnetic stimulation on persistent post-concussion syndrome. *Sci Rep.* (2019) 9:5498. doi: 10.1038/s41598-019-41923-6

68. Stilling JM, Duszynski CC, Oni I, Paxman E, Dunn JF, Debert CT. Using functional near-infrared spectroscopy to study the effect of repetitive transcranial magnetic stimulation in concussion: a two-patient case study. *Front Neurol.* (2019) 10:476. doi: 10.3389/fneur.2019.00476

69. Stilling J, Paxman E, Mercier L, Gan LS, Wang M, Amoozegar F, et al. Treatment of persistent post-traumatic headache and post-concussion symptoms using repetitive transcranial magnetic stimulation: a pilot, double-blind, randomized controlled trial. *J Neurotrauma.* (2020) 37:312–23. doi: 10.1089/neu.2019.6692

70. Neville IS, Zaninotto AL, Hayashi CY, Rodrigues PA, Galhardoni R, Ciampi de Andrade D, et al. Repetitive TMS does not improve cognition in patients with TBI: a randomized double-blind trial. *Neurology.* (2019) 93:e190–9. doi: 10.1212/WNL.0000000000007748

71. Meek BP, Hill S, Modirrousta M. Accelerated repetitive transcranial magnetic stimulation in the treatment of post-concussion symptoms due to mild traumatic brain injury: a pilot study. *Brain Inj.* (2021) 35:48–58. doi: 10.1080/02699052.2020.1857837

72. Zhou L, Huang X, Li H, Guo R, Wang J, Zhang Y, et al. Rehabilitation effect of rTMS combined with cognitive training on cognitive impairment after traumatic brain injury. *Am J Transl Res.* (2021) 13:11711–7.

73. Nguyen JP, Nizard J, Kuhn E, Carduner F, Penverne F, Verleysen-Robin MC, et al. A good preoperative response to transcutaneous electrical nerve stimulation predicts a better therapeutic effect of implanted occipital nerve stimulation in pharmacologically intractable headaches. *Neurophysiol Clin.* (2016) 46:69–75. doi: 10.1016/j.neucli.2015.12.002

74. Nguyen JP, Raoul S, Desal H, Bourcier R, Kuhn E, Dixneuf V, et al. Treatment of refractory headache secondary to intracranial endovascular procedure by transcutaneous electrical nerve stimulation of the occipital nerve. *Neurophysiol Clin.* (2018) 48:309–12. doi: 10.1016/j.neucli.2018.05.041

75. Bales JW, Wagner AK, Kline AE, Dixon CE. Persistent cognitive dysfunction after traumatic brain injury: a dopamine hypothesis. *Neurosci Biobehav Rev.* (2009) 33:981–1003. doi: 10.1016/j.neubiorev.2009.03.011

76. McDonald BC, Flashman LA, Saykin AJ. Executive dysfunction following traumatic brain injury: neural substrates and treatment strategies. *NeuroRehabilitation.* (2002) 17:333–44. doi: 10.3233/NRE-2002-17407

77. Chudasama Y, Robbins TW. Functions of frontostriatal systems in cognition: comparative neuropsychopharmacological studies in rats, monkeys and humans. *Biol Psychol.* (2006) 73:19–38. doi: 10.1016/j.biopsycho.2006.01.005

78. Verduzco-Mendoza A, Carrillo-Mora P, Avila-Luna A, Gálvez-Rosas A, Olmos-Hernández A, Mota-Rojas D, et al. Role of the dopaminergic system in the striatum and its association with functional recovery or rehabilitation after brain injury. *Front Neurosci.* (2021) 15:693404. doi: 10.3389/fnins.2021.693404

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 30 April 2024
DOI 10.3389/fneur.2024.1381390

OPEN ACCESS

EDITED BY
Giovanni Abbruzzese,
University of Genoa, Italy

REVIEWED BY
Matteo Bologna,
Sapienza University of Rome, Italy
Laura Avanzino,
University of Genoa, Italy

*CORRESPONDENCE
Jean-Pascal Lefaucheur
✉ jean-pascal.lefaucheur@hmn.aphp.fr

RECEIVED 03 February 2024
ACCEPTED 16 April 2024
PUBLISHED 30 April 2024

CITATION
Bleton J-P, Cossé C, Caloc'h T, Suarez Moreno A, Diverres E, Derkinderen P, Nizard J, Lefaucheur J-P and Nguyen J-P (2024) Combination of anodal tDCS of the cerebellum with a goal-oriented motor training to treat cervical dystonia: a pilot case series.
Front. Neurol. 15:1381390.
doi: 10.3389/fneur.2024.1381390

Combination of anodal tDCS of the cerebellum with a goal-oriented motor training to treat cervical dystonia: a pilot case series

Jean-Pierre Bleton[1], Charlotte Cossé[2], Tiphanie Caloc'h[2], Alcira Suarez Moreno[2], Elisabeth Diverres[2], Pascal Derkinderen[3], Julien Nizard[4,5], Jean-Pascal Lefaucheur[5,6]* and Jean-Paul Nguyen[2]

[1]Neurology Department, Clinical Research Department, Hôpital Fondation Adolphe de Rothschild, Paris, France, [2]Unité de Stimulation Transcrânienne, Clinique Bretéché, Groupe Elsan, Nantes, France, [3]Service de Neurologie, CHU de Nantes, Nantes, France, [4]Service Douleur, Soins Palliatifs et de Support et UIC22, Hôpital Laennec, CHU, Nantes, France, [5]EA 4391, Équipe ENT (Nerve Excitability and Therapeutics), Université Paris-Est Créteil, Créteil, France, [6]Unité de Neurophysiologie Clinique, Hôpital Henri Mondor, Assistance Publique—Hôpitaux de Paris (AP-HP), Créteil, France

Background: Transcranial Direct Current Stimulation (tDCS) of the cerebellum shows promise for the treatment of dystonia. Specific motor rehabilitation programs have also been developed in this context. However, the combination of these two approaches has not yet been evaluated to determine their therapeutic potential.

Methods: We report a series of 5 patients with cervical dystonia (CD) poorly controlled by botulinum toxin injections. They were initially treated by a protocol of repeated daily sessions (for 3 or 5 days) of cerebellar anodal tDCS (cer-atDCS) applied alone. In a second time, additional protocols of cer-atDCS were performed in combination with a program of goal-oriented motor training exercises (Mot-Training), specifically developed for the treatment of CD. The clinical impact of the procedures was assessed on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).

Results: Compared to baseline, the maximum percentage of TWSTRS total score improvement was 37% on average after cer-atDCS performed alone ($p = 0.147$, not significant) and 53% on average after cer-atDCS combined with Mot-Training ($p = 0.014$, significant). The TWSTRS pain and functional handicap subscores also improved after the combined protocol. A score of (+3) to (+5) was rated on the TWSTRS response scale after cer-atDCS performed alone or the combined protocol, corresponding to a moderate to striking improvement on dystonia and pain. This improvement lasted longer after the combined protocol than after cer-atDCS alone (3.4 vs. 1.4 months on average, $p = 0.011$).

Conclusion: The combination of cer-atDCS with Mot-Training produced a greater and more prolonged improvement than the application of cer-atDCS alone. Such a combined therapeutic procedure is easy to perform and opens important perspectives in the long-term treatment of CD. These results remain to be confirmed by a randomized sham-controlled trial on a larger sample.

KEYWORDS

cerebellar stimulation, cervical dystonia, motor training, neuromodulation, non-invasive brain stimulation, transcranial direct current stimulation, rehabilitation

Introduction

Like other forms of dystonia, cervical dystonia (CD) is marked by an involuntary and inappropriate contraction of certain muscle groups that causes abnormal movements and postures. The main therapeutic strategies are based on the injection of botulinum toxin (BTX), which aims to weaken overactive contracted muscles (agonists) and on physiotherapy, which aims to reinforce the activity of the corrective muscles (antagonists) to improve tonic balance (1). The principle, technique, and results of BTX injections are well known and this treatment is effective in approximately 70% of cases, but the injections must be repeated every 3 months (2). Regarding physiotherapy, a motor training program (Mot-Training) has been developed by Bleton (3) and taken up by other authors (4, 5), which aims to gradually strengthen the activity of the corrective muscles and is well suited for long-term clinical application. The notions of duration, repetition and progressiveness are currently well highlighted in rehabilitation programs for the treatment of dystonia aimed at acting on neuronal neuroplasticity in the medium and long term (6, 7).

Although the cause of dystonia remains unknown, the main pathophysiological mechanism involved lies in a dysfunction within the neural networks connecting the cerebellum, the basal ganglia and the sensorimotor cortex (8). Also, it seems relevant to apply neuromodulation techniques to modulate these networks and correct this dysfunction. In clinical practice, neuromodulation therapy of dystonia is essentially performed invasively, using surgically implanted electrodes and stimulators. Thus, deep brain stimulation (DBS) techniques were developed, mainly targeted at the level of the pallidum and/or the thalamus for the treatment of dystonia. DBS is effective and fully justified in severe forms of generalized dystonia (9). It also seems effective in the context of focal dystonia, including CD (10), but the benefit/risk ratio here is more debatable. On the other hand, there are also non-invasive neuromodulation techniques, mainly repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). In their therapeutic application for focal dystonia, these techniques (rTMS or tDCS) have mainly targeted the motor or premotor cortex and the cerebellum [see review in Lefaucheur et al. (11)] and have shown some efficacy in the treatment of CD. In particular, a beneficial effect of cerebellar anodal tDCS (cer-atDCS) was reported in two patients with CD (12, 13). Despite positive short-term results, the therapeutic effect was reported to be only transient, requiring repeated stimulation sessions to be maintained (13). By analogy with what has been shown for motor rehabilitation of stroke patients (14), we proposed a combined approach, associating tDCS and physical therapy for the treatment of dystonia. Thus, we aimed at improving and prolonging the therapeutic effect of tDCS by combining repeated sessions of cer-atDCS with a program of physiotherapy (Mot-Training) specifically developed for the management of dystonic patients (3, 15). We report five cases of patients with CD initially treated with cer-atDCS alone then with the combination of cer-atDCS and Mot-Training. The objective of this case series was to show the additional value of combining physiotherapy with non-invasive cortical stimulation for the treatment of CD.

Methods

Patients and study plan

All five patients included in this study had reduced efficacy of BTX injections for the treatment of primary idiopathic CD. Study plan includes two phases. The first phase was based on the administration of cer-atDCS protocol alone (three or five daily sessions of 20-min duration within a week). The second phase was based on the administration of cer-atDCS protocol (also three or five daily sessions within a week) combined with Mot-Training. The Mot-Training protocol lasted 20 min, was tailored to the clinical characteristics of each patient (see below) and was performed during the cer-atDCS session (see Supplementary Video S1).

The switch between the first and the second phase was linked to the availability of the physiotherapist when recruited in our center. Thus, patients received the cer-atDCS protocol alone for a variable duration before being able to start with the combined protocol. The duration of follow-up after a stimulation protocol was related to patients' availability to return to our center and the duration of post-session improvement.

Clinical assessment

Patients were assessed at the end of each week of stimulation protocol (cer-atDCS alone or combined with Mot-Training) on the French version (16) of the Toronto Western spasmodic torticollis rating scale (TWSTRS) (17). This scale includes three subscores: a severity score (max: 35), a functional handicap score (max: 30) and a pain score (max: 20) for a total score up to 85, with a more elevated score corresponding to a more severe CD. In addition, this scale includes a response scale, ranging from (−1) to (+5). On this scale, a score of (−1) corresponds to a worsening after treatment; a score of (0) corresponds to the absence of worsening or improvement; a score of (+1) corresponds to a minimal or questionable reduction in dystonia and pain without functional improvement; a score of (+2) corresponds to a mild response with some reduction in dystonia and pain and little functional improvement; a score of (+3) corresponds to a moderate response with a noticeable reduction in dystonia and pain and significant functional improvement; a score of (+4) corresponds to a clear response with obvious reduction in dystonia and pain and excellent functional improvement; a score of (+5) corresponds to a striking improvement with little or no dystonia or pain remaining. Additionally, investigators asked patients about the duration of clinical

response they subjectively experienced after completion of each protocol.

Statistical analyses were performed with a paired t test after confirming that the data were sampled from a Gaussian distribution and passed the normality test using the method of Kolmogorov and Smirnov. Paired comparisons were made for the various TWSTRS scores between data obtained in the two phases of the study (after cer-atDCS alone or combined with Mot-Training) compared to baseline (before any cer-atDCS protocol). Two sets of data were used, either the values observed after the last treatment session or the lowest value observed during the two phases of the study.

Cerebellar tDCS

Initially, patients were treated with cer-atDCS alone. We used the HDC kit stimulator (Inomed, Emmendingen, Germany) which allows stimulation by two anodes and one cathode (large square electrodes). The anodes (5 × 5 cm) were placed on each of the two cerebellar hemispheres (1–2 cm below and 3–4 cm lateral to the inion). The cathode (8.5 × 6 cm) was placed on the right supraorbital region. Each cer-atDCS session lasted 20 min with a stimulation intensity of 2 mA. Repeating one session daily for three to five consecutive days over the course of a week has been shown to produce lasting clinical benefit in dystonic patients, especially on CD in our experience.

Motor training program

As each clinical presentation of CD is unique, there is no standardized physiotherapy rehabilitation program suitable for all patients. Optimal motor training exercises should be selected based on assessment of three-dimensional disorganization of head posture in each patient (18): transverse (torticollis), coronal (laterocollis), or sagittal (retrocollis or antecollis). Disorganization of head posture may be present simultaneously in multiple planes in a patient with CD. For example, a rotational torticollis may be combined with a laterocollis and a retrocollis. They can also be associated with head displacement in the sagittal plane (anterior or posterior shift) or the coronal plane (lateral shift). Postural disorders and disorganization of cervicocephalic movements are linked to the involvement of overactive (dystonic agonists) and underactive (inhibited antagonists) muscles.

Physiotherapy should focus on activating functionally impaired corrective antagonistic muscles (19). Different levels of difficulty of Mot-Training can be proposed according to the severity of their inhibition. First, the head can be turned to the anti-dystonic side in association with facilitation techniques, such as raising the arms or lying on the back, or the head can be rapidly and repeatedly turned as if to say "No." Second, the head can be voluntarily brought to the anti-dystonic side without using facilitation techniques. Third, the head can be controlled and maintained turned to the anti-dystonic side. Fourth, the movement of the head can be controlled through a full range of motion (from the pro- to the anti-dystonic side) and replaced in a stable position on the midline with the eyes open or closed (proprioceptive control) (20, 21). In this case, exercises should be performed slowly so that they can be controlled from the moment they are initiated to the moment the head returns to the resting position. This prevents the phenomenon of overflow and parasitic co-contractions (22). It usually takes 5–10 s to complete an exercise through its full range of motion. Exercises are interspersed with a rest period equivalent to the duration of the exercise. It has been shown that it was necessary to repeat the exercise for about 20 min to obtain a significant clinical impact (3, 15). Thus, motor training is able to promote neuroplasticity and therefore provide lasting effects over time (23).

An example of Mot-Training program is detailed for patient 1 This woman developed a blepharospasm at the age of 56 and a CD consisting of an antecollis with a left laterocollis a few months later. In this patient, two main deformities were present (Supplementary Video S1, segment 1): (i) left rotational torticollis with active rotation to the anti-dystonic side possible but difficult to control, coupled with compensatory involvement of the shoulder girdle; (ii) an anterior shift of the head in (also called "turtleneck"). Also, according to the control modalities described previously, three tailored Mot-Training exercises were proposed, performed in a seated position, and repeated for 20 min (Supplementary Video S1, segment 2):

- Exercise 1: correction of the anterior dystonic shift by the so-called "double chin" exercise. This exercise consists in moving the head back and placing the chin on the neck (flexion of the lower cervical spine) while keeping the gaze horizontal and straightening up. This exercise reduces cervical hyperlordosis related to dystonic muscle activity (24) by a double movement of extension of the lower cervical spine and flexion of the upper cervical spine. This corrective posture involves the active participation of the deficient extensor muscles of the lower cervical spine (such as levator scapulae, semispinalis and longissimus cervicis muscles) and of the upper cervical spine (such as longus colli et captitis muscles), not in force but in endurance.
- Exercise 2: corresponding to the exercise 1 coupled with a corrective cervical rotation toward the anti-dystonic side (to the right in our patient). This exercise consists of performing a slow and complete cervicocephalic rotation while maintaining the "double chin" posture. This corrective movement involves the active participation of deficient cervical spine rotator muscles (such as obliquus capitis inferior, splenius and sternocleidomastoid muscles).
- Exercise 3: active corrective rotation toward the anti-dystonic side without compensatory movement of the trunk and the shoulder girdle. This exercise consisted in placing the hands behind the head, fingers crossed and elbows apart, before turning the face to the anti-dystonic side and holding this position for 5 to 6 s, before finally replacing the head to a neutral position. This endurance exercise had to be practiced without force to avoid a dystonic reaction.

Results

All five patients included had primary idiopathic CD, but an additional contribution of neuroleptic-induced dystonia was suspected in patient 4. Main clinical features are presented in Table 1.

TABLE 1 Patients' demographical data and performed protocol.

	Gender	Age (years)	Disease duration (years)	BTX injection efficacy	Number of cer-atDCS protocols in the first phase	Number of cer-atDCS + Mot-Training protocols in the second phase	Total follow-up duration (months)
Patient 1	F	79	23	Loss of efficacy since 4 months	5 (spaced 3 months apart)	1	22.5 months
Patient 2	F	75	10	Reduced efficacy on pain since 3 months	3 (spaced 1 month apart)	6 (spaced 2 months apart)	17 months
Patient 3	M	63	10	No BTX therapy	2 (spaced 1 month apart)	4 (spaced 3 months apart)	15.5 months
Patient 4	F	40	11	Loss of efficacy since 3 months	1	12 (spaced 2 months apart)	28 months
Patient 5	F	56	4	Reduced efficacy on pain since 2 months	1	8 (spaced 4 months apart)	35 months

BTX, botulinum toxin; cer-atDCS, anodal transcranial direct current stimulation of the cerebellum; Mot-Training, physiotherapy based on motor training exercises.

The patients were four women and one man (patient 3), aged from 40 to 79 years. The duration of CD symptoms ranged from four to 23 years. One patient (patient 3) had refused BTX injection treatment for personal reasons. In the other patients, BTX injections were spaced by 2 months (patient 5), 3 months (patients 2 and 4), or 4 months (patient 1). Overall, BTX injections had lost their efficacy on dystonia (patients 1 and 4) or on pain associated with dystonia (patients 2 and 5) for several months.

In the first phase of the study, the cer-atDCS protocol consisted of one daily session on three consecutive days for patients 2 to 5 and on five consecutive days within a week for patient 1. The number of cer-atDCS protocols was only one for two patients, and two to five (spaced 1 to 3 months apart) for the remaining three patients. Clinical assessment, based on the TWSTRS, is presented in Table 2 and was performed at the end of each week of cer-atDCS protocols, except for patient 2 after the second protocol. The TWSTRS total score ranged from 30 to 58 (mean ± standard deviation: 45.3 ± 10.1) at baseline, from 29 to 46 (34.6 ± 6.7) after the last cer-atDCS protocol ($p = 0.158$, paired t test, not significant), and from 15 to 46 (28.6 ± 13.2) after the most efficacious cer-atDCS protocol for each patient ($p = 0.147$, not significant). Thus, the maximum percentage of TWSTRS total score improvement after cer-atDCS performed alone was 37% on average. For example, the improvement on the TWSTRS total score was marked by a 38% decrease in patient 1 (Supplementary Video S1, segment 3). Only the TWSTRS pain subscore significantly improved after the last or the most efficacious cer-atDCS protocol ($p < 0.01$), but not the other TWSTRS subscores. Overall, a score of (+3) to (+5) was rated on the TWSTRS response scale after cer-atDCS protocols, corresponding to a moderate to striking improvement on dystonia and pain. The duration of subjective improvement after completion of a cer-atDCS protocol ranged from 1 to 3 months (1.4 ± 0.9).

In the second phase of the study, the cer-atDCS protocol was combined with Mot-Training and was performed on three consecutive days in patients 2 and 4 and on five consecutive days within a week in patients 1, 3 and 5. The number of combined protocols was only one for patient 1, and four to 12 (spaced 2 to 4 months apart) for the remaining three patients. The TWSTRS, was scored at the end of each week of combined protocols, except for patients 2 and 5 after the fourth protocol and for patients 4 after the eighth protocol (Table 2). The TWSTRS total score ranged from 12 to 38 (24.2 ± 11.0) after the last combined protocol ($p = 0.033$, significantly reduced compared to baseline), and from 12 to 30 (21.4 ± 8.3) after the most efficacious combined protocol for each patient ($p = 0.014$, also significant). Thus, the maximum percentage of TWSTRS total score improvement after cer-atDCS combined with Mot-Training was 53% on average. As after the cer-atDCS protocol performed alone, the TWSTRS pain subscore significantly improved after the last or the most efficacious combined protocol ($p < 0.01$), but also the TWSTRS functional handicap subscore ($p < 0.05$). Again, a score of (+3) to (+5) was rated on the TWSTRS response scale after combined protocols, corresponding to a moderate to striking improvement on dystonia and pain. The duration of subjective improvement after completion of a combined protocol ranged from 2 to 6 months (3.4 ± 1.7), which was significantly longer than after cer-atDCS performed alone ($p = 0.011$).

Except for patient 3, all patients continued BTX injections, which were performed on the week before the cer-atDCS sessions in all cases. It is not possible to assess whether BTX injections played a synergistic role with cer-atDCS therapy (combined or not with Mot-Training) in the clinical improvement, which was observed even though the schedule and doses of BTX were kept similar to the pre-stimulation period, except in patient 5, for whom, because of the clear clinical improvement, the BTX injections were spaced from 2 to 3.5 months apart.

Discussion

In this open-label pilot case series of patients with CD, the combination of Mot-Training with cer-atDCS produced a greater and more prolonged improvement in dystonia, compared to the application of cer-atDCS alone.

The mechanism of action of tDCS is not fully known (25). The delivered constant current modulates the excitability of neurons by modifying the axonal membrane potential (depolarization or

TABLE 2 Clinical results assessed on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).

	Baseline	Post-Session 1 (cer-atDCS)	Post-Session 2 (cer-atDCS)	Post-Session 3 (cer-atDCS)	Post-Session 5 (cer-atDCS)	Post-Session 1 (cer-atDCS + Mot-training)	Post-Session 4 (cer-atDCS + Mot-training)	Post-Session 6 (cer-atDCS + Mot-training)	Post-Session 8 (cer-atDCS + Mot-training)	Post-Session 12 (cer-atDCS + Mot-training)
Severity score (max: 35)										
Patient 1	22	18	4	3	15	3				
Patient 2	21	4	NA	18		13	NA	15		
Patient 3	13	10	10			7	16			
Patient 4	7	4				8	12	12	NA	8
Patient 5	5	13				11	NA	8	2	
Functional handicap score (max: 30)										
Patient 1	23	11	9	4	8	4				
Patient 2	19	10	NA	11		9	NA	8		
Patient 3	20	17	16			11	7			
Patient 4	18	29				12	15	10	NA	15
Patient 5	10	14				8	NA	8	3	
Pain score (max: 20)										
Patient 1	13	8	5	8	6	5				
Patient 2	8.5	2	NA	3		7	NA	6		
Patient 3	12	8	5			4	5			
Patient 4	20	13				9	11	8	NA	15
Patient 5	15	8				13	NA	8	9	
Total score (max: 85)										
Patient 1	58	37	18	15	29	12				
Patient 2	48.5	16	NA	32		29	NA	29		
Patient 3	45	36	31			22	28			
Patient 4	45	46				29	38	30	NA	38
Patient 5	30	35				32	NA	24	14	
Response score (−1/+5)										
Patient 1		5	4	4	4	5				
Patient 2		3	NA	3		3	NA	4		
Patient 3		3	3			3	5			
Patient 4		0				4	3	4	NA	3
Patient 5		0				0	NA	4	5	

cer-atDCS, anodal transcranial direct current stimulation of the cerebellum; Mot-Training, physiotherapy based on motor trainir

10.3389/fneur.2024.1381390

hyperpolarization) but these currents are too weak to generate action potentials and therefore directly activate a neuronal circuit (26, 27), unlike what happens with rTMS. However, while the current generated by rTMS with a figure-of-8 coil remains relatively focal into the brain, the current generated by a bipolar tDCS montage has a very broad distribution, and potentially the effect of polarization of many neurons (even of glial cells) can produce an amplifying effect. Thus, tDCS can indisputably produce clinical effects in the short term lasting beyond the stimulation session, and also in a longer term, with sustainable changes in synaptic transmission and neuroplasticity effects that can result from repeated sessions.

In this pilot case series, CD was improved by 37% on average on the TWSTRS score after cer-atDCS performed alone, with a duration of subjective improvement ranging from 1 to 3 months. These results support the lasting effect of tDCS and the value of cerebellar targeting for neuromodulation of sensorimotor disorders (28). However, when cer-atDCS was combined with Mot-Training, clinical improvement reached 53% on average on the TWSTRS score, with a significantly longer duration of efficacy of 2 to 6 months. According to the concept of metaplasticity (29, 30), the additional effect of the combined strategy suggests a priming effect of tDCS that would modify the level of synaptic activity of certain neuronal circuits, placing the brain in a favorable state to boost long-term synaptic plasticity processes produced by Mot-Training.

In fact, the place of physiotherapy in the treatment of CD is not well defined, usually considered as an adjuvant therapy in addition to BTX injections (31–33). The physiotherapy program used here (Mot-Training) is a personalized rehabilitation program focused on the activation of anti-dystonic cervical muscles to alleviate their inhibition and integrate them into the correction of cervical posture and movements. As for neuromodulation, the repetition of Mot-Training sessions at short intervals can promote adaptative synaptic plasticity, especially if the sessions are maintained over a long period of time (6, 7, 23). In CD, instrumental techniques based on peripheral nerve stimulation or biofeedback (33–36) require a technical environment that is hardly compatible with long-term application. The same is true with rehabilitation techniques that involve too much physical intensity. The Mot-Training protocol (3) used here responds well to these feasibility criteria in terms of frequency and duration over time and therefore of clinical relevance for treating CD. It is also for this reason that it appeared to us to be ideal for combining with tDCS with a view to potentiating the clinical effects of these two therapies.

Limitations

First, the main limitation of this report lies in the small sample size, which limits the representativeness of the results.

Second, our patients received an open-label treatment, which of course cannot rule out a placebo effect.

Third, the combined protocol had greater efficacy than tDCS alone, but in the absence of a control condition consisting of Mot-Training alone, it is not possible to know whether cer-atDCS has an additive or synergistic effect compared to that of Mot-Training.

Fourth, the methodology presents significant heterogeneity in terms of protocol applied in each patient. For example, the number of cer-atDCS sessions was not the same among the 5 participants, from one to five cer-atDCS sessions in the first phase and from one to 12 cer-atDCS sessions combined with Mot-Training in the second phase. The protocol should have been more standardized and not solely dependent on patients' availability to return to the center, but this is a naturalistic proof-of-concept pilot study.

Fifth, heterogeneity also applies to the clinical profile, such as a variable age, between 40 and 79 years. There is also clinical variability regarding the dystonic pattern and disease severity exhibited by patients. Additionally, the series included a patient with suspected neuroleptic-induced dystonia, introducing a potential confounding factor.

Sixth, four out of five patients continued BTX injections during the experimental procedure, with varying injection intervals and without standardized time between procedures. This factor could have a significant impact on the results obtained, as discussed for the two previously reported cases of patients with CD who benefited from cer-atDCS (11). It is possible that the combined strategy could have restored a certain efficacy to the BTX injections and therefore that this also contributed to the clinical improvement through an additive or synergistic effect. Thus, a potentiating effect of neuromodulation techniques (rTMS or tDCS) with BTX injections could be expected for the treatment of CD or blepharospasm for example (12, 13, 37).

Conclusion and perspectives

Although placebo effects cannot be excluded, this open-label case series suggests that the combination of cer-atDCS with Mot-Training would have a greater potential for clinical efficacy in terms of intensity and duration than either technique taken in isolation. In the context of CD, only one previous study (38) had shown a therapeutic benefit on the severity of dystonia symptoms of a non-invasive brain stimulation technique applied to the cerebellum (an rTMS protocol called intermittent theta-burst stimulation) combined with motor training for the neck and an implicit learning task. In our series, patients reported sustained clinical improvement for several weeks after repeated sessions of cer-atDCS at short intervals, suggesting potential value of this approach for the treatment of CD in daily practice. Furthermore, from the perspective of a clinical application, another favorable element is the fact that the practice of tDCS can be performed at home. As the rehabilitation protocol is also self-applicable by the patient, the combined therapeutic strategy could be entirely performed at home, after initial training of the patient in a hospital environment. This is an extremely important perspective both in terms of the clinical impact of this type of treatment and in terms of healthcare costs.

In conclusion, the results observed in this pilot case series justify considering a larger study comparing the results provided for the treatment of CD in the long term (6 to 12 months) by the application of cer-atDCS alone, Mot-Training alone, and cer-atDCS combined with Mot-Training, including a sham procedure for the stimulation part.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was not required for the studies involving humans because they correspond to retrospective research conducted on already available and anonymous data. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

J-PB: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. CC: Writing – review & editing, Investigation. TC: Writing – review & editing, Investigation. AS: Writing – review & editing, Investigation. ED: Writing – review & editing, Investigation. PD: Writing – review & editing, Investigation. JN: Writing – review & editing, Investigation. J-PL: Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis. J-PN: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1381390/full#supplementary-material

SUPPLEMENTARY VIDEO S1
Clinical examination of patient 1. Segment 1: identification of the "corrective muscles" (antagonists) of the dystonic attitude including an antecollis associated with a laterocollis to the left and shoulder drop. Segment 2: the three motor training exercises: (1) pull the head slightly back and reduce hyperlordosis (double-chin exercise); (2) same exercise combined with rotation of the head and neck to the anti-dystonic side; (3) elevation of the shoulders and rotation the head and neck to the anti-dystonic side. Segment 3: significant improvement after five consecutive days of treatment combining cerebellar anodal tDCS and motor training exercises.

References

1. Comella C, Bhatia K. An international survey of patients with cervical dystonia. *J Neurol.* (2015) 262:837–48. doi: 10.1007/s00415-014-7586-2

2. Hsiung GY, Das SK, Ranawaya R, Lafontaine AL, Suchowersky O. Long-term efficacy of botulinum toxin a in treatment of various movement disorders over a 10-year period. *Mov Disord.* (2002) 17:1288–93. doi: 10.1002/mds.10252

3. Bleton JP. Physiotherapy of focal dystonia: a physiotherapist's personal experience. *Eur J Neurol.* (2010) 17:107–12. doi: 10.1111/j.1468-1331.2010.03061.x

4. Boyce MJ, Canning CG, Mahant N, Morris J, Latimer J, Fung VS. Active exercise for individuals with cervical dystonia: a pilot randomized controlled trial. *Clin Rehabil.* (2013) 27:226–35. doi: 10.1177/0269215512456221

5. van den Dool J, Visser B, Koelman JH, Engelbert RH, Tijssen MA. Cervical dystonia: effectiveness of a standardized physical therapy program; study design and protocol of a single blind randomized controlled trial. *BMC Neurol.* (2013) 13:85. doi: 10.1186/1471-2377-13-85

6. Boudreau SA, Farina D, Falla D. The role of motor learning and neuroplasticity in designing rehabilitation approaches for musculoskeletal pain disorders. *Man Ther.* (2010) 15:410–4. doi: 10.1016/j.math.2010.05.008

7. Snodgrass SJ, Heneghan NR, Tsao H, Stanwell PT, Rivett DA, Van Vliet PM. Recognising neuroplasticity in musculoskeletal rehabilitation: a basis for greater collaboration between musculoskeletal and neurological physiotherapists. *Man Ther.* (2014) 19:614–7. doi: 10.1016/j.math.2014.01.006

8. Bologna M, Berardelli A. Cerebellum: an explanation for dystonia? *Cerebel Ataxias.* (2017) 4:6. doi: 10.1186/s40673-017-0064-8

9. Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B. Treatment of Dycer-atDCS-generalised dystonia by stimulation of the internal globus pallidus. *Lancet.* (2000) 355:2220–1. doi: 10.1016/S0140-6736(00)02410-7

10. Cacciola F, Farah JO, Eldridge PR, Byrne P, Varma TK. Bilateral deep brain stimulation for cervical dystonia: long-term outcome in a series of 10 patients. *Neurosurgery.* (2010) 67:957–63. doi: 10.1227/NEU.0b013e3181ec49c7

11. Lefaucheur JP, Damier P, Nizard J, Nguyen JP. The value of non-invasive brain stimulation techniques in treating focal dystonia. *Neurophysiol Clin.* (2020) 50:309–13. doi: 10.1016/j.neucli.2020.10.001

12. Bradnam LV, Frasca J, Kimberley TJ. Direct current stimulation of primary motor cortex and cerebellum and botulinum toxin a injections in a person with cervical dystonia. *Brain Stimul.* (2014) 7:909–11. doi: 10.1016/j.brs.2014.09.008

13. Nguyen JP, Suarez A, Malineau C, Dixneuf V, Mazaltarine G, Damier P. Treatment of cervical dystonia and blepharospasm by anodal tDCS of cerebellar hemispheres a case report. *Neurophysiol Clin.* (2020) 50:391–2. doi: 10.1016/j.neucli.2020.09.006

14. Graef P, Dadalt MLR, Rodrigués DAMDS, Stein C, Pagnussat AS. Transcranial magnetic stimulation combined with upper-limb training for improving function after stroke: a systematic review and meta-analysis. *J Neurol Sci.* (2016) 369:149–58. doi: 10.1016/j.jns.2016.08.016

15. Portero R, Bleton JP, Garric D, Masson I, Mesure S, Portero P. Kinematic analysis of the head by inertial sensors. Test-retest reproducibility and clinical use feasibility. *Move Sport Sci.* (2016) n° 93:23–31. doi: 10.3917/sm.093.0023

16. Gayraud D, Viallet F. Évaluation d'une dystonie cervicale. Utilité des échelles d'évaluation: échelle TWSTRS [evaluation of cervical dystonia. Usefulness of rating scales: the TWSTRS scale]. *Rev Neurol.* (2008) 164:F263–74. doi: 10.1016/S0035-3787(08)75127-0

17. Consky ES, Basinski A, Belle I, Ranawaya R, Lang AE. The Toronto western spasmodic torticollis scale: assessment of validity and inter-rater reliability. *Neurology.* (1990) 40:445.

18. Phukan J, Albanese A, Gasser T, Warner T. Primary dystonia and dystonia-plus syndromes: clinical characteristics, diagnosis, and pathogenesis. *Lancet Neurol*. (2011) 10:1074–85. doi: 10.1016/S1474-4422(11)70232-0

19. Mezaki T. Dystonia redefined as central non-paretic loss of control of muscle action: a concept including inability to activate muscles required for a specific movement, or 'negative dystonia'. *Med Hypotheses*. (2007) 69:1309–12. doi: 10.1016/j.mehy.2007.03.014

20. Carment L, Maier MA, Sangla S, Guiraud V, Mesure S, Vidailhet M, et al. Does dystonic muscle activity affect sense of effort in cervical dystonia? *PLoS One*. (2017) 12:e0172019. doi: 10.1371/journal.pone.0172019

21. De Pauw J, Mercelis R, Hallemans A, Michiels S, Truijen S, Cras P, et al. Cervical sensorimotor control in idiopathic cervical dystonia: a cross-sectional study. *Brain Behav*. (2017) 7:e00735. doi: 10.1002/brb3.735

22. Boccagni C, Carpaneto J, Micera S, Bagnato S, Galardi G. Motion analysis in cervical dystonia. *Neurol Sci*. (2008) 29:375–81. doi: 10.1007/s10072-008-1033-z

23. Moucha R, Kilgard MP. Cortical plasticity and rehabilitation. *Prog Brain Res*. (2006) 157:111–22. doi: 10.1016/s0079-6123(06)57007-4

24. Flowers JM, Hicklin LA, Marion MH. Anterior and posterior sagittal shift in cervical dystonia: a clinical and electromyographic study, including a new EMG approach of the longus colli muscle. *Mov Disord*. (2011) 26:2409–14. doi: 10.1002/mds.23905

25. Lefaucheur JP, Wendling F. Mechanisms of action of tDCS: a brief and practical overview. *Neurophysiol Clin*. (2019) 49:269–75. doi: 10.1016/j.neucli.2019.07.013

26. Jackson MP, Rahman A, Lafon B, Kronberg G, Ling D, Parra LC, et al. Animal models of transcranial direct current stimulation: methods and mechanisms. *Clin Neurophysiol*. (2016) 127:3425–54. doi: 10.1016/j.clinph.2016.08.016

27. Chase HW, Boudewyn MA, Carter CS, Phillips ML. Transcranial direct current stimulation: a roadmap for research, from mechanism of action to clinical implementation. *Mol Psychiatry*. (2020) 25:397–407. doi: 10.1038/s41380-019-0499-9

28. Grimaldi G, Argyropoulos GP, Bastian A, Cortes M, Davis NJ, Edwards DJ, et al. Cerebellar transcranial direct current stimulation (ctDCS): a novel approach to understanding cerebellar function in health and disease. *Neuroscientist*. (2016) 22:83–97. doi: 10.1177/1073858414559409

29. Abraham WC, Bear MF. Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci*. (1996) 19:126–30. doi: 10.1016/s0166-2236(96)80018-x

30. Müller-Dahlhaus F, Ziemann U. Metaplasticity in human cortex. *Neuroscientist*. (2015) 21:185–202. doi: 10.1177/1073858414526645

31. Smania N, Corato E, Tinazzi M, Montagnana B, Fiaschi A, Aglioti SM. The effect of two different rehabilitation treatments in cervical dystonia: preliminary results in four patients. *Funct Neurol*. (2003) 18:219–25.

32. Tassorelli C, Mancini F, Balloni L, Pacchetti C, Sandrini G, Nappi G, et al. Botulinum toxin and neuromotor rehabilitation: an integrated approach to idiopathic cervical dystonia. *Mov Disord*. (2006) 21:2240–3. doi: 10.1002/mds.21145

33. Queiroz MA, Chien HF, Sekeff-Sallem FA, Barbosa ER. Physical therapy program for cervical dystonia: a study of 20 cases. *Funct Neurol*. (2012) 27:187–92.

34. Korein J, Brudny J. Integrated EMG feedback in the management of spasmodic torticollis and focal dystonia: a prospective study of 80 patients. *Res Publ Assoc Res Nerv Ment Dis*. (1976) 55:385–426.

35. Duddy J, McLellan D. Lack of influence of EMG biofeedback in relaxation training for spasmodic torticollis. *Clin Rehabil*. (1995) 9:297–303. doi: 10.1177/026921559500900404

36. Jahanbazi A, Chitsaz A, Asgari K. Effects of EMG biofeedback on pain and quality of life in cervical dystonia. *J Neurol Disord*. (2013) 2:144. doi: 10.4172/2329-6895.1000144

37. Wagle Shukla A, Hu W, Legacy J, Deeb W, Hallett M. Combined effects of rTMS and botulinum toxin therapy in benign essential blepharospasm. *Brain Stimul*. (2018) 11:645–7. doi: 10.1016/j.brs.2018.02.004

38. Bradnam LV, McDonnell MN, Ridding MC. Cerebellar intermittent Theta-burst stimulation and motor control training in individuals with cervical dystonia. *Brain Sci*. (2016) 6:56. doi: 10.3390/brainsci6040056

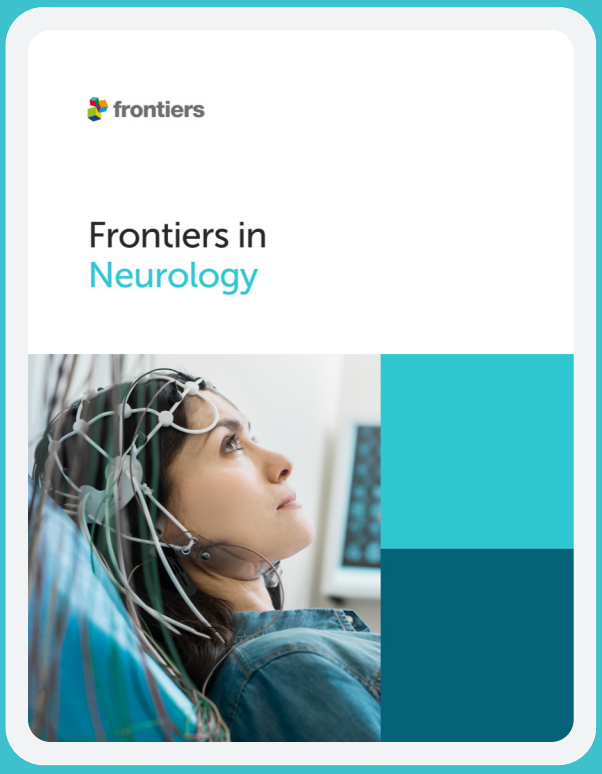
Frontiers in Neurology

Explores neurological illness to improve patient care

The third most-cited clinical neurology journal explores the diagnosis, causes, treatment, and public health aspects of neurological illnesses. Its ultimate aim is to inform improvements in patient care.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact