Narrative Review

Transcranial Direct Current Stimulation for the Management of Neuropathic Pain: A Narrative Review

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Background: Neuropathic pain (NP) is common and often resistant to conventional analgesics. Among different types of noninvasive brain stimulation techniques, transcranial direct current stimulation (tDCS) has been widely used to mitigate pain in patients with NP.

Objective: The aim of this study was to review the effects of tDCS on the management of various types of NP.

Study Design: Narrative review.

Methods: A PubMed search was conducted for articles published until October 1, 2020, using tDCS to treat NP. The key search phrase, transcranial direct current stimulation and pain, was used to identify potentially relevant articles. The following inclusion criteria were applied for article selection: (1) studies involving patients with NP and (2) studies that used tDCS to treat NP. Review articles were excluded from the analysis.

Results: A total of 524 potentially relevant articles were identified. After reading the titles and abstracts and assessing eligibility based on the full-text articles, 34 publications were included in our review. Overall, our results suggest that tDCS induced pain reduction in patients with NP due to stroke or spinal cord injury, multiple sclerosis, or trigeminal neuralgia. There is insufficient evidence to validate the efficacy of tDCS for treating other painful conditions, such as complex regional pain syndrome, phantom pain, or NP of various origins.

Limitations: The review did not include studies indexed in databases other than PubMed.

Conclusion: The results of the included studies suggest that tDCS may be beneficial in treating patients with NP due to stroke, spinal cord injury, multiple sclerosis, and trigeminal neuralgia. Further studies are recommended to validate the efficacy of tDCS in treating other types of NPs.

Key words: Transcranial direct current stimulation, neuropathic pain, central post-stroke pain, spinal cord injury, multiple sclerosis, complex regional pain syndrome, phantom pain, trigeminal neuralgia

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Neuropathic pain (NP) refers to a localized sensation of unpleasant discomfort that results from a lesion or disease of the peripheral or central somatosensory system (1). The symptoms of NP include pain from allodynia (pain from non-painful stimuli) or dysesthesia (abnormal sensation). Patients suffer from spontaneous ongoing or shooting pain, which is associated with evoked amplified pain responses after noxious or non-noxious stimuli. NPs are associated with neuronal overexcitability and exhibit diverse features under various medical conditions. Nerve lesions result in aberrant regeneration, which leads to abnormal neuronal excitability and causes high sensitivity to stimuli (2). In many cases of NP,

patients are non-responsive to conventional analgesics, which include non-steroidal anti-inflammatory drugs, anticonvulsants, or antidepressants. In such cases, neuromodulation treatments such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and deep brain stimulation, are applied for the treatment of NP (3).

TDCS is a noninvasive method of brain stimulation that can modify the excitability of neuronal activity in the cerebral cortex. It is painless, easy to apply, and has been used as a therapeutic intervention to treat many neurological and psychiatric conditions, including motor neurorehabilitation, depression, cognitive enhancement, and chronic pain (4,5). TDCS applies a low voltage, direct current to the scalp via electrodes to modulate cortical excitability through anodal or cathodal stimulation. Anodal, or positive, tDCS depolarizes the resting membrane and increases cortical excitability, whereas cathodal or negative tDCS causes hyperpolarization and decreases cortical excitability (6). The most commonly employed technique to address NP is anodal tDCS, which involves placing the anode over the primary motor cortex (M1) and the cathode over the contralateral supraorbital area, and applying a current intensity of 1 mA for 15-20 min.

The possible mechanisms of pain modulation by tDCS are assumed to be the direct interruption of nociceptive processing in the thalamus and primary somatosensory cortex, or the activation of the limbic system and its connections to descending inhibitory pathways from the brainstem (7,8). Modulation of spontaneous neuronal firing rate by tDCS may occur through polarization of the resting membrane potential and modification of synaptic GABAergic activity or NMDA receptor strength (6,9). TDCS has several advantages over other cortical stimulation techniques: it provides long-lasting modulatory effects on cortical functioning, is inexpensive, and easy to apply to patients (10).

Several studies have demonstrated the positive effects of tDCS on pain control (10-12). The effectiveness of tDCS in treating NP has been investigated through multiple clinical trials in recent years (13). Therefore, the aim of this review was to investigate the efficacy of tDCS in the management of various types of NPs.

Methods

Data Sources

A MEDLINE database (PubMed) search was conducted for relevant studies published until October 1, 2020, which used tDCS to treat NP. The key search phrase (transcranial direct current stimulation and pain) was used to identify potentially relevant articles.

Study Selection

The following inclusion criteria were applied for article selection: (1) studies involving human patients with NP and (2) studies that used tDCS to treat NP. Relevant studies were selected according to the flow diagram shown in Fig. 1. A total of 7,001 articles were searched and 1,479 duplicate articles were removed (Fig. 1). After screening for eligibility, based on a review of the title and abstract, 86 articles were identified for further full-text reading. After a detailed assessment, 52 articles were excluded: 26 articles were review articles, 14 studies were focused mainly on other types of pain, and 12 studies did not primarily investigate tDCS. Finally, 34 publications were included in the review (Table 1).

Results

Central Pain

Central pain occurs due to a lesion or dysfunction of the somatosensory pathways and develops when the spinothalamic tract, thalamus, or tractus thalamocorticalis is damaged (14). It is characterized by NP, and symptoms include allodynia, hyperalgesia, tingling, numbness, chilling, and abnormal sensations (15). Central pain occurs in 10%-30% of patients with brain and spinal cord injuries (15). Below, we separately review the effect of tDCS on central pain after stroke and after spinal cord injury (SCI).

Central Pain After Stroke

Central post-stroke pain (CPSP) is characterized by NP, which includes symptoms such as burning, throbbing, and aching pain, and is caused by cerebrovascular insult to the somatosensory pathway in the brain (16). It usually occurs within 6 months after a stroke and is one of the most common sequelae after stroke. Many cases of CPSP are refractory to medical treatment and are often difficult to manage. Two studies on the effects of tDCS in patients with CPSP were identified after our search. In 2014, Bae et al (14) enrolled 14 patients with CPSP (7 patients received active tDCS and 7 patients received sham stimulation). Anodal tDCS targeting M1 was administered to individuals in the active tDCS group for 20 min at a current intensity of 2 mA. Active tDCS was administered 3 days per week for 3 weeks. The results showed that the visual analog scale

(VAS) scores in the active tDCS group significantly decreased compared to baseline, whereas there was no significant change in the VAS scores in the sham tDCS group. In 2015, Morishita et al (17) reported a case of a patient with CPSP who was treated with 10 sessions of active tDCS. Significant pain reduction was observed following active stimulation compared to sham stimulation. Further studies on CPSP are needed to validate the efficacy of tDCS in stroke patients with NP.

Central Pain After Spinal Cord Injuries

NP is common in patients with SCI and in many cases is refractory, with only a few patients achieving favorable outcomes over the long term (18). It is estimated that more than 50% of patients with SCI suffer from chronic NP. In patients with SCI, NP may be due to the loss of central inhibitory control mechanisms, resulting in an increase in the excitability of dorsal horn neurons (19). It is

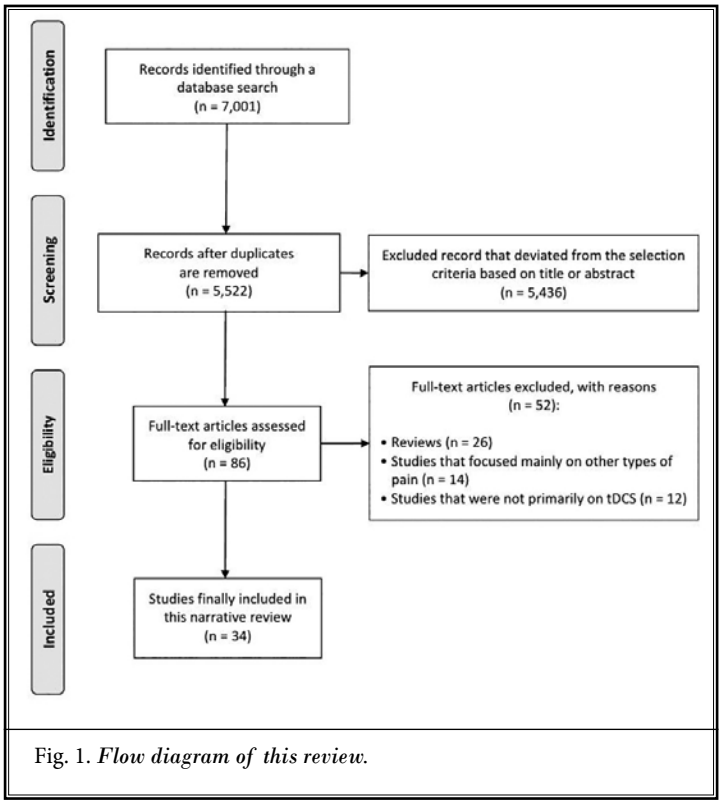

Fig. 1. *Flow diagram of this review.*

Table 1. *Characteristics of the included studies.*

#	First author	Year	No. of Patient (active/ control)	Mode	Site	Intensity (mA)	Duration (min)	No. of Sessions	Outcome Parameters	Results
Central pain after stroke										
1	Bae (14)	2014	14 (7/7)	Anodal	M1	2	20	9	VAS	The tDCS group showed decreased VAS scores from 4.29 to 3.14 3 weeks after the treatment.
2	Morishita (17)	2015	1	Anodal	M1	2.5	20	10	VAS	The mean VAS scores decreased from 6 to 2.69 after active tDCS stimulation.
Central pain after spinal cord injury										
3	Fregni (10)	2006	17 (11/6)	Anodal	M1	2	20	5	VAS	There was a significant pain improvement after active anodal tDCS, but not after sham stimulation (mean VAS pain scores -6.2).
4	Soler (22)	2010	39	Anodal	M1	2	20	10	NRS	The NRS of pain perception was reduced by 29.7% in the patients who received tDCS combined with visual illusion, and experienced a significant improvement in all pain subtypes.

Table 1 *(continued). Characteristics of the included studies.*

#	First author	Year	No. of Patient (active/ control)	Mode	Site	Intensity (mA)	Duration (min)	No. of Sessions	Outcome Parameters	Results
5	Kumru (2013)	2013	18	Anodal	M1	2	20	10	NRS	A mean decrease of 50% in the NRS for NP were observed after tDCS with visual illusion.
6	Wringley (20)	2013	10	Anodal	M1	2	20	5	NRS	tDCS did not provide any pain relief in participants with neuropathic SCI pain.
7	Yoon (24)	2014	16	Anodal	M1	2	20	20	NRS	A significant decrease in NRS for pain was observed in the active tDCS group (NRS from 7.6 ± 0.5 to 5.9 ± 1.8), but not in the sham tDCS group.
8	Ngernyam (25)	2015	20	Anodal	M1	2	20	Single sessions of tDCS and sham	NRS	The active, but not sham, tDCS treatment resulted in significant decreases in pain intensity.
9	Thibaut (27)	2017	9 (6/3)	Anodal	M1	2	20	10	VAS	The overall level of pain was significantly lower for the active tDCS group after repeated tDCS sessions, as compared to sham (P = 0.003).
10	Auvichayapat (26)	2018	10	Anodal	M1	2	20	5	NRS	A significant decrease in pain intensity was observed after anodal tDCS sessions (P < 0.001).
11	Li (28)	2018	12	Anodal	M1	2	20	Single sessions of tDCS and sham	VAS	No significant differences were observed between active and sham tDCS at the group level.
12	Choi (29)	2019	10	Anodal	Thoracic spinal cord	2	20	Single sessions of tDCS and sham	NRS	No significant differences in pain intensity were found between the active and sham transcutaneous spinal DCS groups.
13	Soler (30)	2020	130 (65/65)	Anodal	M1	2	20	10	NRS, Brief Pain Inventory	The combined treatment of tDCS and visual illusion induced a significant reduction in pain (P = 0.001).
MS related neuropathic pain										
14	Mori (12)	2010	19 (10/9)	Anodal	M1	2	20	5	VAS	Anodal but not sham tDCS was effective in reducing persistent pain scores in MS patients by 40.3 ± 10.1%.
15	Ayache (33)	2016	16	Anodal	DLPFC	2	20	3	VAS	The mean VAS showed a significant decrease after active tDCS (P = 0.024), but no change after sham tDCS.
16	Young (34)	2020	30 (15/15)	Anodal	Contralateral to the pain site	2	20	5	VAS	VAS scores were significantly decreased after tDCS compared with sham tDCS (P = 0.00).

Table 1 *(continued). Characteristics of the included studies.*

#	First author	Year	No. of Patient (active/ control)	Mode	Site	Intensity (mA)	Duration (min)	No. of Sessions	Outcome Parameters	Results
Complex regional pain syndrome										
17	Lageux (35)	2018	22 (11/11)	Anodal	M1	2	20	14	NRS	Active tDCS with GMI induced no statistically significant reduction in pain compared with sham tDCS with GMI.
18	Houde (36)	2020	1	Anodal	M1	2	25	5	VAS	Treatments of tDCS alone did not significantly decrease pain. Combining tDCS with TENS slightly reduced pain intensity and unpleasantness.
Phantom pain										
19	Bolognini (40)	2013	8	Anodal	M1	2	15	Single sessions of tDCS and sham	VAS	Anodal tDCS of M1 induced a decrease of PLP and stump pain, and average PLP relief was 56% at the end of the active tDCS stimulation.
20	Bolognini (41)	2013	1	Anodal	M1	2	15	5	VAS	Reductions in PLP and stump pain were shown after active tDCS, but not for the sham stimulation.
21	Bocci (38)	2019	14	Anodal	Cerebellum	2	20	5	VAS	Anodal cerebellar DCS did not change phantom limb and stump pain compared to the sham condition.
22	Miuli (42)	2020	1	Anodal	M1	1	20	22	Episodes of PLP	Only 3 episodes of PLP were reported by the patient during the study period.
Trigeminal neuralgia										
23	DosSantos (45)	2012	1	Anodal	M1	2	20	Single sessions of tDCS and sham	VAS	No significant changes were observed in the clinical pain levels related to tDCS.
24	Hagenacker (46)	2014	10	Anodal	M1	1	20	14 sessions of tDCS or sham	Verbal rating scale	Anodal tDCS reduced pain intensity significantly after 2 weeks of treatment by 18%.
25	Fricova (47)	2017	10	Anodal	DLPFC	1	20	5	NRS	After tDCS, 62.5% of patients reported that pain perception decreased by 53.7 ± 31.5%.
26	Fricova (48)	2019	19	Anodal	DLPFC	1	20	5	VAS	Orofacial pain decreased in 62.5% of patients by 53.7 ± 31.5% after the application of tDCS
Neuropathic pain from various origins										
27	Boggio (49)	2009	8	Anodal	M1	2	30	Single sessions of tDCS with TENS, tDCS only, and sham	VAS	Pain reduction was greater after the combination of TENS with tDCS (reduction by 36.5 ± 10.7%) compared with tDCS alone (reduction by 15.5 ± 4.9%), but not after sham stimulation.

Table 1 *(continued). Characteristics of the included studies.*

#	First author	Year	No. of Patient (active/ control)	Mode	Site	Intensity (mA)	Duration (min)	No. of Sessions	Outcome Parameters	Results
28	Antal (50)	2010	21	Anodal	M1	1	20	5	VAS	Five daily sessions of tDCS over the hand area of M1 induced pain relief with a VAS score change of 27.9% after tDCS compared to 2.7% after sham.
29	Portilla (51)	2013	3	Anodal	M1	2	20	Single sessions of tDCS and sham	VAS	Only one patient had a slight decrease in pain score after active tDCS stimulation.
30	Lewis (4)	2018	30 (13/17)	Anodal	Contra-lateral to the pain site	1	20	5	Brief Pain Inventory	No evidence was provided that 1 mA tDCS was beneficial for people with upper limb NP.
31	O'Neil (52)	2018	21	Anodal	M1	1.4	20	5	NRS	No significant differences were found after anodal, cathodal, or sham tDCS stimulations.
32	Garcia-Larrea (3)	2019	12	Anodal	M1	2	20	20	NRS	Six out of the 12 patients achieved satisfactory relief on a scale combining pain scores.
33	Arul-Anandam (53)	2009	1	Anodal	DLPFC	1	20	10	NRS	Pain severity score changed from 7 to 4 after tDCS treatment.
34	Attal (54)	2015	35 (23/12)	Anodal	M1	2	30	6	NRS	rTMS was superior to tDCS and sham stimulation and tDCS was not superior to sham in reducing pain intensity.

Abbreviations. DLPFC, dorsolateral prefrontal cortex; GMI, graded motor imagery; MS, multiple sclerosis; NP, neuropathic pain; NRS, numeric rating scale; rTMS, repetitive transcranial magnetic stimulation; SCI, spinal cord injury; tDCS, transcranial direct current stimulation; TENS, transcutaneous electrical nerve stimulation, VAS, visual analog scale.

also postulated that neuropathic SCI pain may be associated with abnormal thalamic firing patterns and changes in the thalamocortical rhythm (20). The treatment of NP in patients with SCI is important, as NP has a negative impact on quality of life (21).

Eleven studies that used tDCS to treat NP in patients with SCI were identified. In 2006, Fregni (10) enrolled 17 patients with SCI who had NP for more than 6 months. Patients were assigned to receive either active or sham tDCS in a randomized order. The tDCS stimulation parameters were a current intensity of 2 mA for 20 min for 5 consecutive days. A significant reduction in pain was observed after anodal stimulation of M1 compared to sham stimulation. In 2010, Soler et al (22) divided 39 SCI patients with NP into 4 groups to receive either active tDCS or sham stimulation, with or without a walking visual illusion (VI) intervention for 10 days over a 2-week period. For the VI, a video was turned on after 5 min of active or sham tDCS stimulation that showed a person walking on a treadmill. The VI was continuously administered for 15 min during the tDCS treatment. The control illusion was presented in the same manner as the VI, but consisted of a movie containing graphical illustrations, not images of human movement. The results showed that patients who received a combination of tDCS and VI experienced a significant improvement in all pain subtypes measured by the researchers, which lasted up to 12 weeks after treatment. Similarly, in 2013, Kumru et al (23) reported that 10 sessions of tDCS combined with VI had significant effects on evoked pain and heat pain thresholds in SCI patients with NP, including a mean decrease of 50%

in the numeric rating scale (NRS). In contrast, Wringley et al (20) reported that tDCS did not relieve pain in 10 SCI patients with NP after 5 sessions of 20 min of 2 mA anodal tDCS of M1. In a similar study, Yoon et al (24) enrolled 16 NP patients with traumatic SCI, and patients in the active tDCS group received anodal tDCS of M1 (2 mA, 20 min) twice daily for 2 weeks. The results showed a significant decrease in NRS for pain after treatment in the active tDCS group, but not in the sham tDCS group. Studies conducted by Ngernyam et al and Auvichayapat et al (26) further supported the finding that active anodal tDCS over M1 (single session and 5 sessions, respectively) significantly reduced pain intensity in patients with neuropathic SCI pain (25,26). A randomized clinical trial was conducted in 2017 by Thibaut et al (27), who concluded that 10 sessions of tDCS once a day for 2 weeks, rather than 5 sessions of tDCS for 5 days, significantly decreased the overall level of pain compared to sham stimulation. This study suggests that repeated tDCS stimulation sessions are better at inducing long-lasting effects. In 2018, Li et al (28) investigated whether anodal tDCS of M1 had an additive analgesic effect with breathing-controlled electrical stimulation in 12 patients with neuropathic SCI pain. Although the VAS scores for pain decreased significantly after breathing-controlled electrical stimulation, applying tDCS did not augment this effect. Interestingly, in 2019, Choi et al (29) applied single sessions of transcutaneous spinal DCS (2 mA, 20 min) and sham stimulation in 10 cervical SCI patients with NP, and showed that there was no significant difference in pain reduction between the 2 types of stimulation. A recent study conducted in 2020 by Soler et al (30) included 130 SCI patients with NP to assess the effectiveness of active tDCS combined with VI. The combined treatment of tDCS and VI was administered to 65 patients, whereas the other 65 patients served as the control group. The tDCS parameters were 2 mA anodal of the contralateral M1 for 20 min over 5 consecutive days for 2 weeks. The combined treatment group showed significant improvement in pain, but the control group showed no changes. Taken together, tDCS seems to be effective in relieving NP in patients with SCI. In addition, combining tDCS with VI appears to have a positive effect on pain reduction in these patients.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic progressive inflammatory disease of the central nervous system with no available curative treatment (31). Patients may suffer from sensorimotor, cognitive, emotional, and behavioral symptoms. Chronic NP occurs frequently in patients with MS, with a prevalence of 29%-86% (32). Various types of pain occur in these patients, such as dysesthetic pain, back pain, or painful tonic spasms. The pathogenesis of MS-related NP is associated with central pain due to corticospinal system disinhibition or chronic activation of nociceptive afferents (31). Neuromodulation techniques, such as tDCS, are used when medical management fails. Three studies on MS-related NP using tDCS have been identified. In 2010, Mori et al (12) investigated the effectiveness of tDCS in 19 patients with MS with chronic NP. The results showed that anodal tDCS over the contralateral M1 for 20 min at a current intensity of 2 mA for 5 days was effective in reducing persistent pain scores in 10 patients compared to that in 9 patients who received sham tDCS (12). In 2016, Ayache et al (33) applied 3 sessions of anodal tDCS at 2 mA for 20 min over the left dorsolateral prefrontal cortex (DLPFC) in 16 patients with chronic NP. Compared to sham stimulation, active tDCS yielded a significant analgesic effect according to scores on the VAS and Brief Pain Inventory global scales. Most recently, in 2020, Young et al (34) recruited 30 MS patients with NP and divided them into active or sham tDCS groups (15 patients in each group) . Compared to sham tDCS, VAS scores were significantly reduced after a 5-day course of anodal tDCS. Overall, tDCS seems to reduce the pain intensity of NP in patients with MS and leads to long-lasting clinical effects.

Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) is a chronic pain syndrome characterized by regional pain with vasomotor, sudomotor, sensory, motor, and/or trophic changes. It is divided into 2 types: CRPS type I (no peripheral nerve lesions) or type II (definable nerve lesions) (15). Two studies that used tDCS to treat CRPS were identified after our search. In 2018, Lageux et al (35) enrolled 22 patients with CRPS type I and applied active or sham tDCS treatment (11 patients in each group). Anodal tDCS was administered to M1 for 20 min at a current intensity of 2 mA. A graded motor imagery (GMI), which consisted of a left-right limb discrimination task, imagined movements of the affected limb, and mirror therapy, was also performed at home for 10 min per session, 3 times per day, for 6 weeks. The results showed that active tDCS with GMI resulted in no statistically significant reduction in pain compared with sham tDCS with GMI. Thus, there was no additive effect

of tDCS when GMI was applied to patients with chronic CRPS. Most recently, Houde et al reported a case of a 37-year-old female patient with CRPS who was evaluated after receiving tDCS combined with transcutaneous electrical nerve stimulation (TENS) or tDCS alone (36). She reported that pain intensity and unpleasantness were slightly reduced after tDCS with TENS compared with tDCS alone, suggesting that such a combination of the 2 treatments could provide a greater analgesic effect. Further studies using tDCS for the treatment of CRPS are needed to validate its efficacy.

Phantom Pain

Phantom limb pain (PLP) is a neuropathic syndrome with a disabling sensation or pain that occurs after amputation. Pain is usually characterized as stabbing, throbbing, burning, or cramping, and is often referred to as the distal portion of the amputated limb (37). It is suggested that both peripheral and central factors may contribute to the pathogenesis of PLP, possibly involving topographic reorganization at the cortical and spinal levels (38). PLP is generally difficult to manage and often does not respond to conventional pharmacological interventions (15).

Considering the high prevalence of PLP, which is reported to occur in up to 80% of patients after limb amputation (39), several studies have demonstrated the effect of tDCS as an alternative intervention for PLP. In 2013, Bolognini et al (40) applied a single session of anodal or sham tDCS to 8 patients who experienced PLP after amputation (anodal tDCS targeting M1 at 2 mA for 20 min). Patients reported that anodal tDCS induced a selective short-lasting decrease in PLP and stump pain compared to sham sessions. In the same year, Bolognini et al (41) also reported a case of a patient who received 5 sessions of active and sham tDCS treatments. After a 5-day treatment with active tDCS, the patient showed a reduction in PLP and stump pain. The authors suggested that multiple sessions may induce greater and long-lasting analgesic effects. In 2019, Bocci et al (38) showed that applying tDCS (anodal or sham, 2 mA, 20 min, for 5 days a week) to the bilateral cerebellum of 14 amputee patients with PLP significantly reduced paroxysmal pain and nonpainful phantom limb sensations, but not phantom limb and stump pain (31). The authors explained that tDCS of the cerebellum may modulate pain perception by interfering with the inhibitory tone exerted by the cerebellum over cortical areas, and residual limb pain may be more affected by peripheral factors. In 2020, Miuli et al (42) reported a similar case of an amputee with PLP and showed that fewer episodes of PLP occurred after repeated sessions of anodal tDCS of the right M1 for 20 min at a current intensity of 1 mA. Additionally, this patient had a cardiac defibrillator, suggesting that tDCS could be considered safe and a possible therapeutic option in patients with contraindications to pharmacological treatment. In general, tDCS appears to be effective in managing PLP, but further studies are needed to conclude that tDCS is beneficial for the treatment of PLP.

Trigeminal Neuralgia

Trigeminal neuralgia (TGN) is a type of orofacial pain disorder that leads to paroxysm of short-lasting but severe pain (43). The second and third branches of the trigeminal nerve were affected in most cases. The patient is asymptomatic between the attacks, but a constant dull pain can remain as a sign of pain chronification and central sensitization (44). Four studies that used tDCS for the treatment of TGNs were identified. In 2012, DosSantos et al (45) reported a case of a patient diagnosed with post-herpetic neuralgia, affecting the distribution of the first and second branches of the trigeminal nerve. A single session of anodal 2 mA tDCS stimulation over M1 showed no significant changes in the clinical pain levels when compared with the sham stimulation. However, the authors suggested the possibility of an instant increase in endogenous μ-opioid release after tDCS. In 2014, Hagenacker et al (46) applied anodal (1 mA, 20 min over M1) or sham tDCS for 14 days in a randomized order to 10 patients who were diagnosed with classic TGN. The results showed that anodal tDCS significantly reduced pain intensity after 2 weeks of treatment; however, the attack frequency was not significantly reduced (46). In 2016, Fricova et al (47) enrolled 10 patients with chronic intractable orofacial pain, including TGN, and investigated the effect of active tDCS stimulation. Interestingly, the cathode and anode were placed on the temporal side of the skull, targeting the DLPFC, not M1, and both anode and cathode stimulations were administered. The tDCS parameters were 1 mA for 20 min for 5 consecutive days. The results showed a decrease in orofacial pain, especially after cathode stimulation, suggesting that the application of tDCS improved the perception of pain. In 2019, Fricova et al (48) conducted a similar study, using the same protocol, with 19 patients with chronic intractable orofacial pain, including TGN, to compare the effects of active and sham tDCS stimulation. Again, the results showed that tDCS was effective; orofacial pain

decreased in 62.5% of patients after tDCS stimulation by 53.7 ± 31.5% and the decrease lasted 14 days. Overall, tDCS appears to be a useful alternative treatment method for patients with TGN.

Neuropathic Pain of Other Various Origins

NP can arise from various sources, and some studies have focused on the presence of NP, rather than the underlying cause that might have triggered NP. Our literature search identified 6 studies that examined the clinical usefulness of tDCS to control chronic NP derived from various origins, including patients with stroke, SCI, TGN, fibromyalgia, brachial plexus injury (BPI), and back pain. In 2009, Boggio et al (49) investigated whether a combination of tDCS and TENS was superior to tDCS alone or sham treatment. Eight patients with localized NP of the arms were recruited, and the tDCS parameters were 2 mA anodal of the contralateral M1 for 30 min. The results showed that the combination of TENS with tDCS had a superior effect compared with tDCS alone, and both methods reduced pain as opposed to the sham stimulation. Similarly, Antal et al (50) showed that 5 daily sessions of tDCS over the hand area of M1 (1 mA, 20 min) produced long-lasting pain relief in 21 patients with chronic NP of various origins, such as CPSP, TGN, and fibromyalgia. A case study by Portilla et al (51) in 2013, which reported that tDCS decreased overall cortical excitability in patients with chronic NP following burn injury, was in accordance with the results of these previous studies. In contrast with these studies, in 2018, Lewis et al (4) reported that 5 days of active 1 mA tDCS over M1 did not provide a beneficial effect for patients with upper limb NP. This study included 30 patients with NP of various origins, such as BPI or CRPS, who were allocated to receive either active tDCS or sham treatment. In the same year, O'Neil et al (52) also showed a similar result in patients with unilateral NP of various origins (e.g., CPSP, SCI, TGN, or phantom pain). Although active tDCS over the contralateral M1 (1.4 mA, 30 min) was administered for 5 consecutive days, no significant difference was observed between anodal, cathodal, or sham tDCS treatments in 21 patients. Recently, in 2019, Garcia-Larrea et al (3) reported that 6 out of 12 NP patients with various conditions (e.g., CPSP, SCI, or BPI) achieved satisfactory changes in pain intensity. This study demonstrated that 20 sessions of tDCS over the M1 (2 mA, 20 min) were safe and provided long-lasting pain relief. Overall, the results are inconsistent as to whether tDCS stimulation is effective for various types of NP. It appears that including studies that focus on a specific origin of NP, rather than various origins of NP, is a better and more useful approach in assessing the effectiveness of tDCS in the management of NP.

Neuropathic Pain Associated With Central Sensitization

Besides central NP, which results from direct CNS injury, NP may also occur due to central sensitization. Central sensitization is usually triggered by injury- or inflammation-induced increase in nociceptive input, which results in long-lasting changes in the central nociceptive pathways. Increased primary afferent fiber responses and excitability of the dorsal horn neurons are associated with central sensitization.

Two studies investigated patients with chronic NP associated with radicular pain, which may have occurred due to central sensitization and maladaptive plasticity due to a peripheral lesion. Treatment aimed at reversing or modulating central processing is applied to treat radicular pain that causes NP. In 2009, Arul-Anandam (53) applied tDCS over the left DLPFC of a female patient with chronic radicular pain. Compared with sham tDCS, she reported significant improvement in pain following 10 sessions of active tDCS (1mA, 20 min). In 2016, Attal et al (54) compared the efficacy of rTMS and tDCS and compared their effects with sham stimulation in 51 patients with chronic radicular pain. The results showed that although the analgesic effects of tDCS were correlated with those of rTMS, rTMS was superior to tDCS and sham stimulation, and tDCS was not superior to sham stimulation in reducing pain intensity. Further studies investigating the effect of tDCS in patients with NP due to radiculopathy are needed.

Conclusion

TDCS is a noninvasive method for brain stimulation that can modify the excitability of neurons in the cerebral cortex. This review suggests that tDCS may be a promising treatment for patients with various types of NP. The results of the included studies suggest that tDCS may be beneficial in treating patients with NP caused by stroke, spinal cord injury, MS, and TGN. Although robust evidence of the efficacy of tDCS on NP could not be provided in this review, the current literature suggests a trend toward efficacy, and further studies are warranted to obtain conclusive results. Since tDCS is painless and easy to apply, further studies with larger patient populations are needed in the future to validate the efficacy of tDCS in treating various types of NP.

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