Neurostimulation for traumatic brain injury

A review

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Traumatic brain injury (TBI) remains a significant public health problem and is a leading cause of death and disability in many countries. Durable treatments for neurological function deficits following TBI have been elusive, as there are currently no FDA-approved therapeutic modalities for mitigating the consequences of TBI. Neurostimulation strategies using various forms of electrical stimulation have recently been applied to treat functional deficits in animal models and clinical stroke trials. The results from these studies suggest that neurostimulation may augment improvements in both motor and cognitive deficits after brain injury. Several studies have taken this approach in animal models of TBI, showing both behavioral enhancement and biological evidence of recovery. There have been only a few studies using deep brain stimulation (DBS) in human TBI patients, and future studies are warranted to validate the feasibility of this technique in the clinical treatment of TBI. In this review, the authors summarize insights from studies employing neurostimulation techniques in the setting of brain injury. Moreover, they relate these findings to the future prospect of using DBS to ameliorate motor and cognitive deficits following TBI.

(key words • traumatic brain injury • neuromodulation • neurostimulation • deep brain stimulation • transcranial magnetic stimulation • direct cortical stimulation

There are multiple therapy modalities for attenuating neurological disabilities in traumatic brain injury (TBI) patients, including occupational, physical, and cognitive rehabilitation, but there is a critical need for more effective therapies, especially pharmacological or surgical treatments. The pathophysiology of TBI is complex and includes inflammation, oxidative stress, apoptosis, excitotoxicity, and mitochondrial dysfunction. After almost a century of translational science, there has yet to be a successful Phase III clinical trial investigating a pharmacological intervention for TBI. Recent advances in our understanding of brain circuitry and technical advances in neurostimulation technologies have created enthusiasm for the potential of electrical stimulation of the nervous system to promote functional recovery in patients with acquired brain disorders.

There is burgeoning interest in the development of implanted brain stimulation devices to treat patients suffering from the motor and cognitive consequences of TBI. For instance, the Defense Advanced Research Projects Agency (DARPA) recently announced a funding opportunity with the intent of developing “a prototype implantable neural device that enables recovery of memory in a human clinical population” (Restoring Activity Memory, DARPA-BAA-14-08; https://www.fbo.gov/index?s=opportunity&mode=form&id=55e9fb2eb571bfa462cb165b97264837&tab=core&cview=1). While bold, this path would leapfrog other potential comorbidities of TBI that may be better suited for neuromodulation in the near future. We aimed to clarify the opportunities in this nascent field by reviewing relevant experimental literature, including stroke studies that may offer important lessons. In general, electrical treatment strategies include both noninvasive methods, where an electrical stimulus is provided transcranially, and the direct application of electrical current to the cerebrum, either on the cortical surface via subdural electrodes or to subcortical targets via deep brain stimulation (DBS). Preliminary studies employing neurostimulation in the setting of brain injury have indicated

Abbreviations used in this paper: ANT = anterior nucleus of the thalamus; cAMP = cyclic adenosine monophosphate; DARPA = Defense Advanced Research Projects Agency; DBS = deep brain stimulation; DLPFC = dorsolateral prefrontal cortex; GPi = globus pallidus internus; MCS = minimally conscious state; PD = Parkinson’s disease; SCC = subgenual cingulate cortex; TBI = traumatic brain injury; tDCS = transcranial direct-current stimulation; TMS = transcranial magnetic stimulation; TRD = treatment-resistant depression; VIM = ventralis intermedius; VOA = ventralis oralis anterior; VOP = ventralis oralis posterior.
functional improvements in motor tasks, as well as cognitive improvements in memory, arousal, and language. In addition, molecular and functional imaging studies have proposed various mechanisms to explain these benefits. This review will compare and contrast different neurostimulation studies to provide a framework for the future development of neurosurgical stimulation therapies to treat acquired brain injury.

Brain Stimulation for Recovery of Motor Function

Noninvasive Stimulation for Motor Deficits

Two noninvasive techniques to deliver electrical stimulation in various brain regions are transcranial magnetic stimulation (TMS) and transcranial direct-current stimulation (tDCS), both of which have been used in stroke patients. In TMS, an electrical current is conducted in a coil overlying the scalp, which creates a magnetic field that passes through the skull.70 Electrical current is formed secondarily to this field in a target area, causing neuronal depolarization. In contrast, tDCS works by influencing the resting membrane potential of neurons to modulate their spontaneous firing rates.128 Two or more electrodes are placed over the scalp, and a weak direct current flows through the skull into the cortex. The current enters the brain through an anode, exits by a cathode, and depolarizes or hyperpolarizes neurons in the targeted region depending on the polarity.

The use of noninvasive electrical stimuli has been studied in stroke patients with various degrees of success, but there are few reported studies in patients with TBI. It has been proposed that the variance in cortical response to different parameters of TMS can be used to modulate the excitability of injured brain regions and to fine-tune motor function enhancement.45 Bursts of high-frequency stimulation can facilitate activity in a target region, whereas long-duration, low-frequency stimulation can suppress activity.8 Following stroke, patients undergo cortical reorganization over a period of 1–6 months.38 The unaffected hemisphere may become hyperexcitable (increased motor evoked potential amplitude at a given test stimulus intensity), possibly due to lack of inhibition from the damaged hemisphere.7,118 In injury settings, low-frequency TMS has been applied to decrease hyperexcitability in the contralesional motor cortex,44,91 and high-frequency TMS has been applied to increase the excitability of ipsilesional motor cortex or dorsolateral prefrontal cortex (DLPFC).84 Using these different responses to changing frequencies, TMS near the time of motor training of the affected hand after stroke was determined to enhance hand function.96,141 Also, combining intermittent and continuous stimuli using the theta burst stimulation TMS protocol significantly increased injured motor cortex excitability as measured by motor evoked potentials.33

The interaction between the injured and uninjured hemispheres is more complex. Inhibition of the intact hemisphere by the lesioned hemisphere was found to not be decreased in stroke patients compared with controls in one study.11 Increased inhibition of the lesioned hemisphere by the intact hemisphere was proposed in one study as an alternative mechanism to limit motor recovery,107 while a different study suggested that stroke patients with severe motor deficit may have hyperactivity of local inhibitory interneurons in the lesioned hemisphere.27 Although TMS has been effective in improving motor function in some studies,86,91,141 others have shown no benefit90 or only modest improvements in motor function.5,25 Interestingly, patients with subcortical injury have shown improvements in movement kinematics, whereas patients with cortical injury had no improvement in the same study.5 Despite promising results in early TMS studies, the mechanisms by which such improvements occur are not clear, and motor cortex stimulation may provide only mild beneficial effects in certain settings.

There is some evidence that tDCS can increase motor cortex excitability in stroke patients with hemiparesis.147 tDCS, similar to TMS, can produce either inhibitory or facilitatory effects on the motor cortices depending on the electrode polarity. Cathodal tDCS is thought to have an inhibitory effect through neuronal hyperpolarization, and anodal tDCS exerts an excitatory effect on cortical activity by depolarizing neurons. The use of cathodal and anodal tDCS in dominant and nondominant motor cortices, respectively, has been shown to enhance motor performance of the nondominant hand, presumably by modulating inhibitory projections between the two hemispheres.152

Cortical Stimulation

Unlike noninvasive neuromodulation techniques, direct stimulation of the cortex after surgical exposure enables more specific access to the target structures and may allow more precise stimulation of cortical areas. Direct cortical stimulation can induce plasticity in somatosensory areas of macaque monkeys, and cortical stimulation enhances functional recovery and cortical plasticity in the setting of neural injury, such as stroke in squirrel monkeys.69,119,144,162 Stimulation during rehabilitation following motor cortex injury improves motor function in both rats and primates.190,191 In animal experiments using intracortical microstimulation, cortical surface electrodes stimulating the motor cortex at subthreshold levels during rehabilitation after focal motor cortex ischemia can increase forelimb function.99,119 This functional improvement following motor cortex infarction is induced by restoration of movement representation in peri-infarct areas, as well as the emergence of novel representations. Areas of movement representation shifted several microns after repeated stimuli122 and increased in size102 when rats received intracortical microstimulation in the forelimb area of the motor cortex. Histological examination revealed an increase in spine density in pyramidal cell layers III and V.

Similarly, cortical electrical stimulus parameters that improved motor performance in rats following focal ischemic injury to the motor cortex were also associated with increased dendritic processes in perilesional areas.1 The improvement in motor function following electrical stimulation correlated with increased markers of dendritic plasticity and decreased markers of astrogliosis by immunohistochemistry in both the perilesional cortex and the contralesional anterior horn of the cervical spinal cord.163 Thus, cortical electrical stimulation may lead to
motor function improvements due to increased neuronal structural plasticity. Likewise, direct cortical stimulation has also been used to drive plasticity in rodents subjected to a lesioning injury. Unilateral corticospinal tract injury followed by 10 days of electrical stimulation of the motor cortex resulted in forelimb function recovery and increased axon outgrowth.45 A follow-up study by the same group demonstrated that motor cortex stimulation after pyramidalotomy can increase the length of axons from the primary motor cortex to the spinal cord, as well as to the red nucleus and cuneate nucleus.21 Increased outgrowth with stimulation may be due to neurotrophin release, such as brain-derived neurotrophic factor, and increased activity. The pyramidalotomy is a mechanism of injury that is different from TBI, but one can cautiously extrapolate that electrical stimulation may enhance neurotrophin release in brain tissue damaged by diffuse axonal injury or cortical contusion. These preclinical studies suggest that direct cortical stimulation may enhance functional plasticity after cortical injury.

Human Trials of Direct Cortical and Spinal Cord Stimulation

Motor cortex stimulation has been clinically tested in patients with trigeminal neuralgia and central pain from stroke62,99,111,149 with mixed results. A meta-analysis of motor cortex stimulation to reduce pain showed efficacy in approximately 50% of patients (40%–50% improvement).52 However, most of the studies were retrospective series with no control groups, and long-term loss of pain relief following stimulation was common. Extradural motor cortex stimulation has also been used in patients with Parkinson’s disease (PD) with a contraindication to or lack of response to DBS. Several studies resulted in promising reduction in PD symptoms assessed by the Unified Parkinson’s Disease Rating Scale and reduced levodopa dosage.18,31,16,141 However, others reported no major improvement in motor function.20,133

Based on anecdotal reports showing improved motor function when stroke patients with chronic pain were treated by motor cortex stimulation,81,148 an initial study using subthreshold epidural motor cortex stimulation on a hemiparetic stroke patient was performed.14 Stimulation for 3 weeks during stroke rehabilitation led to improved pincer movement of the previously paretic hand, improved scores on the upper-extremity Fugl-Meyer motor scale and Stroke Impact Scale, and reduced flexor posture. This single-patient study suggesting the efficacy of epidural motor cortex stimulation prompted several prospective trials using the same techniques on stroke patients with motor deficits. In a small prospective randomized trial of 12 stroke patients assigned to either rehabilitation and motor cortical stimulation or rehabilitation alone, the group receiving electrical stimulation showed Fugl-Meyer motor scale improvements in upper-extremity function compared with the control group during 6 months of follow-up.54 Similarly, prospective multicenter studies using motor cortex stimulation during 3 weeks15 or 6 weeks39 of the rehabilitation phase have reported improvements in measures of upper-extremity function. In general, data demonstrating the long-term efficacy of motor cortex stimulation are lacking.

In addition, a few studies have attempted spinal cord stimulation.50,160 Cervical spinal cord stimulation using an electrode placed at the C2–4 levels was shown to increase cerebral blood flow, upper-extremity motor function, and speaking/communication in patients in a minimally conscious state (MCS) resulting from TBI, stroke, or encephalomyelitis.60 Similarly, stimulation at the same level in patients who are in vegetative states after anoxia, stroke, or head injury led to improvement in signs of awareness of self and surrounding in 109 of 201 patients (54%) in a nonrandomized observational study.50 However, it is difficult to distinguish these outcomes from spontaneous recovery after injury because the subjects were not randomized. The utility of spinal cord stimulation will need to be clarified with randomized controlled studies.

DBS

In patients who meet surgical criteria, DBS is the gold standard for treating motor symptoms of PD when medications begin to fail.126,155 DBS can be even more effective in patients with essential tremor and is also efficacious in the treatment of generalized and cranio-cervical dystonia. The mechanism by which DBS is thought to improve symptoms in these diseases is disruption of abnormal neural synchrony between affected brain regions.30 Rather than inhibiting neural activity, DBS alters activity patterns to moderate abnormal brain function related to disease symptoms.16,96 For example, DBS of the subthalamus nucleus in patients with PD induces widespread normalization of activity by increasing activation of motor areas during movement execution and decreased overactivity at rest,48 as well as modulating metabolic changes in the globus pallidus internus (GPi), caudal midbrain, and posterior parietal lobe.140 Because some of the most common sequelae of TBI are movement disorders, including tremor, dystonia, and parkinsonism,72 the utility of DBS in a medically refractory posttraumatic movement disorder is a topic of significant interest.

DBS for Posttraumatic Tremor. Posttraumatic TBI tremor has been reported as early as a few weeks and as late as 2 years following injury.83 Limited data exist for the effectiveness of DBS on posttraumatic tremors, with limited follow-up intervals. Successful stimulation of the ventralis intermedius (VIM) nucleus of the thalamus, which is the accepted stimulation target for essential tremor, has been reported in several single case reports.13,130 Cerebellar projection neurons are concentrated in the VIM, and high-frequency stimulation can modulate the activity of these projections.8,55 Foote et al.45 employed a strategy to target both the cerebellothalamic and pallidothalamic circuits in posttraumatic tremor by implantation of two ipsilateral DBS electrodes in parallel in the VIM and ventralis oralis anterior/posterior (VOA/VOP, receives inputs from the basal ganglia, in particular from the GPi) with good tremor response, but the percent reduction (38%–67%) did not differ considerably between VIM plus VOA/VOP stimulation and VIM stimulation alone. Issar et al. recently published a small case series in which posttraumatic tremor patients received unilateral VIM DBS (n = 3), bilateral VIM DBS (n = 1), or bilateral GPi DBS (n =

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Among the 4 patients who underwent VIM stimulation, all reported reduction of their tremor that significantly improved their ability to perform daily activities. However, all patients experienced some side effects, such as dystonic movements of upper extremities, gait and balance problems, paresthesia, and slurred speech. Similarly, of 9 posttraumatic tremor patients reported in a broad cases series, 3 patients who received bilateral thalamic implants developed speech impairments. Lim et al. reported the case of a patient with a poststroke Holmes’ tremor who underwent simultaneous implantation in the unilateral VIM, VOA, and GPi. This patient experienced moderate tremor reduction with GPi stimulation alone, but neither VIM nor VOA stimulation provided additional benefit, demonstrating the need for patient-specific target selection.

DBS for Posttraumatic Dystonia and Parkinsonism. Another common sequela of TBI is dystonia, occurring at a wide range of time points after injury from 1 day up to 6 years. Posttraumatic dystonia is most commonly found in patients with injuries in the basal ganglia and thalamus. Reduced inhibitory control in basal ganglia-thalamocortical motor loops leading to hyperactivity in frontal motor areas has been suggested to result in dystonia, but the mechanisms of posttraumatic dystonia are complex, as different injury constellations will produce different dystonic symptoms.

Deep brain stimulation for posttraumatic dystonia has been reported in a few case reports and one small case series. In a posttraumatic patient with right hemidystonia, DBS of the ventroposterolateral nucleus of the thalamus resulted in a drastic reduction of symptoms. Similarly, a patient with a left-sided low-frequency tremor and hemidystonia 9 years post-TBI received contralateral GPi stimulation, resulting in reductions of arm dystonic movements and abnormal posture for at least 4 years. In another case study, a patient with chronic dystonic posturing and tremor who received DBS of the GPi showed a significant reduction of symptoms up to 2 years after stimulation. Recently Kim et al. reported a 38%–94% improvement in Burke-Fahn-Marsden Dystonia Rating Scale movement and disability scores in 4 patients who underwent unilateral GPi DBS for the treatment of secondary hemidystonia associated with TBI. Improvement in dystonia secondary to anoxic brain injury has also been reported following stimulation of either the GPi or the VOA nucleus of the thalamus.

Postrumatic parkinsonism, which can involve tremor, hypokinesia, rigidity, and postural instability, is another potential sequela of TBI that may be amenable to DBS. Although the mechanism of these symptoms after TBI is unclear and more direct comparisons are needed between patients with idiopathic PD and those with postrumatic parkinsonism, there may be common pathophysiological elements that could suggest the potential for a therapeutic response to DBS.

Brain Stimulation for Recovery of Cognitive Function

Cognitive sequelae of TBI range from a state of minimal consciousness, to problems with memory and executive functioning, to the long-term development of neuropsychological disorders. Noninvasive techniques have been clinically applied to treat the cognitive sequelae of stroke, while in TBI, DBS has been studied as a way to arouse patients from MCS. In addition, DBS is currently under investigation for the treatment of depression, a common neuropsychological disorder following TBI. In fact, TBI patients commonly show symptoms of depression as measured by multiple depression scales and major depressive disorder is reported as the most common psychiatric illness resulting from TBI.

As DBS has shown encouraging results in depression in both humans and animal models, it may be a useful treatment option for TBI survivors suffering from depression. Other potential sequelae of TBI, such as deficits in memory and arousal, may also be amenable to DBS. DARPA recently recognized the importance of the mental health sequelae of TBI through a major funding initiative (Systems-Based Neurotechnology for Emerging Therapies, DARPA-BAA-14-09; https://www.fbo.gov/index?s=opportunity&mode=form&id=5180458df226b0de3b0c9ec626368542&tab=core&_cview=1) targeted at the development of novel, implantable neurotechnology for recording and stimulation to treat these disease entities.

Noninvasive Stimulation for Posttraumatic Cognitive Sequelae

In addition to its putative effects on motor function, TMS has been shown to enhance various cognitive functions. In healthy subjects, TMS has been suggested to enhance performance in analogical reasoning, recognition memory, and choice-reaction time. Working memory may also be enhanced in a frequency-dependent manner when the midline parietal cortex is stimulated by TMS. However, whether TMS results in functional enhancement or impairment may depend on the stimulation site and parameters as working memory impairment has been reported with TMS of the cerebellum or DLPCF.

There are some data demonstrating the benefit of TMS for acquired brain injury. Among patients with unilateral stroke, TMS of the unaffected parietal cortex reduced symptoms of contralesional visuospatial neglect. In a pilot study of 2 patients with right hemispheric infarction who had unilateral spatial neglect, 2 weeks of TMS to the unaffected parietal cortex led to significant improvements in skills relevant to visual neglect. In addition, TMS may also be effective in improving recovery from poststroke aphasia. Aphasic patients show increased metabolic activation of the nondominant inferior frontal and superior temporal areas as evaluated by PET. Previous studies used low-frequency TMS to suppress the hypothetical overactivity of the contralesional inferior frontal gyrus in patients with chronic aphasia that resulted in a significant increase in discourse productivity and improved picture naming.

Likewise, several studies show enhancement of specific aspects of cognitive function when tDCS is applied in the injured brain, such as with recovery of language function. Following ischemic stroke, stimulation of the ipsilateral left frontotemporal area has been shown to...
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improve picture naming, possibly due to decreased excitability of cortical inhibitory circuits, while stimulation of homologous areas on contralateral side of injury may also enhance aphasia recovery assessed by naming ability. The application of anodal tDCS placed over the left DLPFC in stroke patients has also been suggested to improve working memory performance, specifically in recognition accuracy. Although tDCS has had limited application for the purpose of TBI therapy, one report suggested a tendency for improved attention \((p = 0.056)\) in TBI patients when applied to the left DLPFC.

**DBS**

There are only a few studies reporting the use of DBS in TBI patients despite numerous applications of DBS in other neurological diseases (Table 1). This is due in part to the wide heterogeneity of functional deficits and anatomical damage in patients with TBI, and equally to the ethical considerations for initiating DBS studies in this patient population. Identifying a specific subset of TBI patients with a functional deficit that would be expected to respond to DBS targeting a specific location is a central challenge for the design of clinical trials in TBI patients.

**DBS in the MCS.** A few studies have explored the use of DBS in increasing arousal in TBI patients, first reported by Tsubokawa et al. It has been proposed that DBS in patients who are in a chronic MCS after injury may facilitate the recovery of consciousness. A clinical trial involving vegetative or minimally conscious patients studied DBS of the midbrain reticular formation or central thalamus in vegetative or minimally conscious patients, beginning 4–8 months following injury. The patients were continuously stimulated and observed for 10 years, and 8 of the 21 patients emerged from a vegetative state after DBS (8 out of 10) compared with the patients not treated by DBS (2 out of 6). Caution, however, must be applied in interpreting the effectiveness of DBS within an early time frame following injury, since patients are likely to exhibit some spontaneous recovery. Recovery from MCS has been commonly documented within 6 months of TBI or stroke and even more than 1 year following injury. These challenges in interpreting the efficacy of DBS in treating consciousness disorders may be overcome through the use of double-blind and/or placebo-controlled prospective studies.

In a more recent case report by Schiff et al., DBS of the central thalamus was shown to lead to behavioral improvements in an MCS patient. The patient was minimally conscious prior to DBS for 6.5 years following injury but still showed improvements, specifically with regard to arousal state, limb control, and verbalization. As explained by Schiff et al., this impressive change in behavioral function may have been due to general preservation of cerebral networks in this patient and widespread innervation of frontal cortex and basal ganglia by thalamic association nuclei. By activating the association nuclei of the thalamus with DBS, general arousal and awareness may have been enhanced.

**DBS for Memory Enhancement.** DBS may also be useful for enhancing cognitive function in patients suffering from the cognitive sequelae of moderate TBI. Stimulation of the rodent entorhinal cortex has been reported to result in spatial memory improvement and increased neurogenesis in the dentate gyrus in rodents, suggesting that modulation of the perforant pathway may enhance memory function. A recent clinical study by Suthana et al. reported that entorhinal stimulation applied while human subjects learned landmark locations enhanced their subsequent memory of these locations. In that study, 6 patients undergoing intracranial monitoring for seizure

<p>| TABLE 1: Neurostimulation research on clinical TBI patients and animal studies* |</p>
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Authors &amp; Year</th>
<th>Target Region</th>
<th>Stimulus Method</th>
<th>Injury</th>
<th>Functional Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>humans</td>
<td>Fitzgerald et al., 2011†</td>
<td>bilat DLPFC</td>
<td>LF/HF rTMS</td>
<td>TBI w/ depression</td>
<td>increased recovery from depression</td>
</tr>
<tr>
<td></td>
<td>Louise-Bender Pape et al., 2009</td>
<td>rt DLPFC</td>
<td>HF rTMS</td>
<td>TBI w/ VS</td>
<td>increased neurobehavioral function (by DOCS)</td>
</tr>
<tr>
<td>Kang et al., 2012</td>
<td>lt DLPFC</td>
<td>anodal tDCS</td>
<td>TBI w/ attention deficit</td>
<td>increased attention</td>
<td></td>
</tr>
<tr>
<td>Schiff et al., 2007</td>
<td>central thalamus</td>
<td>DBS</td>
<td>TBI w/ MCS</td>
<td>improved limb control, oral feeding</td>
<td></td>
</tr>
<tr>
<td>Yamamoto &amp; Katayama, 2005</td>
<td>midbrain RF, CM-pf</td>
<td>DBS</td>
<td>TBI, stroke w/ VS, MCS</td>
<td>emergence from VS, able to follow verbal instructions</td>
<td></td>
</tr>
<tr>
<td>rats</td>
<td>Lee et al., 2013</td>
<td>medial septal nucleus</td>
<td>DBS</td>
<td>TBI (FPI)</td>
<td>improved spatial working memory (Barnes maze)</td>
</tr>
<tr>
<td></td>
<td>Carballosa Gonzalez et al., 2013</td>
<td>midbrain median &amp; dorsal raphe nuclei</td>
<td>DBS</td>
<td>TBI (FPI)</td>
<td>improved spatial working memory (water maze), reduced cortical volume loss</td>
</tr>
</tbody>
</table>

* CM-pf = central thalamus parafascicular formation; DOCS = disorders of consciousness scale; FPI = fluid percussion injury; HF = high frequency; LF = low frequency; RF = reticular formation; rTMS = repetitive TMS; VS = vegetative state.
† In this study, a session of low-frequency right-sided TMS was immediately followed by high-frequency left-sided TMS.
mapping via depth electrode placement in the entorhinal cortex completed a spatial learning task during half of which focal electrical stimulation was delivered (below the afterdischarge threshold). In addition to the clinical effect of this stimulation applied during learning, the authors observed theta-phase resetting, an electrophysiological measure known to be important for hippocampal cognitive processing. Enhancement of memory and augmentation of relearning processes in patients recovering from brain injury may be possible using DBS; however, the fact that the temporal lobe itself is a common site of injury in TBI may create a challenge for translating these results to TBI patients. Extratemporal targets may present an alternative, such as DBS of the bilateral fornix, which is currently under investigation for memory preservation in patients with Alzheimer’s disease.

Animal studies also support the continued investigation of DBS in other brain regions to enhance cognition after TBI. In a rat model of TBI, stimulation of the medial septal nucleus postinjury was reported to improve spatial working memory. Stimulation in the theta frequency range (5–12 Hz), hypothesized to enhance theta input from the medial septal nucleus to the hippocampus, resulted in a transient increase in hippocampal theta activity. Fluid percussion injury in rats induces deficits in hippocampal theta frequency that correlate with deficits in spatial working memory function as assessed by the Barnes maze test. Theta frequency oscillations are known to play an important role in learning, as pharmacological blocking of this rhythmicity in the medial septum can inhibit spatial learning in the Morris water maze and radial maze.

Similarly, DBS of the midbrain raphe nuclei following TBI in rats was reported to improve the acquisition of reference memory and spatial working memory function. Improvements in forelimb motor function, as well as reversal of cortical volume loss, were also reported. Low-frequency (8 Hz) stimulation of the raphe nuclei induces the release of serotonin, and activation of several serotonin receptor types is known to increase levels of major trophic signaling molecule cyclic adenosine monophosphate (cAMP). In a previous study, TBI was shown to decrease cAMP and its downstream target protein kinase A in the hippocampus and cortex. This effect could be reversed by DBS treatment of the raphe nucleus, which increased hippocampal and cortical cAMP levels. DBS of the raphe nucleus has therefore been hypothesized to reverse a TBI-induced pathology in cAMP signaling. These studies suggest the potential for DBS to reverse region-specific pathophysiology induced by TBI.

Increased learning and memory in rats was also shown by a novel object recognition test after DBS of the central thalamus. Although it was unclear if improvement was due to enhanced acquisition, storage, or retrieval, repeated stimulation for 3 days resulted in progressive improvement in object recognition each day. This effect was also accompanied by increases in expression of immediate early genes implicated in learning such as c-fos and Zif268 in various locations, including the neocortex, dentate gyrus, and anterior cingulate cortex. In addition, enhanced general arousal was evidenced by increased motor activity and grooming and rearing events. The central thalamus receives numerous projections to regulate arousal, including cholinergic input from the brainstem and basal forebrain, noradrenergic input from the locus coeruleus, and serotonergic input from the raphe nuclei. The midline and intralaminar nuclei of the central thalamus have diverse connectivities with both cortical and subcortical structures likely supporting information processing that results in increased arousal.

Though not yet tested in TBI, the modulation of hippocampal neurogenesis is a potential mechanism through which DBS may influence cognitive function following injury. Specifically, DBS of the anterior thalamus or entorhinal cortex has been reported to regulate memory function in healthy rats. Increased neurogenesis has been hypothesized to be an underlying mechanism contributing to memory improvement, as immunohistochemistry studies showed increased neuronal cell counts in the dentate gyrus of the hippocampus following stimulus of the anterior nucleus of the thalamus (ANT). Similarly, DBS of the rat entorhinal cortex increased neurogenesis in the dentate gyrus in conjunction with improved performance in the Morris water maze. Given the plasticity of the neurogenic niche following TBI and that newborn neurons in the normal brain likely play distinct roles in memory formation as they slowly integrate into the existing dentate gyrus network, these studies suggest that enhancement of neurogenesis may be a potential mechanism underlying the therapeutic benefits of hippocampal circuit stimulation in TBI patients. The timing, location, and electrophysiological parameters of stimulation on the potential functional integration of increased numbers of newborn neurons remain to be explored.

Lastly, with regard to neurogenesis, DBS of the striatum in a mouse middle cerebral artery occlusion stroke model was reported to reduce infarct volume with a concomitant increase in the number of proliferating cells from the subventricular zone migrating to the ischemic penumbra. Induction of trophic factors may be a mechanism underlying reduced infarct volume since stimulation is followed by increases in glial-derived neurotrophic factor vascular endothelial growth factor. However, there are many differences between rodent and primate neurogenesis that might preclude similar results, such as lack of the rostral migratory stream in the human brain that serves as a corridor of neuronal migration from the subventricular zone in lower mammals. It would not be prudent to suggest that DBS may stimulate the birth of new neurons in the injured brain via the subventricular zone without the replication of similar findings in the nonhuman primate brain.

DBS for Posttraumatic Depression. Depression is very common after TBI, with prevalence rates as high as 77%. Although a history of TBI has traditionally been considered an exclusion criterion for repetitive TMS trials due to the increased risk of seizure, there is one case report of a patient with TBI-related depression who was successfully treated with repetitive TMS to the right DLPFC. The DLPFC was likely chosen as the TMS target due to the fact that PET studies have shown that a pattern of increased metabolism in the subgenual cingulate cortex
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(SCC) and decreased metabolism in the DLPFC is correlated with active depression, and reversal of this pattern is associated with symptom resolution. On this basis, several trials of SCC DBS for treatment-resistant depression (TRD) have been undertaken.

Stimulation of the SCC was described originally by Mayberg et al. in 6 patients, with follow-up in a larger group of 20 patients. At 12 months, 55% of patients were responders (50% or greater reduction in the 17-item Hamilton Rating Scale for Depression [HRSD-17]), and 35% achieved or were within 1 point of remission (scoring 8 or less on the HRSD-17). More recently, a group at Emory University reported a study of 17 patients with treatment-resistant unipolar and bipolar depression undergoing DBS of the SCC. Patients underwent a single-blind lead-in sham stimulation phase for 4 weeks followed by open-label active stimulation for 24 weeks. Patients then entered a single-blind discontinuation phase that was discontinued after the first 3 patients experienced complete relapse of symptoms when stimulation was stopped. At 2 years after the onset of active stimulation, 92% of patients were responders and 58% were in remission (n = 12). A multicenter study of SCC DBS yielded more modest results, with 29% of 21 patients achieving responder status at 12 months. Multiple clinical trials in the US, Canada, and Europe are underway to continue the evaluation of SCC DBS in TRD. The anterior limb of the internal capsule and adjacent ventral striatum/nucleus accumbens, structures that have been shown to have significant overlap with the SCC in connections to the medial temporal lobes, frontal limbic cortices, and autonomic subcortical structures, have also been the focus of several investigations as a DBS target for TRD. In general, open-label trials in this target area have reported a 40%–70% response rate, but supportive randomized controlled data are lacking. Although promising, DBS as a treatment for depression is still at an early stage of application, and these results must be interpreted with caution.

**DBS for Posttraumatic Epilepsy.** Epilepsy is a significant comorbidity occurring in TBI patients, with 30-year cumulative incidences of 2.1%, 4.2%, and 16.7% for mild, moderate, and severe injuries, respectively. The clinical study of DBS in pharmacoresistant epilepsy has included the targeting of the ANT, centromedian nucleus of the thalamus, hippocampus, caudate nucleus, subthalamic nucleus, and cerebellum, as previously reviewed. DBS targeting the ANT was approved for the treatment of epilepsy in the European Union in 2010, but still awaits FDA approval in the US. Human studies have shown that ANT stimulation results in prominent activation in the ipsilateral cingulate gyrus, insular cortex, and lateral neocortical temporal structures and suggest that thalamic DBS may drive cortical inhibitory circuits. Greater benefit from ANT stimulation has been observed in patients with temporal seizure foci, potentially reflecting participation of the mesial temporal lobe and the ANT in the limbic circuit of Papez.

Epilepsy provides an example of another aspect of DBS that may be critical for its application in the setting of TBI: the concept of closed-loop stimulation. Clinical DBS experiences to date have mostly involved open-loop stimulation, where the device is programmed for the constant delivery of stimulation within selected, fixed parameters. In closed-loop stimulation, the system is capable of performing real-time seizure detection and delivering responsive stimulation, and the stimulation target depends on each patient’s seizure focus or foci. The responsive neurostimulation system (RNS) (NeuroPace, Inc.) was recently approved by the FDA for use in the US and employs separate electrodes for seizure detection and stimulation delivery. Alternating current systems that allow detection and stimulation on the same electrode lead are currently under investigation. As electrophysiological biomarkers of other TBI comorbidities are discovered, closed-loop stimulation may have potential for application in TBI beyond the treatment of epilepsy.

**Considerations for Future Work**

The various neurostimulation strategies being investigated for their potential role in recovery of cognitive and motor sequelae of TBI will continue to be developed independently, but they may ultimately be used in combination for individual patient treatments. Direct cortical stimulation causes morphological changes in neurons similar to those induced by rehabilitative training. Both supra- and subthreshold electrical stimuli may strengthen synaptic connections and trigger neuronal reorganization leading to functional improvements. Although animal experiments have shown the efficacy of this approach in many studies, the invasive nature of this method brings into question whether noninvasive methods such as TMS and tDCS are preferable. Early studies showing beneficial effects of noninvasive transcranial neurostimulation modalities on motor and cognitive function suggest that improvements in these technologies may aid in augmenting recovery from TBI, but there is no rigorous evidence for functional improvement in this patient population. Noninvasive stimulation methods hold several advantages over neurosurgery-based stimulation techniques: they are less expensive, easier to administer, and painless for the patients. Due to these advantages, they may have an important role in the treatment of specific subsets of patients with neurological injury. However, there are also many limitations compared with paradigms involving direct brain stimulation through implanted neuromodulatory devices.

Despite the simple principles underlying the mechanisms of TMS, the exact shape of the induced current can be complicated by variations in intracranial anatomy. Preferential current flow can occur toward areas of CSF, which has higher conductance, and the precise current location can be widely variable. Many TBI patients will have undergone craniotomy, craniectomy, or other neurosurgical treatments, and skull defects or skull plates are common in patients who may benefit from neurostimulation therapy. Plates or defects can alter the direction of the current flow in tDCS, and finite element modeling of various sizes of defects and plate types has shown differences in the distribution of electrical current passing into the brain.

Another important disadvantage of noninvasive techniques is that precise access to deeper brain structures is
severely limited. Problems such as current shunting via scalp and CSF make targeting of deeper structures difficult to predict and control. Similarly, the electrical field generated by TMS decreases dramatically for deeper targets.\(^1\)\(^4\)\(^6\) Coil design studies have shown that larger coils are needed to access deeper structures, but larger coils cannot provide focal targeting; thus, the stimulated tissue area will be larger.\(^1\)\(^2\)\(^1\)\(^3\) Moreover, both TDCS and TMS are temporary stimulation techniques; the effects of noninvasive stimulation techniques diminish months to years later. Due to these limitations, a stimulation technique that provides direct access to both superficial and deep structures with continued long-term neurostimulation may be favored. The advent of closed-loop neurostimulation devices, where cortical recording and stimulation could be combined with deep brain recording and stimulation, may provide an avenue for translating and improving results previously obtained with noninvasive cortical stimulation methods (Fig. 1).

Conclusions

Deep brain stimulation has been used to treat movement disorders for the past 15 years and more recently to neuropsychiatric disorders. The use of DBS in movement and psychiatric disorders does not necessarily justify its use in TBI, but as our understanding of the therapeutic mechanisms of DBS and the pathophysiological mechanisms of TBI continue to develop, it is likely that DBS will be applied to counteract the network abnormalities responsible for some TBI symptoms. The studies outlined in this review suggest potential applications of DBS to improve motor function, mood, memory, and arousal in TBI patients. Major challenges in developing these approaches include the identification of specific phenotypes of TBI patients whose symptoms are amenable to therapeutic DBS. TBI is not one disorder; rather, it is a heterogeneous mix of brain injuries and associated deficits. There is increasing recognition of the importance of in recognizing brain network abnormalities related to altered functional\(^1\)\(^7\)\(^1\)\(^4\)\(^3\) and structural\(^1\)\(^3\) abnormalities in TBI patients. Given the expanding view of the potential to modulate functional brain networks with spatially precise DBS delivery,\(^8\)\(^9\) structural and functional neuroimaging studies should be used in future TBI trials to target biomarkers of functional deficits in a patient-specific fashion.

Disclosure

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