Archives of Anesthesiology and Critical Care (Mar-Apr 2026); 12(2): 192-202.

Available online at http://aacc.tums.ac.ir

Review Article

Application of Transcranial Direct Current Stimulation in Neurocritical Care

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ARTICLE INFO

Article history:
Received 23 June 2025
Revised 14 July 2025
Accepted 28 July 2025

Keywords:
tDCS;
Neuro-intensive care;
Critical care;
Transcranial direct current stimulation;
Review

ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is an emerging, non-invasive neuromodulation technique with massive potential in neurocritical care settings. This review covers the applications, mechanisms, and outcomes of tDCS in patients with severe neurological disorders.
Methods: tDCS uses low-intensity direct current to modulate cortical excitability and induce neuroplasticity, which aids in recovering motor, cognitive, and sensory functions. Its simplicity and noninvasive nature enable bedside use, making it a good alternative to invasive interventions.
Results: The evidence suggests that tDCS improves recovery in stroke, TBI, and DOC by affecting synaptic plasticity, releasing neurotrophic factors, and improving cerebral perfusion. However, due to the variability in the methodology and stimulation parameters of the studies, further research is required to determine standardized protocols. Safety appears minimal, with most side effects including mild discomfort.
Conclusion: This review underlines the promise of tDCS as an adjunctive therapy in neurocritical care and recommends its integration into traditional rehabilitative strategies to enhance patient outcomes. Future studies should investigate optimizing stimulation parameters, long-term efficacy, and condition-specific applications to exploit tDCS's therapeutic benefits.

Introduction

Neurocritical care is the intensive management of patients with primary or secondary neurological disorders accompanied by actual or potential organ dysfunction, necessitating rigorous medical monitoring and intervention [1]. Due to the severe state of these patients, a thorough and integrated treatment and rehabilitation strategy is essential. Over the past 30 years, neuromodulation via diverse invasive and noninvasive modalities at central or peripheral levels has presented promising opportunities for therapeutic intervention in these patients [2]. Consequently, extensive clinical and fundamental research has been conducted on neuromodulatory therapies for these patients, encompassing both invasive techniques, including vagus nerve stimulation (VNS), deep brain stimulation (DBS), and spinal cord stimulation (SCS), as well as non-invasive approaches including transcranial magnetic stimulation (TMS), transcranial ultrasound stimulation (TUS), and transcranial direct current stimulation (tDCS) [3].

tDCS is one of the innovative non-invasive brain stimulation methods that has gained significant popularity during the past years due to its practicality and safety. According to previous studies, there are no

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significant adverse effects of tDCS other than moderate tingling, itching, mild burning, and light pain [4]. This technique uses direct current to modulate cortical neurons' excitability and intrinsic neural activity and augment critical brain networks' functional connectivity strength [5]. Evidence indicates that tDCS improves cognitive functions like memory, attention, and perception [6-7]. It can also influence the expression of essential proteins such as brain-derived neurotrophic factor (BDNF) and the inflammatory cytokines IL-6 and IL-10, leading to enhanced synaptic plasticity [8-9].

During tDCS, a steady, low-intensity direct current efficiently traverses the skull and elicits bipolar, polarity-dependent alterations via skull conduction in the associated cortex [10].

Several technical factors, such as the stimulation location, current intensity, polarity, and electrode surface area, influence the stimulation impact [11]. At the neuronal level, tDCS modulates excitability in the cerebral cortex, which primarily results from alterations in the stimulus polarity, leading to variations in resting membrane potential: depolarization or hyperpolarization [12]. Anodal stimulation typically enhances the excitability (i.e., depolarization) of the cerebral cortex, whereas cathodal stimulation diminishes cortical excitability (i.e., hyperpolarization) [13].

tDCS has considerable potential for neurocritical care professionals, as it can modulate cortical excitability and enhance neuroplasticity, both essential approaches for treating critical neurological disorders. The non-invasive characteristics of tDCS and its straightforward administration enable its use at the bedside without requiring intricate surgical interventions, which is especially beneficial in critical care environments where reducing further patient risks is necessary. Also, in the clinical context, tDCS has demonstrated efficacy in enhancing physical and cognitive recovery, alleviating pain, and regulating mood in individuals with illnesses such as stroke, traumatic brain injury, and disorders of consciousness (DOC) [13-14]. Furthermore, recent research indicates that tDCS may facilitate neuroprotection and increase neurodegenerative processes, presenting a unique strategy to improve current neurocritical care protocols [15-17]. These applications underscore the potential for tDCS to be included as a supplementary therapeutic approach, paving the way for novel research and clinical treatments focused on improving patient outcomes.

This review thoroughly examines the present applications of tDCS in neurocritical care environments, encapsulating the available data, investigating the underlying processes, and addressing the possible advantages and limitations linked to its implementation. The objective is to provide insights into the efficient integration of tDCS into conventional neurocritical care methods to enhance the management and recovery of patients with severe neurological disorders.

The Current Landscape of Neurorehabilitation in ICU

Irrespective of the underlying pathophysiology, extended ICU admission commonly necessitates sedation and immobilization, usually in a prone orientation. This pertains to the development of secondary neurological impairments affecting both the central and peripheral nervous systems, as well as muscular function, resulting in motor, sensory, and cognitive deficits, along with frequent emotional disorders, collectively referred to as Post Intensive Care Unit Syndrome (PICS) [18-19]. The intricacy of managing neuro ICU patients is exacerbated when the underlying condition affects the nervous system in the first place. In particular, it was shown that a significant number of patients with acute neurological conditions, including stroke or TBI, experience enduring DoC, deficits in autonomic respiratory drive, severe paresis, and difficulty in swallowing, all bringing them to the point that they would even require invasive ventilation [20-21].

In this context, early rehabilitative therapies (defined as those occurring during and soon after ICU discharge) are essential for mitigating the potential further neurological burden of the condition. As previously noted, tDCS has attracted considerable attention in the domain of critical care rehabilitation in recent years. Due to its noninvasive characteristics and simplicity of delivery, tDCS is especially beneficial for critically ill patients who may not endure more invasive neuromodulatory methods. In neurocritical care patients, particularly those with stroke or TBI, tDCS can be utilized to focus on motor and cognitive circuits affected by pre-existing neurological damage. Its early administration in the rehabilitation process can alleviate the consequences of extended immobility, sedation, and prone placement by facilitating brain reprogramming, specifically its motor areas. The last interesting fact about tDCS is that it can be tailored to specific therapeutic objectives, such as augmenting motor cortex excitability to mitigate paresis or adjusting prefrontal activity to facilitate cognitive recovery, making it a very versatile approach.

A Technical Overview of tDCS

tDCS is a non-invasive neurostimulation method that administers a mild direct current, ranging between 0.5 to 2 mA, to the cortical regions beneath two opposing electrodes: the "active electrode" is positioned over the targeted area, while the other serves as the "reference electrode" [22]. The electrodes are linked to a 9-volt battery and enveloped by conductive sponges saturated

with saline or alternative conductive substances [23-24]. When both electrodes are positioned over a conductive region, such as the scalp, a direct current circulates between the anode and the cathode, inducing particular alterations in the cortical excitability of the tissue [25].

Appropriate stimulation settings are crucial in the practical use of tDCS. To ensure the safe and successful use of tDCS, it is essential to define the current intensity [26]. The other critical stimulation parameter is the electrode size, which is available in 4 × 4, 5 × 5, 5 × 7, and 6 × 6 sizes [25]. The current intensity and electrode size are two factors that determine the current density, which is calculated by dividing current intensity by the entire surface area occupied by the electrode, represented in research as $\mu A/cm^2$, mA/cm^2, and A/cm^2, with the most common range being between 0.028 and 0.06 mA/cm^2 [27].

The position of the active electrode is another crucial factor in the practicality of tDCS and is often established using the electroencephalogram (EEG) 10-20 System [28]. tDCS has its most pronounced effects at sites where the electrode is placed; however, research utilizing advanced neurologic imaging modalities, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), has demonstrated that its weak current stimulation produces widespread and even unexpected impacts on other regions of the CNS [29-30]. This is unsurprising given the intricate architecture of the human CNS, but it underscores the need for a comprehensive investigation to determine the intensity and durability of such impacts [31-32].

The Safety and Applicability of tDCS in Different Patient Populations in Neuro-ICU

Neuro-ICU management may include a range of patient populations that could benefit from specific neurorehabilitative interventions, such as tDCS, although safety and applicability may vary depending on the condition. Ischemic and hemorrhagic stroke patients primarily present with severe motor and cognitive deficits due to impaired neural circuits and are thus considered ideal candidates for early neuromodulatory interventions that aim at augmenting neuroplasticity. Similarly, patients with TBI experience impaired motor functions, cognitive impairments, and, in severe instances, DoCs, whereby tDCS may be of help in enhancing cortical responsiveness and connectivity. Patients with brain hemorrhages, presenting either as extra- or subdural or intraparenchymal hemorrhages, have a different set of neurovascular dynamics and, therefore, present various concerns for the safety of tDCS application. Advancing the clinical usefulness of tDCS in neuro-ICU will require understanding specific risks, potential benefits, and tailored protocols for each of these populations.

Stroke

Stroke, a leading cause of adult disability in Western societies, constitutes a significant portion of the neuro-ICU patient population [33]. The concept of using electricity to pursue more successful stroke rehabilitation therapy has been around for a long time [34]. In recent years, more reports have been seen on the possible therapeutic advantages of tDCS for enhancing brain function post-stroke [35].

Significant synapse architecture and plasticity alterations occur post-stroke, which can contribute to specific spontaneous recovery in sensation, mobility, or cognition loss [36]. Some proposed recovery pathways include increased cortical excitability and alterations in synaptic plasticity, including LTP-like regulation, enhanced calcium currents, and neurotrophic factor activation in the damaged hemisphere [36]. Consequently, it would be prudent to assess the effects of tDCS in post-stroke recovery, as it has been shown to enhance some of these pathways.

Animal studies have demonstrated that tDCS can augment cerebral blood flow perfusion via neurovascular coupling [37]. Additionally, an adequate duration of tDCS can elicit long-term potentiation (LTP) and long-term depression (LTD) influenced by facilitating the release of brain-derived neurotrophic factor (BDNF) and dopamine, thereby altering synaptic plasticity [38-39]. Furthermore, human trials, including five days of tDCS in addition to occupational therapy in a crossover, indicated a notable enhancement in motor results that persisted for at least one week [40]. The findings of this cathodal tDCS study (stimulation directed at the contralesional hemisphere) contrast with those of an anodal tDCS study by Hesse et al. [41], which involved subacute stroke patients undergoing multiple sessions of anodal tDCS (applied to the lesional hemisphere) alongside a robot-assisted arm training protocol yet did not yield significant motor enhancements. The disparities between the cathodal stimulation of the unaffected hemisphere and the anodal stimulation of the lesional hemisphere may result from factors like the size of the lesion, the degree of cortical involvement, or the engagement of the pyramidal tract in the lesional hemisphere [14].

Despite a growing body of research validating the efficacy of tDCS in stroke survivors, its effects on the prefrontal cortex are inconsistent [42]. This was also portrayed in the latest tDCS guidelines that emphasized the use of tDCS for patients with post-stroke motor function and aphasia above those with cognitive impairments in their recommendations [16, 43]. The low-level recommendation may stem from the fact that the

majority of studies on tDCS for post-stroke cognitive impairment featured low sample size and crossover design and relied mainly on subjective neuropsychological scales rather than more objective modalities [44-46]. Thus, further data is required to regard tDCS as a conventional therapy modality for stroke patients in neuro ICUs.

Brain hemorrhage

The potentially advantageous effects of tDCS on perfusion necessitate the assessment of tDCS in hemorrhagic brain disorders alongside ischemic ones. Intracerebral hemorrhage (ICH) constitutes around only 15% of stroke occurrences, while it is linked to a worse outcome compared to ischemic stroke, owing to the severity of the damage involved [47]. However, currently available research has predominantly focused on the impact of tDCS in individuals with ischemic stroke rather than ICH.

Heidarzadegan et al. [48] performed an animal investigation to critically assess the effects of the four primary paradigms of transcranial electrical stimulation, namely tDCS, transcranial alternating current stimulation (tACS), pulsed current stimulation (tPCS), and random noise stimulation (tRNS) on collagenase-induced ICH rat models. Their findings demonstrated that implementing these four paradigms substantially mitigated motor abnormalities in collagenase-induced ICH groups. Structural modifications and stereological evaluations also corroborated the findings of behavioral functions in their research. A further controlled trial by Mortensen et al. [49] examines the synergistic impact of transcranial tDCS and occupational treatment on activities of daily living (ADL) and grip strength in patients with upper limb motor deficits post-ICH. Both groups enhanced ADL, while only the anodal group exhibited enhanced grip strength. Nonetheless, this disparity was diminished at the one-week follow-up. They concluded that adding tDCS to occupational therapy helps patients achieve better outcomes compared with occupational treatment.

Subarachnoid hemorrhage (SAH) is another severe cerebral hemorrhagic condition that predominantly impacts younger individuals, exhibiting elevated death and morbidity rates along with subsequent functional impairment [50-51]. Given that cerebral perfusion plays a pivotal role in the pathophysiological processes of SAH, tDCS may positively influence delayed ischemic consequences post-SAH through its regulation of cerebral perfusion. However, reports on tDCS in the context of SAH are still limited, akin to ICH. Recent research by Malinova et al. [52] investigated the effects of tDCS on vasospasm in a rat model of SAH. This study demonstrated that the cathodal group had the lowest occurrence of fresh vasospasm ($p = 0.01$) and the lowest average number of vasospastic vessels per rat ($p = 0.02$). Nonetheless, to the best of our knowledge, no human trials investigating tDCS in patients with SAH have been published yet.

Overall, tDCS appears to be a potential adjunctive strategy for the rehabilitation of individuals with a history of cerebral hemorrhage. It is well-accepted by patients and may be readily utilized for home-based training. Nonetheless, more trials with prolonged follow-up are required to investigate the potential effects of tDCS in patients with ICH, SAH, and other types of cerebral hemorrhage.

Traumatic brain injury (TBI)

Traumatic brain injury (TBI) is a change in brain function, including consciousness, memory, cognition, sensorimotor functions, or other indications of brain pathology, such as radiologic or laboratory evidence of brain damage resulting from an external agent [53]. These neurological dysfunctions following TBI arise from localized and diffuse damage, complicating the identification of specific anatomy-clinical correlations [54]. Previous clinical research indicates that recovery following TBI appears to be inferior to that after a stroke [55]. Neuroplastic alterations following TBI and findings from animal research suggest that tDCS may enhance motor deficits in TBI; nevertheless, clinical trials investigating tDCS for motor recovery in TBI are now insufficient [56]. The frontal poles [57], dorsolateral prefrontal cortex (DLFPC) [58], and M1 [59] were the targeted regions for tDCS in the previous research, which indicates that the selection of tDCS targets is pertinent to the chief complaints of the population under investigation.

For instance, studies regarding TBI-induced cognitive impairment mainly targeted DLPFC. The DLPFC plays a crucial role in cognitive function, with several studies indicating its association with attention and working memory capabilities [60]. Leśniak et al. [61] researched to ascertain if cumulative anodal tDCS of the DLPFC may augment the rehabilitation of memory and attention in patients with TBI. Participants were randomly assigned to two groups: the experimental group, who had anodal tDCS, succeeded by rehabilitative cognitive training, conducted daily for 15 days, and controls, who had anodal tDCS only for 25 seconds (sham condition) with identical therapy. Test scores in both groups were compared three weeks before and immediately following treatment. Post-treatment, the experimental group had more significant effect sizes in 6 out of 8 cognitive outcome measures; however, these differences were not statistically significant.

Other pertinent brain regions may be engaged for motor results. For instance, Park et al. [59] utilized tDCS on M1 to enhance balance and posture in their rat model of TBI. Balance and posture are affected by several interacting

CNS regions, including the spinal cord, cerebellum, cortex, and brainstem [62-63]. Some may contend that the cerebellum is another optimal target for tDCS in enhancing balance and postural control. To prove this hypothesis, Yosephi et al. [64] proposed that bilateral stimulation of the cerebellar hemispheres is more productive than M1 stimulation for enhancing balance in elderly persons at elevated risk of falls. Nonetheless, a prior investigation by Sussman et al. [65] found that TBI correlated with reductions in white and gray matter volume and cortical thinning in regions including M1, but the cerebellum remained unscathed. Recent research emphasized the essential linkages between M1 and the cerebellum for optimal motor performance [66], and evidence suggests that tDCS can affect distant brain regions [67-69]. Consequently, researchers must meticulously evaluate the stimulation's possible direct and indirect effects and identify brain targets that will most significantly impact the examined population.

Lastly, it would also be interesting to mention a recent systematic review by Zaninotto et al. [70], which indicated that non-invasive brain stimulation modalities, such as tDCS, may enhance neurorehabilitation by promoting adaptive neuroplasticity and mitigate pathological consequences after TBI. Among the 14 investigations considered in their study, the majority employed anodal tDCS targeting the left DLPFC; however, there was a lot of heterogeneity among studies regarding the exact technique used. Many included studies also showed enhanced coma recovery scores in patients with DoC and increased cognitive performance on neuropsychological evaluations. Several investigations also demonstrated neurophysiological metrics (like EEG) alterations, correlating with their clinical observations.

In summary, tDCS is a safe, readily available, and noninvasive neuromodulatory method that may be administered as a standalone treatment. However, it may provide superior clinical cognitive and motor outcomes when integrated with additional therapeutic approaches, such as cognitive rehabilitation and physical therapy.

Clinical Application of tDCS in Neuro-ICU Patients: Challenges and Opportunities

Seizures

tDCS has been widely used in neuro-intensive care units for patients. On the one hand, Fisher et al. reported four cases of focal status epilepticus who got tDCS to reduce spikes and seizures [71]. Patients in the intensive care unit were referred for tDCS treatment when focal status epilepticus or significant lateralized periodic discharges persisted despite standard antiseizure medicines and anesthetics. An ActivaDose (Caputron) tDCS device administered battery-powered direct cathodal current at 2 mA through a saline-soaked sponge applied to the scalp above the seizure focus. The positively charged electrode was positioned on the opposite side of the forehead or shoulder. The procedure lasted 30 minutes, was given twice daily, and was followed up with 1 to 4 additional sessions on the succeeding days. tDCS significantly reduced interictal spikes in three and electrographic seizures in two [71]. In this case series, the sole adverse effect of tDCS was a temporary erythema under the sponge in only one patient. Fregni et al. also demonstrated that in a group of drug-resistant adult patients with cortical development abnormalities, a significant decrease in EEG epileptiform discharges appeared promptly after one session and lasted for as long as four weeks, with an average reduction of 64.3%. However, the frequency of seizures during the post-stimulation time did not statistically decrease. Considering safety issues, no seizures were induced, nor was there an increase in EEG discharge rates pendant or exactly post-stimulation [72]. Auvichayapat et al. [26] conducted a subsequent trial involving children suffering refractory epilepsy, predominantly of unrecognized origin. They observed a slightly considerable decline in seizure frequency in the active group (4.8% 30 days after intervention) and a 54.7% decrease in EEG discharge rate that elongated for up to two days. The stimulation techniques for both studies were a single 20-minute tDCS stimulation with a one mA current, applying the negatively charged electrode to the area exhibiting the highest EEG epileptiform activity. The seminal investigation on tDCS treatment in epilepsy was conducted by Shelyakin et al. [73], demonstrating notable enhancements in clinical seizures, basic EEG, and IED rates among a cohort of 18 children. These favorable outcomes prompted specialists to create novel tDCS protocols aimed at various etiologies of epilepsy. Even though there is variability of uncontrolled trials in sample size, electrode dimensions, montage, clinical condition, applied electrical current, and the time of sessions, further research will provide valuable insights that significantly contribute to the advancement of randomized clinical trials.

On the other hand, two case reports focused on the application of tDCS in subjects with cortical dysplasia [74-75]. Despite varied durations and stimulation sites, both reported marked reduced seizure frequency [76]. In the latter of the above studies, there was a temporary reduction in seizure frequency only during the tDCS, returning to the pre-stimulation characteristics afterward. In this study, no effects of active tDCS on seizure frequency or IEDs were found.

These findings may stimulate additional research on tDCS in critical care environments; however, validation through controlled trials would be necessary. Results may

be complicated by various concurrent alterations in drugs, therapies, and the patient's general condition, highlighting the importance of further investigations in seizure-critical conditions. Previous literature varied in sample characteristics, methodologies, and stimulation protocols. This heterogeneity and the moderate risk of bias identified in the included studies were the primary reasons for our decision to forgo a quantitative synthesis approach. Other clinical outcomes, such as seizure duration or intensity, which are particularly pertinent for drug-resistant individuals, were not routinely evaluated in controlled trials. Moreover, limited research has evaluated clinical outcomes beyond seizures, such as post-tDCS quality of life, in addition to depression and memory.

TBI and Strokes

Traumatic brain injury and cerebrovascular accidents: neurocritical patients also have been targeted for tDCS to improve the level of consciousness. A hundred subjects in neurological ICU were screened, and 40 individuals were enrolled within the first one to two weeks following injury after meeting the inclusion criteria. Anodal tDCS targeting the motor region (C3/C4 ipsilesional), sensory area (P3/P4 ipsilesional), and left dorsolateral prefrontal cortex (F3), following the 10/20 EEG montage for two treatments of 20 minutes each day over the following 7 days, in conjunction with standard physiotherapy, was done for the cases. The control group received only standard physiotherapy, akin to the experimental groups. The pretest and post-test GCS and RLAS scores demonstrated statistical significance at $p<0.01$, while the tDCS group demonstrated superior significant improvement [77]. Prior evaluations indicated that individuals with Disorders of Consciousness (DOC) might derive benefits from tDCS [70,78-79]. However, the overall quality of evidence was insufficient.

A study of 28 articles systematically assessed the rehabilitation impact of non-invasive brain stimulation (NIBS) on DOC following brain trauma and compared the impact of various NIBS techniques [80]. NIBS, such as tDCS combined with standard rehabilitation, yielded a more significant effect compared to standard rehabilitation alone and sham NIBS combined with standard rehabilitation. The hierarchy of interventions in the network meta-analysis, using GCS as the outcome measure, showed that rTMS along with standard rehabilitation was followed by tDCS along with standard rehabilitation and then regular rehabilitation alone. The hierarchy of interventions in the network meta-analysis, using CRS-R as the outcome measure, showed rTMS combined with standard rehabilitation, followed by the combination of tDCS and routine rehabilitation, then NIBS sham stimulation combined with regular rehabilitation, and finally, the aforementioned rehabilitation alone. The influence of tDCS on patients with DOC of unclear condition was superior to that observed in patients suffering critical DOC, where the effect was not statistically significant [80]. Another systematic review and meta-analysis by Feng et al. examined the impact of NIBS on patients with DOC [81]. The findings indicated that anodal tDCS might markedly improve the CRS-R scores in DOC patients, aligning with the outcomes of our meta-analysis. Meta-regression revealed an absence of association between stimulation dose and effect sizes, as behavioral changes might be too slight to be identified by CRS-R in short-term tDCS [81]. In a recent meta-analysis by Ma et al. [82], the subgroup analysis was categorized by total stimulation sessions and discovered that just more than 20 stimulation sessions significantly improved GCS and CRS-R scores. Consequently, patients with consciousness instability necessitate recurrent tDCS to effect behavioral improvements. Furthermore, patients with disorders of consciousness may exhibit varying susceptibility to tDCS intervention based on their distinct diagnoses. The authors concluded that patients with DOC diagnosed with Minimally Conscious State (MCS) saw significant improvements in Coma Recovery Scale-Revised (CRS-R) scores due to tDCS. However, patients diagnosed with Unresponsive Wakefulness Syndrome (UWS) or Vegetative State (VS) did not show similar benefits, corroborating Feng's results [81]. The potential explanations include an elevated degree of under-excitability and a diminished capability for neuronal plasticity in individuals with UWS or VS [83-84]. Discovered that global cerebral excitability was elevated in both MCS and VS patients following tDCS treatment; however, the enhancement in excitability for VS patients in temporal and spatial sites was inferior to that of MCS patients, which partially elucidates the less pronounced behavioral changes observed in VS patients compared to MCS patients.

The stimulation variables of tDCS for patients suffering disorders of consciousness, including the position of the electrodes, intensity, and duration of stimulation, lack standardization. The targets of tDCS in the brain are contingent upon the properties of the anode electrode used to modulate cortical excitability and the functional brain areas associated with consciousness. Anodal or cathodal current may promote depolarization or hyperpolarization of cortical neurons [85]. Koninck et al. conducted a study protocol with two phases of validation and a randomized controlled trial on medically stable adult patients with brain injuries, specifically those with traumatic brain injury and hypoxic-ischemic encephalopathy, who have a GCS $\leq$12 following the withdrawal of continuous sedation. They offered that the intervention consist of a 20-minute session of 10 Hz tACS at one mA intensity or a sham session applied to

parieto-occipital cortical regions, conducted over five days. The frequency of the target alpha brain oscillations (8-13 Hz) and resting-state EEG recordings occur four times a day over five straight days: before and after the intervention, as well as at 60 and 120 minutes following transcranial alternating current stimulation (tACS) [86].

Researchers proposed that behavioral changes assessed by the CRS-R may be observable through motor cortex stimulation [87]. The intensity employed in all investigations was 1–2 mA, considered a safe level for tDCS, resulting in no reported adverse events. Current density serves as the primary metric for assessing the safety of electrical stimulation; however, limited research has addressed this concept within their stimulation protocols. Unfortunately, no trials have investigated the association between stimulus intensity and therapeutic result. The stimulation doses in the included studies vary. A session of tDCS can influence cortex excitability; however, behavioral effects are either negligible or temporary [13]. Additionally, regarding the electrode materials, one study utilized round rubber electrodes (12 cm^2) [88], another employed eight gelled ones (3.14 cm^2 Ag/AgCl) [89], while the remaining studies predominantly applied saline-soaked surface sponges (35 cm^2) [90-94]. The material is associated with the definition of tDCS; however, the limited number of investigations makes it challenging to assess the therapeutic effects of various materials. Furthermore, no research has explored the relation between the definition of tDCS and its therapeutic effects in patients with DOC. Establishing long-lasting aftereffects is contingent upon changes in membrane potential and N-methyl-D-aspartic acid receptor effectiveness modulations, which can lead to long-term potentiation and depression-like effects [95-96].

tDCS may effectively improve the GCS and the RLAS in patients exhibiting reduced consciousness during the acute phase following injury. The procedure is cost-effective, has low contraindications, is noninvasive, and does not interfere with other interventions in the intensive care section. However, further research should be conducted regarding the mechanical and optimal stimulation parameters of tDCS for DOC.

Delirium

Age, opioid use, and haloperidol administration were linked to persistent delirium. Further investigation is required concerning the effects of haloperidol and opioids on persistent delirium [97]. There are a handful of assessments on the impact of tDCS on delirium. A survey of older subjects undergoing primary lower extremity arthroplasty demonstrated that 2 mA active tDCS for 20 minutes within the initial three postoperative days, applied to the left dorsolateral prefrontal cortex, may reduce the occurrence of postoperative delirium in elderly individuals undergoing primary lower limb arthroplasty in the intensive care unit [98]. The effects of tDCS on delirium may be associated with alterations in brain function and a decrease in inflammation. The temporary enhancement in behavior following tDCS could be associated with the maintenance of grey matter observed in structural MRI and residual metabolic activity in cortical and subcortical areas pertinent to attention and working memory, particularly in the left dorsolateral prefrontal cortex (DLPFC), as indicated by fluorodeoxyglucose positron emission tomography (FDG-PET) analysis [99-100].

Conclusion

tDCS is a versatile and promising tool in neurocritical care, offering a noninvasive, low-cost approach to neurological recovery. The fact that tDCS could modulate cortical excitability, enhance neuroplasticity, and promote functional restoration makes it a necessary adjunctive treatment for severe neurological conditions such as stroke, traumatic brain injury, disorders of consciousness, and epilepsy.

The studies' results suggest that tDCS can improve motor and cognitive outcomes, facilitate early rehabilitation, and mitigate the adverse effects of prolonged immobilization and sedation in critically ill patients. However, further research will be required to optimize and improve therapeutic efficacy because the responses, stimulation parameters, and methodologies showed sizeable individual variability. Future studies should focus on standardizing stimulation settings, condition-specific applications, and long-term outcomes. As the concept of tDCS mechanisms continues to evolve, its use in routine neurocritical care protocols may be essential for improving patient recovery and quality of life. Further research could rework rehabilitation strategies in critical care, enabling innovative, evidence-based clinical interventions.

Acknowledgment

The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, for their support and cooperation.

Authors' Contribution

Study concept and design: MRH, MM. Drafting of the manuscript: KM, MZ.; critical revision of the manuscript for important intellectual content: MG.; administrative, technical, and material support: MM and MRH.; study supervision: MM

Funding/Support

The Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, supported this study.

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