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Review

Neurostimulation for Traumatic Brain Injury: Emerging Innovation

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Abstract

Traumatic brain injury (TBI) is a significant source of brain deficit and death among neurosurgical patients, with limited prospects for functional recovery in the cases of moderate-to-severe injury. Until now, the relevant body of literature on TBI intervention has focused on first-line, invasive treatment options (namely craniectomy and hematoma evacuation) with underwhelming focus on non-invasive therapies following surgical stabilization. Recent advances in our understanding of the impaired brain have encouraged deeper investigation of neurostimulation strategies, owed largely to its demonstrated livening of damaged neural circuitry and capacity to stabilize erratic network activity. The objective of the present study is to provide a scoping review of new knowledge in neurostimulation published in the PubMed, Scopus, and Google Scholar databases from inception to November 2022. We critically assess and appraise the available data on primary neurostimulation delivery techniques, with marked emphasis on restorative opportunities for accessory neurostimulation in the interdisciplinary care of moderate-to-severe TBI (msTBI) patients. These data identify two primary future directions: 1) to relate obtained gain-of-function outcomes to hemodynamic and histological changes and 2) to develop a clearer understanding of neurostimulation efficacy, when combined with pharmacologic interventions or other modulatory techniques, for complex brain insult.

Keywords
Traumatic brain injury; neurosurgical stimulation; rTMS; tLNS; tDCS; pharmaceutical management; interdisciplinary care

1. Introduction

Traumatic brain injury (TBI), or an acquired insult to the brain via an external force, is a major health and socioeconomic concern throughout the world with an estimated 10 million individuals affected by TBI annually [1, 2]. In high income countries, TBI is largely a result of falls in older patients [3]. In younger patients in these countries, TBI is predominately due to traffic accidents. While preventative measures have been shown to decrease this source of injury, it continues to be a leading contributor to mortality and disability within this population [3, 4]. Furthermore, TBI due to traffic accidents is also of significant concern in low-middle income countries. Current projections demonstrate the already high levels of mortality and morbidity are increasing in prevalence with the rapid adoption of motor vehicle transportation, signaling an international scale of the crisis [5]. The median age of onset of TBI is relatively low, even in high-income countries. Therefore, the ensuing fallout of TB is disproportionally costly to productive years lost, resulting in an outsized detriment to society [6]. In the USA alone, the financial impact is in excess of $60 billion dollars per annum with an estimated prevalence of 3.2 million citizens living with disability after a TBI associated hospitalization [7].

The pathophysiology of traumatic brain injury is multifactorial, including inflammation, oxidative stress, apoptosis, mitochondrial damage, shearing of white-matter tracks, focal contusions, and hematomas [8]. More, a diagnosis of traumatic brain injury encompasses a range of severities. Using the Glasgow Coma Scale (GSC, TBIs are classified as mild (14-15), moderate (9-13), and severe (3-8) [9, 10]. In a systematic review, Buhangiar et. al. delineated the emerging effects of neuromodulation in TBI patients with an initial GCS of 13-15 and found neuromodulation had a positive effect on measured symptoms and neurophysiological functioning [11]. Consequently, the GCS may be of use when considering the relevance of neuromodulation in treatment, although more literature is needed to support such a claim. However, the proposed mechanism by which neuromodulation is theorized to influence such outcomes as discussed by Buhangiar et. al. is via adaptive neuroplasticity [11]. More precisely, neuromodulation can stimulate the cerebral cortex, inhibiting or activating neuronal cells. Such an effect has been evidenced to reorganize neural networks following traumatic brain injury and even improve cognitive dysfunction [12].

Considering the complex disease processes and varied severities, different forms of neurosurgical management of TBI are necessary and include operative and non-operative intervention. However, as surgical interventions are no longer the gold-standard of TBI management, nonoperative interventions such as neuromodulation are of increased relevance in the management of TBIs. Further, it is necessary to understand how this novel innovation may be combined with other, non-surgical management of TBIs such as pharmacological management [13-

15]. Currently, there is a paucity of reviews summarizing the results of this neuromodulation in the context of current TBI management standards and practices. Thus, the objective of the current review is to discuss the current innovative techniques in neuromodulation, what the standard of pharmacological management of TBI is and how it can be accentuated by neuromodulation, and how best practice of TBI neuromodulation treatment may be within an interdisciplinary setting for increased effect.

2. Discussion

2.1 Novel Findings in Neurostimulation for Brain Injury

Several areas of intense focus in brain stimulation theory and practice have been identified: most notably in translingual neurostimulation and transcranial magnetic stimulation (Figure 1). Measured success in these domains primarily center on posturography analysis (e.g., Sensory Organization Test and dynamic gait index) and physiologic analysis (e.g., wavelet power analysis in electroencephalography).

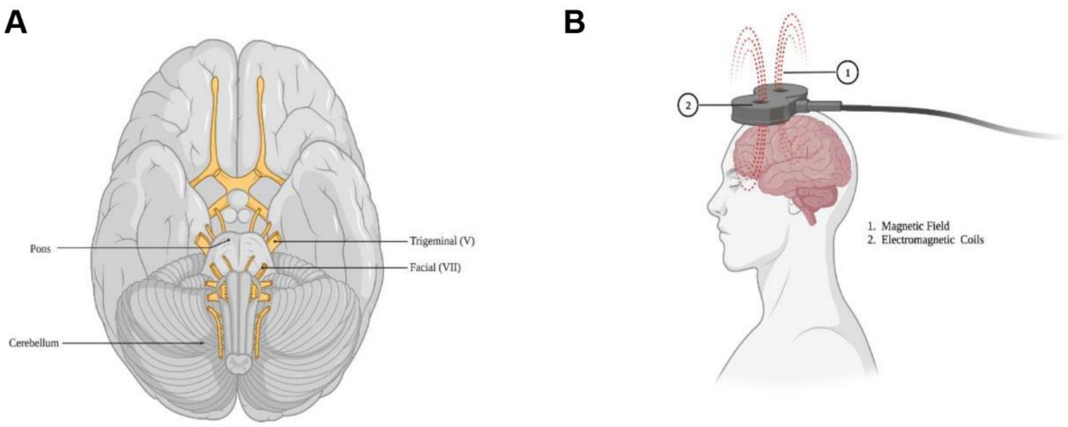

Figure 1 Images depicting targets of translingual neurostimulation and transcranial magnetic stimulation. **(A)** Translingual neurostimulation is achieved though neuroplastic changes. These changes are induced by facial and trigeminal nerve stimulation, excited by neural impulses to the pons Varolii and cerebellum. **(B)** During a rTMS session, an electromagnetic coil is placed against the scalp and a magnetic pulse is delivered to stimulate nerve cells in the brain. Figure created with BioRender.com.

2.1.1 Translingual Neurostimulation

Successful translingual neurostimulation (tLNS) is achieved by targeted stimulation of cranial nerves V and VII and represents a prime candidate for combination therapy of neurologic disease and stroke, inciting deserved interest in its clinical utility for traumatic brain injury [16, 17]. In a 2019 double-blinded, randomized controlled trial investigating the efficacy of tLNS for improving mild-to-moderate TBI (mmTBI) outcomes, Tyler et al. first reported that tLNS administered over a 14-week period significantly improved related balance deficits from baseline (N = 44) ($p < 0.0001$) [18]. These findings corroborate even newer evidence validating tLNS for adjunct balance and gait rehabilitation, as measured by observable increases in Sensory Organization Test score and neuroplasticity, particularly for mmTBI patients with limited response to conventional physical therapy [19, 20]. Moreover, available data indicates that tLNS may realistically provide clinical benefits beyond traditional therapeutic windows for TBI patients. A longitudinal case study detailing a retired Army Captain's cognitive recovery reported that combined tLNS and physical therapy, delivered 14 years after the initial 2006 TBI event, yielded striking increases in basic attention (via P300 response analysis) and cognitive processing (via N400 response analysis) [21]. They additionally self-reported amelioration of ongoing symptoms related to the TBI event, indicating that incorporation of tLNS was commensurate with recognizable clinical benefit.

2.1.2 Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) provides profound therapeutic benefit via unique delivery of focal to diffuse brain stimulation involving brief magnetic pulses generated from an iron-core coil. Previous research exploring rTMS protocols revealed its strength for treatment-resistant depression symptomology, lessening chronic orofacial pains, and obsessive-compulsive disorder, among several other ailments [22-24]. A hallmark characteristic of rTMS is its depth-focality tradeoff, which results in stimuli applied to non-targeted brain structures when probing deeper regions [25, 26]. This feature seems to suggest that rTMS may prove highly efficacious in repairing dysfunctional neural networks (via activity-dependent modulation of synaptic plasticity), particularly in TBI patients with diffuse axonal injury. Supporting evidence reported by Wang et al. demonstrated that rTMS delivered to the left motor cortex significantly altered right cerebellar activity, which, in addition to specialized balance and coordination, plays established roles in verbal [27-29]. Pulse frequency too impacts clinical outcomes. At low frequency, rTMS enables cortical inhibition, perhaps by induced suppression of parvalbumin and calbindin, whereas high frequency rTMS (3-50 Hz) enables targeted excitation of the lesioned cortex, benefiting stroke patients, though the latter finding remains debated in the literature [30-32]. Moreover, emerging data purports that TMS can be safely delivered to infants with perinatal brain damage (N = 6) and in persons with co-occurring TBI and complex neuropsychiatric comorbidities [33-35]. Still, further research is needed to establish the safety and scoping efficacy of high-frequency rTMS in seizure-prone (or otherwise compromised) patient populations.

Other opportunities for functional recovery at the hands of electrical neuromodulation techniques have been described for a motley of conditions. For instance, a number of surfacing studies have explored the utility of deep brain stimulation for focal targeting of midbrain structures implicated in treatment-resistant depression [36-38], however sweeping conclusions remain ill-generalizable in the TBI patient population [39]. Hofer and Schwab further reviewed the therapeutic benefits afforded by electrical stimulation for spinal cord injury patients years after the initial injury event [40], owed to previously described activity-dependent restoration of residual brain and spinal cord networks [41].

2.2 Current Pharmacological Management

Seizures after TBI cause increased ICP and decreased cerebral perfusion [42]. Therefore, treatment with prophylactic anticonvulsant medications such as phenytoin are recommended to reduce the number of seizures in the first week following TBI; however, anticonvulsant medications do not prevent seizures after one week [43]. Many patients with TBI are placed on psychotropic medications following the TBI due to the presence of psychiatric problems, the most common being depression, bipolar disorder, generalized anxiety disorder, and substance abuse [44]. Beta blockers and mood-regulating epileptics can be administered as first-line treatments for agitation and aggression depending on comorbidities, while antidepressants, buspirone, neuroleptics, and benzodiazepines are second-line treatments [45]. SSRIs are considered the first-line treatment for TBI-related depression [46].

2.3 Emerging Pharmacological Management with Neurostimulation

At the time of writing, very limited research exists on the efficacy of combining pharmacological treatments of TBI with neurostimulation. Bender Pape et al. found that in post-TBI patients with disordered consciousness who had low probability of making a significant recovery, combining rTMI with amantadine improved neurobehavioral outcomes [47]. Auditory-language skills specifically were improved in patients who received rTMS prior to a combination therapy of rTMS and amantadine [48]. For psychiatric symptoms post-TBI, some research has looked into the use of rTMS after failed pharmacological management of symptoms. A systematic review conducted by Narapareddy and colleagues reported that while SSRIs, specifically sertraline, shows the best evidence for improving depression symptoms after TBI, rTMS might be effective for those patients that do not respond to pharmacological treatment [46]. Included patients took from 25 to 2000 mg/d of sertraline for time periods ranging from 3-30 weeks and were assessed by results on the Hamilton Depression Scale, Patient Health Questionnaire 9, and the Beack Depression Inventory. In patients that did not respond to pharmacological treatments of TBI depression, rTMS (Figure 1B) showed some immediate improvement in depression symptoms, but the long-term efficacy showed mixed results [46]. An independent case study revealed that high frequency DBS to the anterior limb of the internal capsule and nucleus accumbens at 100 Hz improved defects from a TBI on a patient with severe psychiatric symptoms who had showed no improvement using antipsychotic drugs [49]. Frequencies below 100 Hz to the nucleus accumbens improved auditory hallucinations in the patient, while high frequency stimulation to the anterior limb of the internal capsule improved emotional deficits [49]. While these two studies looked at rTMS after failed pharmacological treatment of depression symptoms, future research is needed to investigate the utility of combining pharmacological treatment with neurostimulation.

2.4 Neuromodulation in Interdisciplinary Care: Alternative Avenues

A growing body of evidence in TBI literature supports the application of interdisciplinary care models acutely as well as during the rehabilitative phase for achieving the most favorable patient outcomes. Frequent associations of the disease with comorbid diagnoses of a related etiology (i.e., accidental trauma, post-deployment conditions) such as post-traumatic stress disorder (PTSD) and major depressive disorder (MDD) require the simultaneous management of multiple clinical sequalae, often by different specialists (primary care, psychiatry, neurology, and others), in the same patient [50, 51]. Beyond the management of comorbidities, addressing the complex pathophysiology of TBI alone has also been demonstrated to benefit from multidisciplinary care. As just one example, a quasi-experimental study of 56 TBI patients who were assigned to either multidisciplinary rehabilitation or single specialty care showed that patients who were cared for by multidisciplinary teams demonstrated significantly higher gains in independent living, cognitive and motor skills at the end of a 2-year rehabilitation period [52]. These findings have been consistent with the results of other experiments involving combinations of neuropsychologic and family, occupational as well as speech-language pathology therapy [53-56].

In this context, the application of neurostimulation needs to be considered alongside other therapeutic and rehabilitative approaches which are likely to be deployed concurrently for the holistic management of a patient with TBI. Recent advances in our understanding of TBI pathology and management have given rise to several new in-hospital TBI treatment innovations which likewise rely on interdisciplinary involvement. Alongside tLNS and rTMS, applications of transcranial direct current stimulation (tDCS), low-level laser therapy (LLLT), and transcranial doppler sonography (TDS), which were originally intended for medication-resistant depression, pain, spasticity, hand-eye coordination, gait, and speech and language pathologies are increasingly emerging as powerful complementary and/or alternative therapeutic modalities for TBI [57, 58]. Among these, TDS (Figure 2A) provides particularly strong support for the synergistic effects of interdisciplinary collaboration as the development of this typically diagnostic method for therapeutic purposes in TBI is an apt example of convergent technological evolution with another emerging technique, focused ultrasound (FUS) (Figure 2B), which was first used in oncological surgery and later adapted to neurosurgery and TBI [59-61]. While most efforts around FUS are still centered validation of different adaptations of the technology to TBI in animal models, TDS therapy has already been demonstrated as clinically effective in humans [62-66]. It is conceivable that neurostimulatory approaches such as tLNS and rTMS will likewise benefit from technological integration with these new therapeutic alternatives in order to provide patient-centered care encompassing TBI as well as multiple comorbidities which may be present within the same individual. Despite this potential, a recent review by Marklund et al. reports that there is still a relative lack of robust trial data demonstrating the clinical efficacy of neurostimulation in the context of other simultaneous therapeutic approaches for TBI and/or comorbidities [67]. More research needs to be done to define the role and guide the development of neurostimulation as a standard of care tool within the toolbox of precise, patient-centered TBI care.

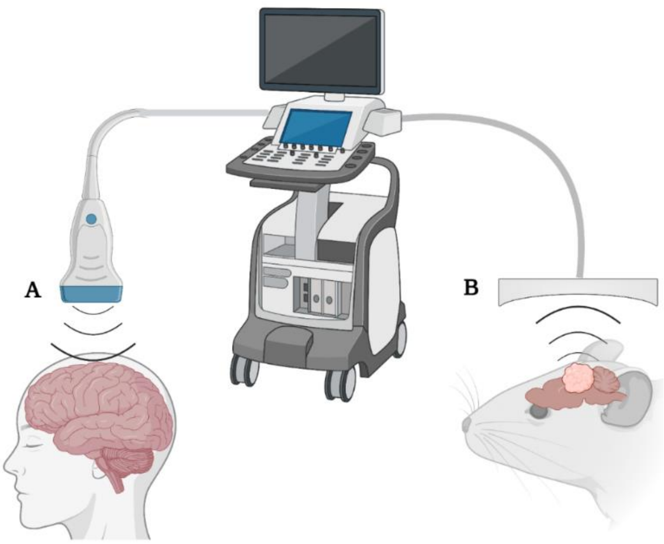

Figure 2 Ultrasound applications in TBI. **(A)** transcranial doppler sonography in humans. **(B)** focused ultrasound adaptations from animal tumor models. Figure created with BioRender.com.

3. Concluding Remarks

Here we rigorously reviewed the current state of neurostimulation with due emphasis on its potential role in treatment of mild-to-severe TBI patients. Recent advances suggest that neurostimulation stands to immensely benefit our understanding and treatment of TBI and related neurological deficit. Notable data points in the field include the following: tLNS evidences unique neuromodulation benefits for stroke victims and widens the traditional therapeutic window; rTMS shows early signs of promise for treatment of diffuse axonal injury; the potential for pharmacologic co-intervention represents a gravely understudied area; alternative (namely non-electrical and non-magnetic) neuromodulation techniques remain promising, suggesting a role for co-administration possibilities. The present review is limited by the scarcity of available literature (at the time of writing) and inconsistent measured outcomes reporting. Still, the authors maintain that the body of evidence shared here provides meaningful insights into stimuli management for complex brain injury. Key advantages to this study are its focus on impactful discoveries in the neurostimulation arena for an understudied neurosurgical patient population, due reflection on prior landmark advancements, and the breadth of the literature search. These all represent salient points to clinicians and researchers alike. Future research should focus on bridging inconsistencies in measured outcomes and correlating realized motor improvements with histological results. Finally, we hope that the present review serves to inspire continued investigation of neurostimulation theory and practice towards the ultimate benefit of the TBI patient population.

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None.

Author Contributions

MJD – Conceptualization, Writing/Editing – Original Manuscript. KTR – Conceptualization, Writing/Editing – Original Manuscript. AB – Conceptualization, Writing/Editing – Original Manuscript. YP – Conceptualization, Writing/Editing – Original Manuscript. BLW – Conceptualization, Project Administration/Supervision.

Competing Interests

The authors have declared that no competing interests exist.

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