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REVIEW

Clinical utility of brain stimulation modalities following traumatic brain injury: current evidence

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Abstract: Traumatic brain injury (TBI) remains the main cause of disability and a major public health problem worldwide. This review focuses on the neurophysiology of TBI, and the rationale and current state of evidence of clinical application of brain stimulation to promote TBI recovery, particularly on consciousness, cognitive function, motor impairments, and psychiatric conditions. We discuss the mechanisms of different brain stimulation techniques including major noninvasive and invasive stimulations. Thus far, most noninvasive brain stimulation interventions have been nontargeted and focused on the chronic phase of recovery after TBI. In the acute stages, there is limited available evidence of the efficacy and safety of brain stimulation to improve functional outcomes. Comparing the studies across different techniques, transcranial direct current stimulation is the intervention that currently has the higher number of properly designed clinical trials, though total number is still small. We recognize the need for larger studies with target neuroplasticity modulation to fully explore the benefits of brain stimulation to effect TBI recovery during different stages of recovery.

Keywords: traumatic brain injury, brain stimulation, neuroplasticity

Introduction

Traumatic brain injury (TBI) is one of the leading causes of disabilities and death of young adults. It is estimated that 1.7 million cases occur each year in the United States, in which nearly 80% are treated and released from an emergency department.[1] Cognitive impairment and neuropsychiatric disorders are the main disabilities,[2–4] followed by motor deficits.[5] To date, there is no optimal pharmaceutical treatment for acute TBI,[6] and brain stimulation techniques appear promising as treatment options to improve neuropsychiatric conditions and motor deficits.[7] Our review presents the underlying neuroplasticity mechanisms and maladaptive plasticity involved in stages of recovery of TBI. It focuses on the primary and secondary injury phases. To better understand the mechanism, rationale, and current clinical evidence of noninvasive and invasive brain stimulation, we will provide a comprehensive review on how stimulation techniques modulate brain activity, promote recovery, and prevent further damage after TBI.

The effect of neuroplasticity on TBI

Considerable evidence has shown that the brain has an extensive ability of reorganization after damage. Better understanding of neuroplasticity mechanisms permits more appropriate selection of neuromodulation techniques for the treatment of TBI. Neuroplasticity is defined as an intrinsic property of the human nervous system and occurs in adaptation to environmental stress, physiological changes, and life experiences.[8] Neuroplasticity plays a role in neural development, homeostasis,[9] and in the dynamic recovery process after injury. In TBI, neuroplasticity can be regarded as

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an adaptation and reorganization to compensate for the initial insult and to attempt to restore function. We will describe the pathophysiological changes and neuroplasticity in the primary and secondary phases of TBI.

The primary injury phase in TBI

Depending on the mechanism of the trauma, the immediate insult to the brain might be focal (subdural, subarachnoid, or epidural hematoma/hemorrhage/contusion), diffuse (widespread disruption of neuronal circuitry/axonal injury), or mixed (diffuse axonal injury with intracerebral hemorrhage). The initial neuronal injury occurs instantly[10] and oftentimes causes irreversible damage to the central nervous system, due to impairment of neuronal cell functions or cell death.[11] Irreversible damage occurs due to the impact of a traumatic event at the origin of acceleration–deceleration shearing, or penetrating injury to the tissues and structures of the brain. Initial shearing of axons and blood vessels can cause intracerebral bleeding, which leads to parenchymal hemorrhage resulting in mass effect[10] to the brain tissue. In diffuse axonal injury[10] there is deformation to complete disruption of the axons. This disruption/deformation causes loss of connectivity between different areas of the brain, and can negatively impact neural regeneration, leading to dysfunctional interactions. Thus, even a relatively local lesion can lead to extensive functional damage of other areas of the brain.[12]

The secondary injury phase in TBI

As a result of an early reduction of cerebral vascular autoregulation and loss of blood–brain barrier integrity, gradual diffuse microvascular damage occurs.[13] This diffuse damage increases the risk of ischemic injury and leads to cellular death.[11] Other changes include release of neurotransmitters, decreased glucose utilization, lactic acid accumulation, reduced activity of adenosine triphosphate (ATP)-reliant ion pumps, increased release of glutamate, Ca^{2+}-induced depolarization, and excitotoxicity. All of these changes may cause anatomical and functional modifications of synaptic transmission.[14] The modulation of the series of actions on a synaptic transmission is an important way to promote brain plasticity.

In the first few weeks after brain injury, brain plasticity and functional recovery involve resolution of edema and inflammation.[15] After this initial period, neuroplasticity and remyelination are the most important alterations occurring within the first 3 months after injury.[15] It is in the acute and subacute stages that there is greatest potential for modification of neural networks, leading to the formation of new anatomical neural connections.[16]

Therefore, the improvement of function after TBI needs to be targeted at different points in time. In the acute phase, inhibition of glutamatergic neural activity may reduce neurologic injury.[17] In the subacute phase, modulation of gamma aminobutyric acid (GABA)ergic suppression may be crucial to minimize the insult and promote recovery. In the chronic phase, modulation of neuroplasticity is desirable to inhibit maladaptive changes and to promote neural network connections. Ultimately, the final outcome in any stage of injury is to maximize functional recovery. A comprehensive review of the neuroplasticity of TBI can be found in Villamar et al.[14] In the following "Methods" section, we will discuss the mechanism, rationale, and current evidence of noninvasive and invasive brain stimulation techniques.

Methods

We searched PubMed (1960–2015), CINAHL (1984–2015), ClinicalKey (2012–2015), EMBASE (1974–2015), and OVID databases (1946–2015). As search term keywords, we used: "Transcranial Magnetic Stimulation (TMS)", "Transcranial Direct Current Stimulation (tDCS)", "Transcranial Low-Level Light/Laser Therapy (LLLT)", "Transcranial Light-Emitting Diode (LED)", "Deep Brain Stimulation (DBS)", "Disorders of Consciousness (DOC)", and "Traumatic Brain Injury (TBI)". Based on our search, 37 clinical studies were included in this review.

Noninvasive brain stimulation

Noninvasive brain stimulation (NIBS) has the ability to modulate neuron firing. It increases synaptic strength, modulates neurotransmitters and excitotoxicity, and modifies neural network connections, and is therefore a promising therapeutic intervention for TBI. The NIBS methods used to modulate brain plasticity discussed in this article include TMS, tDCS, LLLT, and LED.

TMS

TMS is a NIBS instrument that induces electrical currents via Faraday's principle of electromagnetic induction. Since its first clinical use in 1985 by Barker et al[18] the variety of neuropsychiatric conditions being treated by TMS has increased tremendously.[19] The coil placed on the scalp generates a magnetic field that induces a flow of an electric current to neural tissue. This type of stimulation can depolarize/hyperpolarize targeted stimulated areas. For this purpose, there are several protocols of single-pulse and paired-pulse TMS. Thus, TMS may be used as a diagnostic tool to

evaluate the integrity of the corticospinal tract, spinal cord, and peripheral nerves.

If TMS is used repetitively, ongoing changes in neuronal excitability can be facilitated or inhibited. Those effects are dependent on stimulation parameters. Low-frequency repetitive TMS (rTMS; 1 Hz) is known to reduce the neural activity in the direct stimulated cortical areas, while high-frequency (>5 Hz) TMS generally increases the neural activity. Repetitive rTMS can modulate the activity of the functionally connected brain regions, reorganizing the neuronal network after injury.[20] Theta burst stimulation (TBS) – a mode of patterned rTMS – can modulate cortical excitability.[21] This stimulation can be given continuously (cTBS) or intermittently (iTBS). When given continuously, it decreases cortical excitability and given intermittently, it facilitates cortical excitability.

The short effects of TMS on brain activity are partially induced by changes in flow of ionic concentration affecting the synaptic activity in the stimulated area.[14] The modulatory effects of TMS can outlast the duration of its application. The after-effect duration is influenced by the magnitude and frequency of stimulation.[20] Long-term effects are the result of long-term potentiation (LTP)/long-term depression (LTD), which are mechanisms involved in learning. Therefore improvements in cognitive performance are the result of long lasting changes in synaptic strength induced by cumulative effects of consecutive sessions of rTMS. TMS can also mediate release of glutamate or GABA, which may be the reason for its therapeutic effects.[14]

Clinical results

Our review of the literature yielded seven clinical studies in which, five studies[21–25] are case reports, one is an open label study,[26] and one is a cross-sectional survey.[27] None of the studies addressed use of TMS in the acute phase. Details are included in Table 1.

Case reports using TMS addressed neurobehavioral improvements in chronic TBI patients. The aims of these studies were to reduce music hallucinations,[24] promote tinnitus relief,[25] and decrease depression symptoms[22] by using low-frequency rTMS. High-frequency rTMS[23] and cTBS[21] were used to improve consciousness[23,27] and visuospatial neglect,[21] respectively. After the stimulation, the outcomes were reduction of depressive symptoms,[22] visuospatial neglect,[21] and tinnitus.[25] In regards to improvement of consciousness[23] and music hallucinations,[24] there were only short-term effects observed.

The number of treatment sessions in these studies varied from 10 to 30 sessions. Targeted areas involved the dorsolateral prefrontal cortex (DLPFC),[22,23,26] and the temporal[24–26] and posterior parietal cortex.[21] Only two cases used target neuronavigated rTMS.[22,24]

The largest TMS study was an open label study with 15 mild TBI patients; however, only 12 patients completed the protocol.[26] In this study, patients received 20 sessions of high frequency rTMS (10 Hz) at 110% motor threshold over the left DLPFC. The aim of the study was to alleviate post-concussion syndrome (PCS) symptoms, with positive results observed. Reported side effects included headache and sleep disturbances.[26]

These studies showed potential benefits of TMS in improving neural conductivity by means of recruitment of neurons, axons, and/or dendritic circuits. Thus far, studies with TMS have included highly variable parameters of stimulation (frequency, number of sessions, treatment duration) and targeted areas. As a consequence of the variability, it is still unclear which TMS protocol is more effective. An important issue that deserves attention is the safety of the method. In the reviewed studies, the side effects were transient and no seizures were reported. A major limitation of these studies is that they were all case reports or case series without sham rTMS to verify the findings.

tDCS

Current modulation of human brain function was first described over 200 years ago,[28] and the description was further developed in the animal model in the 1950s and 1960s.[29–33] tDCS has been used as a NIBS technique, by means of two comparatively large rubber electrodes (25–35 cm^2) placed on the scalp. This allows a weak current (1 mA–2 mA) to stream from the anode to the cathode. This stimulation is generally applied for 10–20 minutes. Even though the brain scalp absorbs most of the current, the electrical current that reaches the cerebral cortex has sufficient intensity to modify the resting membrane potential and to modulate the activity level of spontaneous excitatory neurons. Therefore, tDCS is regarded as a neuromodulatory NIBS technique.[34]

Short-term effects of tDCS may be induced by non-synaptic mechanisms due to neuronal resting membrane depolarization. Such changes may alter the transmembrane proteins and electrolysis-related hydrogen ions.[35] It has been reported that a 13-minute, single session of tDCS can lead to a 90-minute period of cortical excitability post-stimulation.[36] Consecutive sessions of tDCS can prolong those effects for weeks.[37] Long-term effects may be associated with LTP and LTD mechanisms.[38] Such long-term effects are dependent

Table 1 TMS use in TBI

Author/year	Type of study (n)	TBI type	TMS protocol	Results	Side effects
Louise-Bender Pape et al[23] 2009	Case report (1)	Chronic, severe TBI	300 trains per session (100 μs pulse with 100 ms rest per train), 30 sessions in total; target: right DLPFC	Transient neurobehavioral improvements	No significant adverse effects
Cosentino et al[24] 2010	Case report (1)	Chronic TBI associated with music hallucinations	1 Hz (1,200 stimuli in 20 min) at 90% MT 5 days/week, 2 weeks; target: right temporal cortex (navigated rTMS)	Significant reduction of auditory hallucinations	N/A
Bonnì et al[21] 2013	Case report (1)	Chronic, severe TBI	Three-pulse burst at 50 Hz repeated every 200 ms for 40 s at 80% MT for 2 weeks; target: left posterior parietal cortex	Marked cognitive improvement	Without any adverse effects
Kreuzer et al[25] 2013	Case report (1)	Severe tinnitus after TBI	1 Hz with 2,000 stimuli each at 110% MT in ten sessions; target: left primary auditory cortex	Improvement of patient's symptoms	N/A
Pistoia et al[27] 2013	Cross-sectional survey (6)	Brain-injured with vegetative state	Ten trains of pulses, with each train including 15 stimulations, total number of TMS for each was 150 TMS (3 consecutive days); target: cortical motor hand area (contralateral to the dominant hand)	Long-term, with higher CRS-R scores and improved autonomy in daily life activities in patients 1, 3, and 4	N/A
Nielson et al[22] 2015	Case report (1)	Chronic, severe TBI	1 Hz at 110% of MT 5, sessions weekly for 6 weeks (30 sessions); target: right DLPFC (navigated rTMS)	Improvement of depression, anhedonia, and global function	No significant adverse effects
Koski et al[26] 2015	Open label (15)	Chronic, mild TBI with PCS	20×5-second trains of 10 Hz stimulation at 110% MT with an intertrain interval of 25 s (20 sessions); target: left DLPFC	Reduction in PCS symptoms' severity	12/15 patients completed all sessions; headache (3/12), vertigo (1/12), sleep disorders (3/12); no seizures reported

Abbreviations: DLPFC, dorsolateral prefrontal cortex; PCS, post-concussion syndrome; TBI, traumatic brain injury; TMS, transcranial magnetic stimulation; rTMS, repetitive transcranial magnetic stimulation; N/A, not applicable; min, minutes; s, seconds; CRS-R, Coma Recovery Scale – Revised; MT, motor threshold.

on modulation of N-Methyl-D-aspartate (NMDA) receptor activation, as well as neuronal hyperpolarization and depolarization. Previous studies[35–37] showed that anodal tDCS increases the excitability of the cerebral cortex, and that cathodal stimulation decreases it. On a behavioral level, anodal tDCS may improve motor task performance, language, and memory. In contrast, cathodal tDCS may also increase performance by decreasing over-activation in an area of maladaptive plasticity.

Clinical results

Due to steady maturation of the technology, relatively low cost, and the ease of use there is increased interest in the potential application of tDCS for treatment of TBI. Our literature review yielded no clinical research on tDCS during the acute phase of TBI. Table 2 details seven tDCS studies.[39–45] Six clinical studies were found in the chronic phase of TBI, and there was only one study[39] in the subacute phase. In contrast to TMS studies, most tDCS studies were randomized controlled trials or crossover studies. Outcome measures in most of the studies were changes in consciousness and cognitive performance.[40–44] The first pilot study was designed to assess whether anodal tDCS applied to left DLPFC could improve attention in patients with chronic TBI compared to sham stimulation.[40] Nine patients received anodal tDCS (2 mA for 20 minutes) or sham stimulation (2 mA for 1 minute), in a double-blind, crossover manner with intervals of at least 48 hours.[40] It was found that anodal tDCS applied to left DLPFC can significantly shorten reaction times when compared to sham. Two randomized controlled trials have explored whether successive applications of anodal tDCS (15 or 10 sessions of 1 mA for 10 minutes) placed over the left DLPFC would promote changes in attention control and memory track formation in severe TBI.[39,41] Those trials revealed no significant improvement in cognitive outcome measures.[39,41] However, in one study there were changes in electroencephalography (EEG) recordings associated with an LTP-like mechanism in neural networks, and this method was more likely to be sensitive enough to detect cortical changes than attention/working memory performance.[41] One double-blind sham-controlled crossover study provided Class II evidence that short-duration tDCS over the left DLPF cortex transiently improves consciousness as measured by Coma Recovery Scale – Revised (CRS-R) assessment in patients with minimally conscious state (MCS).[43]

The variance of results of all trials is likely to be related to the differences on number of sessions and timing of application during TBI recovery (chronic vs subacute). In conclusion, the potential application of tDCS as a neuromodulatory tool for blocking or suppressing maladaptive plasticity is still unknown.

In regards to motor function recovery after TBI, we found one study that included chronic TBI participants among stroke patients. All patients received bihemispheric tDCS over M1 paired with standard upper extremity physical therapy (24 sessions of 40 minutes, three times per week). They monitored lasting motor function improvement[45] and reported positive results 6 months after tDCS stimulation.

LLLT and transcranial light-emitting diode

LLLT is a NIBS technique used to stimulate biological reactions[46] typically used in the recovery of neuropsychiatric conditions.[47,48] LLLT uses low-powered laser light at wavelengths from 632–1,064 nm, ranging from 1–1,000 mW. In acute phase after TBI, a decrease in energy transduction and ATP levels occur due to excessive calcium in the mitochondria within nerve cells impairing the oxidative phosphorylation process. The mechanisms involved in LLLT include the modulation of neurobiological function by improving mitochondrial function, promoting increased ATP and release of nitric oxide locally. This process enhances regional cerebral blood flow and brain oxygen, thereby augmenting metabolic capacity.[49,50] Light-modulated cell adhesion and proliferation can be increased or decreased depending on wavelengths used and radiation dose.[51] Recently, light-emitting diodes (LEDs) have been used as an alternative light source for LLLT.[51,52]

Rojas et al[53] were the first to record LLLT transcranial tissue response in vivo. They observed brain metabolic and antioxidant beneficial effects measured by increases in cytochrome oxidase expression in neuronal cultures. LLLT-induced up-regulation of cytochrome oxidase in the cortex plays a key role in neuronal physiology, serving as an interface between oxidative energy metabolism and cell survival signaling pathways.[54,55] In addition, LLLT partially restores enzyme activity obstructed by potassium cyanide – a cytochrome oxidase inhibitor – reducing neuronal cell death caused by this mitochondrial toxin.[52] This enzymatic restoration improves cellular activity of brain tissue that has been damaged by TBI.[45] Thereby, transcranial LLLT may become a novel therapy to enhance cognitive performance; emotional functions; and neurological conditions[47,56] linked to mitochondrial dysfunction,[47] a ubiquitous finding in brain injury due to TBI.

Table 2 tDCS use in TBI

Author/year	Type of study (n)	TBI type (n)	tDCS protocol (n)	Results	Side effects
Kang et al[40] 2012	Double-blind, cross-over design (9)	Chronic closed TBI with attention deficit	20 min anodal tDCS (2 mA), one session anodal: left DLPFC	A tendency of shortened reaction time relative to baseline	N/A
Lésniak et al[41] 2014	Randomized controlled trial (23)	Chronic, severe TBI	10 min anodal tDCS (1 mA), 15 sessions anodal: left DLPFC	No significant difference in cognitive outcome measures	No significant adverse effects; one patient dropped out due to stimulation-induced subjective symptoms
Angelakis et al[42] 2014	Case series (10)	Chronic, severe TBI, UWS, or MCS	Stimulation included 3 consecutive weeks of (1) sham tDCS; (2) anodal tDCS (1 mA); (3) anodal tDCS (2 mA); 20 min per session, total 15 sessions; anodal: left DLPFC or left M1	Immediate clinical improvement in four patients	N/A
Ulam et al[39] 2015	Randomized controlled trial (26)	Subacute TBI	20 min anodal tDCS (1 mA); ten sessions; anodal: left DLPFC	Decrease in delta correlated to improvement in neuropsychological tests in tDCS group	No significant adverse effects
Middleton et al[45] 2014	Open label (8)	Chronic, severe TBI or stroke	Bihemispheric tDCS (1.5 mA for 15 min), 24 sessions; bihemispheric tDCS: C3 and C4	Improvement of motor function	No significant adverse effects; five out of eight patients completed the study, three patients dropped out for unrelated reasons
Thibaut et al[43] 2014	Double-blind sham-controlled crossover study (30)	Severe traumatic (19) and nontraumatic (11) in MCS; traumatic (6) and nontraumatic (19) in VS/UWS	Left DLPFC (2 mA, 20 min); shams were tested in random order in two separate sessions separated by 48 hours	Transiently improved consciousness as measured by CRS-R assessment in patients with MCS	No tDCS-related side effects were observed
Naro et al[44] 2015	Crossover study (25)	Severe disorders of consciousness	Anodal tDCS over the orbitofrontal cortex (OFC) for one session; sham tDCS in a separate session 1 week apart	OFC-active tDCS, increased M1 excitability, and modulated premotor–motor connectivity up to 60 min in HC and in some DOC patients	No significant adverse effects

Abbreviations: tDCS, transcranial direct current stimulation; TBI, traumatic brain injury; DLPFC, dorsolateral prefrontal cortex; N/A, not applicable; UWS, unresponsive wakefulness syndrome; MCS, minimally conscious state; VS, vegetative state; min, minutes; DOC, disorders of consciousness; CRS-R, Coma Recovery Scale – Revised; HC, healthy control; n, number of patients.

Animal studies showed benefits in laser phototherapy in damaged TBI cerebral tissue. Those benefits were smaller lesions,[57–59] improved motor behavior performance,[60] increased neurogenesis,[56] and changes in biochemical levels.[61]

Clinical results

To the best of our knowledge, there are only three clinical studies[48,51,62] published using light therapy (LLLT and LED) in patients with TBI. Table 3 details the manuscripts that evaluated those clinical findings. They were either case reports or open label studies. Nawashiro et al[62] studied bilateral transcranial LED irradiation in a patient with persistent vegetative state (VS) following severe TBI. They applied the technique to the forehead of the patient to quantify changes in cerebral blood flow. Single-photon emission computerized tomography (SPECT) analysis showed unilateral increase in cerebral blood flow after 30 minutes of LED therapy applied twice a day. Stimulation on left DLPFC was felt to be responsible for improved akinesia in this patient. Naeser et al[51] described two cases of chronic mild TBI. The first case was a patient with chronic attentional problems after 7 years of injury. After 8 weeks of LED treatment applications, there was an improvement of attention. This improvement was observed to gradually decline with interruption of treatment for 2 weeks. The second case was a patient treated after multiple concussions who stopped working due to cognitive dysfunction. After 4 months of LED treatment, the patient reportedly returned to full-time work.

Naeser et al[48] examined the effect of two identical LED console units placed over the frontal, parietal, and temporal areas in eleven chronic mild traumatic brain injury patients in an open-protocol study. Their study suggested a reduction in post-traumatic stress symptoms and an improvement in working memory and executive functions after treatment application. Those improvements were still reported at 2-month follow-up.

DBS for TBI

In contrast to noninvasive methods, deep brain stimulation (DBS) is a neurosurgical technique that consists of electrical stimulation through electrodes surgically implanted to subcortical areas. In some neurological conditions, DBS is one of the main procedures in functional neurosurgery.[63,64] In patients refractory to drug treatment, DBS is the gold standard for the treatment of motor symptoms of Parkinson's disease.[64,65] This surgery involves the implantation of electrodes through electrical conductors in the basal ganglia in both hemispheres.[64,65] The areas usually targeted are the thalamus, subthalamic nuclei, and the globus pallidus. Those areas are subjected to electrical signals that stimulate or inhibit neuronal activity on these nuclei and associated circuitry.[65–67] The electrodes uses high-frequency stimulation of 70–185 Hz and amplitudes of 0.75–4 V.[66–70] This technique has greater potential for serious complications and psychiatric and cognitive side effects due to the current spread into brain structures surrounding the electrode. Accordingly to Wolz et al[71] the side effects may be due to electrode malposition.

Therefore, in patients with TBI,[72,73] clinical application of DBS has been less investigated. This technique has been approved by the US Food and Drug Administration (FDA) for the treatment of disabling symptoms of essential tremor and advanced Parkinson's disease, and is also approved for dystonia and obsessive compulsive disorder.[71] In Europe, in addition to these indications, it is used in epilepsy.[72] Research has indicated potential positive outcomes for chronic pain,

Table 3 LLLT/LED use in TBI

Author/year	Type of study (n)	TBI type	LLLT and LED protocol	Results	Side effects
Naeser et al[51] 2011	Case report (2)	Chronic mild TBI	12–15 mW per diode, total power 500 mW; bilateral and middle sagittal areas using LED cluster heads	Transient cognitive and neurobehavioral improvement	No negative side effects
Nawashiro et al[62] 2012	Case report (1)	Chronic severe TBI in persistent vegetative state	L-light, 23 diodes; peak wavelength, 850 nm; total power, 299 mW; L-light on the left and right forehead areas	Improved neurological condition and cerebral blood flow	N/A
Naeser et al[48] 2014	Open label (11)	Chronic mild TBI	LED cluster head (500 mW, 22.2 mW/cm^2 for 10 min) midline from front-to-back hairline; and bilaterally on frontal, parietal, and temporal areas	Transient cognitive and neurobehavioral improvement	N/A

Note: L-light (SUN-MECHATRONICS, Tokyo, Japan).
Abbreviations: TBI, traumatic brain injury; LED, light-emitting diode; N/A, not applicable; LLLT, low-level light/laser therapy; min, minutes.

affective disorders, and a small cohort of patients in minimum state of consciousness.[73]

Despite application for symptomatic post-traumatic diseases such as tremor,[73–76] Parkinsonism,[77] and hemidystonia,[68] there is expectation that the use of DBS might be also beneficial to improve cognitive and consciousness deficits in TBI patients.[73–77]

Clinical results

We found 20 studies[68–70,75,77–92] testing DBS in chronic TBI patients. Table 4 details those studies. There were 13 case reports,[68–70,75,78–80,85–87,89,91,92] two case series,[77,81] and five open label studies.[82–84,88,90] Tsubokawa et al[81] reported significant improvements in a series of eight patients, but the intervention was performed early, within less than a year after TBI. Yamamoto et al[82–84,88,90] studied series reports of VS and MCS[90] caused by various kinds of brain damage. One of these studies[82] described that eight of the 21 patients emerged from the VS and became able to obey verbal commands. The criticism of this study arises from the inclusion of patients 4–8 months following injury during a period of spontaneous recovery. Clinical improvements observed in these studies were based on small series or case reports. There are many variables in which functional and biological aspects warrant further investigation. The precise targets in patients with important anatomical injuries need to be defined before DBS can take a therapeutic role in clinical practice in patients with TBI.

Some studies were related to improvement of movement disorders,[68–70,75,77,79,89,91,92] pain,[70,86] and self-mutilation.[87] The main targets of those studies were the internal globus pallidus and the ventralis intermedius nucleus. The target for self-mutilation symptoms was the posterior hypothalamus. Some studies reported delayed complications, particularly infarction and infection.[68,77,78] Animal studies showed that vagus nerve stimulation, another type of invasive stimulation,[93] could improve the prognosis of TBI. Since this technology has not been used in clinical studies, it was not included in this review.

Discussion

We discuss our findings in four separate sections: 1) the "Brain stimulation and biomarkers" section; 2) the "Clinical outcomes and recovery" section; 3) the "Comparison of techniques: which one is better for TBI?" section; and 4) the "Safety" section.

Brain stimulation and biomarkers

There are specific types of biomarkers that assist with finding a prognosis, response to treatment, and extent of TBI. Although their utility is clear, there are limited data regarding their reliability as a clinical tool and what the optimal biomarker is in TBI. We discuss a few biomarkers that are currently being tested.

Commonly tested biomarkers are either proteomic, genetic, or observed changes in brain metabolism.[94] Changes in motor-evoked potential via single or paired pulse stimulation and effects of rTMS measured by changes in metabolic activity or cerebral oxygen levels using neuroimaging techniques[95] can be considered neurophysiologic biomarkers.

EEG is another potential biomarker. It provides variation in brain activity during stimulation via tDCS or rTMS. There is a suggestion that changes on EEG frequencies, particularly decrease in delta and increase in alpha, can be a biological marker for response of anodal tDCS reflecting increased cortical activity.[39]

The technique that has been more studied with biomarkers in TBI is DBS. Unlike NIBS techniques, DBS enables more precise access to target structures. It uses electrophysiological effects on feedback control as a biomarker to establish the timing and intensity of stimulation. In addition to changes in brain signals, functional magnetic resonance imaging (fMRI) has also been used to assess cerebral activity related to post-traumatic Parkinsonism symptoms.[96]

In summary, EEG and neuroimaging are reliable methods to reflect the effects of brain stimulation and could be suitable biomarkers. These markers indicate correlations between structural lesions, metabolic dysfunction, and cortical activity.

Clinical outcomes and recovery

Numerous studies have implied a relationship between clinical severity measures (eg, the Glasgow Coma Scale [GCS] and duration of post-traumatic amnesia [PTA]) and various types of functional outcome measures at different times after brain injury.[97] All protocols in this review addressed the subacute or chronic phase of recovery and used different outcome measures, varying from clinical to functional scores.

While neuroimaging as an assessment tool can provide insights into potential relationships between the GCS, PTA, cognitive function, and outcome after TBI,[98] it does increase cost. Only four TMS studies assessed functional recovery assisted with neuroimaging technologies, such as positron emission tomography (PET) and resting fMRI.[21,22,24,26] The clinical endpoints in those studies were related to clinical neurobehavioral improvements and also other clinical outcomes, such as transitory reduction of music hallucinations.

Table 4 DBS use in TBI

Author/year	Type of study (n)	TBI type	DBS protocol	Results	Side effects
Hassler et al[78] 1969	Case reports (3)	Chronic TBI MCS	Target: right lamella pallidi interna and the left lateral polar nucleus of the thalamus	Improvement of consciousness	Two patients died from unspecified infection a few months later
Tsubokawa et al[81] 1990	Case series (8)	Chronic TBI PVS	Target: mesencephalic reticular formation and/or nonspecific thalamic nucleus	Three patients were able to communicate	No complications
Sellal et al[79] 1993	Case report (1)	Chronic TBI	Target: left ventroposterolateral nucleus of the thalamus	Improvement in the dystonic postures and movement of the upper right limb	No complications
Loher et al[70] 2000	Case report (1)	Chronic TBI	Target: globus pallidus internus	Improvement of pain and hemidystonia	No complications
Yamamoto et al[83] 2002	Open label (20)	Chronic VS (8/20)*	Mesencephalic reticular formation (two cases) and centromedian-parafascicular nucleus CM-pf complex (18 cases)	7/20 patients emerged from the VS, and became able to obey verbal commands; however, they remained in a bedridden state	No complications
Yamamoto et al[84] 2003	Open label (21)	Chronic VS (9/21)*	Mesencephalic reticular formation (two cases) and CM-pf complex (19 cases)	8/21 patients emerged from the VS, and became able to obey verbal commands	No complications
Yamamoto and Katayama[82] 2005	Open label (26)	Chronic VS (9/21)* and MCS (3/5)*	Target: thalamic CM-pf complex 19/21# (VS) and 5/5# (MCS); mesencephalic reticular formation 2/21# (VS)	8/21 patients emerged from the VS, and became able to obey verbal commands; however, they remained in a bedridden state except for one case. 4/5 MCS patients emerged from the bedridden state, and were able to enjoy their lives in their own homes	No complications
Capelle et al[85] 2006	Case report (1)	Chronic TBI – painful tonic dystonia	Target: thalamic nucleus ventralis lateralis posterior and the posteroventral lateral globus pallidus internus on the right side	There were no changes in the patient's condition during a 10-month follow-up period	No complications
Foote et al[75] 2006	Case reports (4)	Chronic TBI (3) post-traumatic tremor and multiple sclerosis tremor (1)	Target: two DBS leads (one at the VIM/VOP border and one at the VOA/VOP border)	The effects of the DBS were cumulative over time; significant and sustained collision or microthalamotomy effect from implantation of two electrodes; significant placebo effect	No complications
Son et al[86] 2006	Case report (1)	Chronis TBI and previous persistent chronic pain	Target: subdurally along the mediolateral somatotopy of the precentral gyrus and epidurally, parallel to the course of the superior sagital sinus	Mild improvement in burning pain and heaviness, and deep pressure relief after 12 months	Not reported

(*Continued*)

Table 4 (*Continued*)

Author/year	Type of study (n)	TBI type	DBS protocol	Results	Side effects
Schiff et al[80] 2007	Case report (1)	Chronic severe TBI and MCS	Target: bilateral DBS, central thalamus	Improved in Coma Recovery Scale, Revised	No complications
Kuhn et al[87] 2008	Case report (1)	Chronic TBI	Target: posterior hypothalamus	Elimination of self-mutilation during 4 months observation	No complications
Yamamoto et al[88] 2010	Open label design	Chronic VS (9/21)* received DBS, and VS (18/86)* without DBS	Target: MRF (two patients) and CM-pf complex (19 patients)	Better recovery rate to DBS group compared to non-DBS group	Not referred
Reese et al[89] 2011	Case report (1)	Chronic severe TBI	Target: VIM and subthalamic nuclei	Decrease of kinetic tremor and akinetic–rigid symptoms	No adverse effect during 3 years; infection of the stimulation system and worsening of Parkinsonian symptoms after explanted for 5 years
Giacino et al[92] 2012	Case report (1) from a case series protocol	Chronic TBI MCS	Target: central thalamus	Increase in functional communication, motor performance, feeding, and object naming	No complications
Kim et al[68] 2012	Case reports (4)	Chronic severe TBI	Target: unilateral internal globus pallidus	Improvement in Burke–Fahn–Marsden Dystonia Rating Scale movement scores and quality of life (SF-36)	Two patients had post-encephalic hemidystonia involving the putamen, and one patient had posterolateral putamen and globus pallidus infarction
Issar et al[77] 2013	Case series (5)	Chronic severe TBI	Target: ventral intermediate nucleus and bilateral DBS of the globus pallidus internus	Reduction of tremor	Delayed complications included decreased tremor control and increased impedance in 3/5 patients, requiring replacement of wires in 2/5 patients
Yamamoto et al[90] 2013	Open label	Chronic VS (9/21)* and MCS (3/5)* in DBS and MCS (6/10)* in SCS	Target in DBS: MRF and CM-pf complex	Increased recovery in VS and MCS patients when the candidates were selected on the basis of the electrophysiological inclusion criteria	
Carvalho et al[69] 2014	Case report (1)	Chronic severe TBI	Target: right internal globus pallidus	Improvement on tremor and clinical effect	No complications
Follett et al[91] 2014	Case report (1)	Chronic severe TBI	Target: bilateral VIM; first on the left side, and 6 months after the implantation, on the right side	Reduction of tremors in both arms, improvement in voice tremor; mild leg tremor and facial dystonia did not improve	No complications

Notes: *TBI patients/total patients: TBI, cerebrovascular accident, and anoxia. #cases per total cases.

Abbreviations: DBS, deep brain stimulation; TBI, traumatic brain injury; MCS, minimally conscious state; VS, vegetative state; VIM, ventralis intermedius nucleus; VOP, ventralis oralis posterior nucleus; VOA, ventralis oralis anterior; CM-pf, centromedian–parafascicular nucleus; MRF, mesencephalic reticular formation; SF-36, health-related quality of life 36-item short-form; SCS, spinal cord stimulation; PVS, persistent vegetative state.

tDCS studies measured cognitive function using computerized contrast reaction time task[39] and attention/working memory task.[41] They used the JFK Coma Recovery Scale Revised to assess consciousness in persistent VS or MCS[41] and monitored improvement of motor function using functional independence measures as a primary outcome.[45] Three LLLT/LED studies[48,51,62] addressed improvement of cognition after TBI, but only one study included detailed psychological measurements using the Posttraumatic Stress Disorder Checklist – Civilian; the Beck Depression Inventory – II; and the Visual Analog Scale for pain.

The primary outcomes of DBS studies[23] were level of consciousness and changes in JFK Coma Recovery Scale. The secondary outcomes included neurophysiological evaluation, EEG, and auditory brainstem response. Further studies using comparable and standardized clinical and functional outcomes are warranted to investigate benefits of each brain stimulation technique for different post-traumatic conditions. In fact, some studies, especially those using NIBS, used surrogate cognitive outcomes, such as reaction time in neurophysiological tests, thus making it difficult to determine the clinical utility of these techniques. Given that functional outcomes are associated with more variability and less power, future studies need to test functional outcomes in large sample size studies.

Comparison of techniques: which one is better for TBI?

One important question is which technique is most beneficial for the treatment of TBI. Although data to date do not give enough information to respond this question, a few topics can be explored when comparing techniques: 1) efficacy of these techniques when comparing them; 2) differences of the techniques that may be advantageous for TBI treatment; and 3) safety. There is not enough evidence on efficacy to recommend for or against any of these techniques. Most of the studies are open label or case reports, and the few randomized controlled trials are small and/or used surrogate outcomes. Although the most remarkable clinical improvements have been shown with DBS, comparison is difficult as DBS uses longer protocols of stimulation that may be associated with larger clinical and placebo effects. Therefore, two steps are necessary to determine efficacy of these techniques: 1) development of appropriately designed placebo randomized clinical trials with large sample sizes; and 2) development of randomized clinical trials comparing these techniques.

In terms of differences between the techniques, one point for discussion is the focality. tDCS and LLLT are both nonfocal interventions, while rTMS and DBS are more focal interventions. It is unclear whether the nonfocality of tDCS and LLLT are associated with less effect. It may be argued that less focality in TBI may be beneficial to promote neuroplasticity in a wider area, or that focalization may be achieved when combined with behavioral interventions.

Regarding targeting, for the more focal techniques, there is also the question of what target is most optimal. NIBS methods may be applied over several brain areas involved in neuroplasticity processes. How the target is determined plays an important role during the stimulation. Some studies have stimulated the DLPFC region in order to improve neurobehavioral function, PCS, and depression.[22,23,26] With the development of functional imaging techniques, there are more options to achieve this goal. Reviewed rTMS studies applied navigational stimulation before and after the stimulation to achieve the specific target[22,24] using MRI and PET scan. This enabled visualization of the lesion and assessment of response to cortical excitability or connectivity of brain network.[21,22,24]

DBS alters activity patterns to moderate abnormal brain function related to a specific target. Successful stimulation of the ventralis intermedius nucleus of the thalamus, reduced post-traumatic tremors,[98] and DBS targeting the subgenual cingulate cortex were used for the treatment of refractory post-traumatic depression.[99–101] In this context, development of this field will come with best definition of specific targets for specific behaviors.

The use of neurostimulation strategies and their potential role in recovery of TBI needs to be further developed. Different techniques may be optimized when used in combination, depending on the stage of the recovery and the specific needs of the individual.[73] In addition, the use of closed loop systems that can in real time change parameters of stimulation according to the neurophysiological response, may optimize the response to brain stimulation. Finally, the combination of chemical stimulation with drugs and brain stimulation may also result in better clinical outcomes.[102]

Safety

Considering that TBI is characterized by a chronic hyperexcitability state that increases seizure risk, NIBS, especially rTMS, is regarded as a relative contraindication. In the case where there is a remarkable clinical need, the benefits may outweigh the risks of rTMS, especially when these risks can be minimized. A potential venue to reduce risk would be the use of navigated brain stimulation to ensure safely delivered stimulation to the target area, thereby reducing any

adverse effects. In addition, studies[103,104] with low-frequency stimulation have reported antiepileptic effects. The current evidence for application of NIBS recommends exclusion of subjects with a history of seizure, subjects taking medications that lower seizure threshold, or those who have metal implants or brain tumors. DBS, on the other hand, is a controversial modality due to its invasive nature. So far, this stimulation is only used on VS or MCS to regulate arousal. The guidelines of safety for each brain stimulation modality used in TBI needs to be further developed.

Conclusion

This review addresses the clinical utility of brain stimulation modalities to reduce disability and enhance recovery after TBI. Neurostimulation may be applied to a great number of debilitating neurological conditions associated with TBI. For this purpose, brain stimulation techniques may play an important role in inducing neuroplasticity and suppressing pathological disinhibition of circuits implicated in maladaptive networks. Improvements of altered state of consciousness, cognition, and psychiatric and motor function have been the main goals of these therapeutic strategies. Although the mechanisms of neuroplasticity induced by those methods are not fully understood, these instruments have shown great potential for clinical application, significantly changing the current rehabilitation protocols of patients with neurological sequelae post-TBI.

Disclosure

The authors report no conflicts of interest in this work.

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