Received: October 10, 2011 Revised: March 25, 2012 Accepted: May 1, 2012

(onlinelibrary.wiley.com) DOI: 10.1111/j.1525-1403.2012.00474.x

Noninvasive Brain Stimulation to Modulate Neuroplasticity in Traumatic Brain Injury

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Objective: To review the use of noninvasive brain stimulation (NBS) as a therapeutic tool to enhance neuroplasticity following traumatic brain injury (TBI).

Materials and Methods: Based on a literature search, we describe the pathophysiological events following TBI and the rationale for the use of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) in this setting.

Results: The pathophysiological mechanisms occurring after TBI vary across time and therefore require differential interventions. Theoretically, given the neurophysiological effects of both TMS and tDCS, these tools may: 1) decrease cortical hyperexcitability acutely after TBI; 2) modulate long-term synaptic plasticity as to avoid maladaptive consequences; and 3) combined with physical and behavioral therapy, facilitate cortical reorganization and consolidation of learning in specific neural networks. All of these interventions may help decrease the burden of disabling sequelae after brain injury.

Conclusions: Evidence from animal and human studies reveals the potential benefit of NBS in decreasing the extent of injury and enhancing plastic changes to facilitate learning and recovery of function in lesioned neural tissue. However, this evidence is mainly theoretical at this point. Given safety constraints, studies in TBI patients are necessary to address the role of NBS in this condition as well as to further elucidate its therapeutic effects and define optimal stimulation parameters.

Keywords: Diffuse axonal injury, neuroplasticity, transcranial direct current stimulation, transcranial magnetic stimulation, traumatic brain injury

Conflicts of Interest: The authors reported no conflict of interest.

INTRODUCTION

Traumatic brain injury (TBI) is a major health problem with devastating consequences and an enormous socioeconomic burden on individuals and their families. It has been estimated to affect around 1.5 million people in the USA each year, resulting in 290,000 hospitalizations and 51,000 deaths (1), and lifetime costs that may reach $2 million per patient (2). An estimated 5.3 million U.S. citizens live with long-term disabilities following TBI (3). Although cognitive and emotional derangements are most common, sensory and motor impairments are also seen to a lesser extent (4).

While significant progress has been made in understanding TBI pathophysiology, current interventions are still insufficient to prevent long-term disabilities. However, recent insights on the brain's innate plastic capacity provide an array of therapeutic possibilities, yet to be fully understood, that may allow for brain activity modulation via its inherent properties in the setting of TBI. In this regard, we will now review the acute and long-term mechanisms of TBI as to create a framework to understand the rationale and possible approaches for the use of noninvasive brain stimulation (NBS), in order to limit damage and promote recovery after brain injury.

ACUTE CHANGES FOLLOWING TBI

TBI has been divided into primary and secondary injury. The former involves the initial disruption of brain tissue by a cortical contusion, hemorrhage, or axonal injury (5), oftentimes causing irreversible damage to the central nervous system (CNS) (6). The secondary injury consists of a series of events that lead to impairment of cell functions, cell death (7), and consequent dissemination of damage (8), which will eventually determine the degree and magnitude of long-term deficits (9). From a pathophysiological point of view, this secondary injury involves derangements in metabolic processes (10), excitotoxicity, inflammation, edema, disruption of the blood-brain barrier (BBB), damage to the vasculature, and white matter destruction, ultimately leading to a collapse of brain tissue (5,10).

Immediately after the trauma, nerve cells enter a progressive path of degeneration initiated by unrestrained neuronal depolarization.

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For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/bw/submit.asp?ref=1094-7159&site=1
Sources of financial support: Departmental funds.

This results in a massive release of glutamate from presynaptic vesicles and damaged cell membranes (11). The mechanical injury inflicted on nerve cells also alters the *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, resulting in more excitatory overstimulation and increasing the likelihood of neuronal dissolution (12).

It has been observed that after the primary injury, affected axons become torn and fragmented, triggering an inflammatory process. As a result, destruction of the cytoskeleton and axonal swelling occur, causing disconnection (13) and a future harmful effect on neurogenesis (14). This array of phenomena is known as diffuse axonal injury. All these changes can affect the connectivity of thousands of neurons, resulting in an impairment of their functional interactions. In this way, a relatively localized injury can result in widespread damage to the brain (15).

The increased release of glutamate causes influx of sodium and calcium into the cells. As a result, calcium homeostasis is lost and its overload at the injured area causes disruption of the metabolic processes inside the nerve cells. This leads to an early neuronal swelling followed by a late ongoing neuronal disintegration (a process termed excitotoxicity [16]), as well as apoptosis and postsynaptic receptor modification (5).

Within the axons, calcium activates enzymes (e.g., calpain) that cleave proteins responsible for maintaining axonal shape and function (e.g., spectrin), causing axons to disintegrate (17). This breakdown is caused by swelling and proteolysis of the cytoskeleton, deforming the axolemma and likely resulting in disconnection or axotomy (18). At the same time, activation of calpain also results in lysosomal rupture, contributing to cell lysis and neuronal necrosis (19).

In an attempt to stabilize and decrease excessive calcium concentrations inside the nerve cells, the mitochondria sequester it (20) as a protective mechanism. However, the increased amount of calcium inside the mitochondria impairs the oxidative phosphorylation processes leading to a decrease in energy transduction and a lack of adenosine triphosphate (21) despite high demands, and a resultant accumulation of reactive oxygen species (22). Together with cytochrome c, reactive oxygen species leak to the cytosol, activating caspases and causing more damage to the cell (23).

On the other hand, activation of NMDA receptors (24) and the overload of calcium inside the cells trigger endothelial and neuronal nitric oxide synthase (25) leading to increased levels of nitric oxide, which in turn reacts with oxygen species, causing DNA fragmentation, lipid peroxidation, and cell death (24). The presence of high concentrations of calcium, free radicals, and glutamate create an unstable environment that leads to increased production of these components, potentiating each other's effects (8). All these events, initiated by the TBI, set off a cascade in which pro-inflammatory and anti-inflammatory cytokines and chemokines intensify tissue damage (26).

The hemorrhage caused by the initial insult to brain tissue also contributes to exacerbate the secondary injury. Blood outside the vessels is pro-inflammatory and creates a more vulnerable environment by releasing excitatory amino acids. Consequent red blood cell lysis causes the release of iron, which in turn, together with thrombin activation, induces more oxidative stress and inflammation, and predisposes to early edema development (27–29).

Because of this neuroinflammation, the BBB is also injured and its ability to autoregulate becomes impaired (8). This damage to the BBB drives the astrocytes and endothelium to produce more inflammatory mediators, therefore potentiating the progression of neuroinflammation (14). The immune response that follows TBI can be considered unfavorable for the aforementioned reasons, but it is also advantageous because it can ultimately induce a beneficial effect on tissue regeneration and plasticity (30) following the acute inflammatory period. Resolution of this acute inflammation is mediated by apoptosis of the inflammatory cells and endogenous mediators that operate together in an anti-inflammatory mechanism (31).

Because an intact BBB together with cerebral vascular tone play an important role in cerebral blood flow (CBF) autoregulation, the abovementioned damage to the BBB creates a vulnerable environment, in which oxygenation and perfusion cannot be maintained, placing the brain at an increased risk of ischemic injury. As a result of brain injury, CBF is compromised, with an initially decreased perfusion and cerebral ischemia during the first hours after the injury. This is followed by a second phase of increased perfusion with increased intracranial pressure, and a final phase of vasospasm and reduced perfusion (32).

Cerebral edema is another consequence of the damage caused by TBI and also contributes to the processes that take place during the secondary injury. Two types of edema, vasogenic and cytotoxic, often coexist following a TBI. Vasogenic edema results from reflex vasodilation and from the damage inflicted on the BBB, resulting in an increased permeability and accumulation of molecules and interstitial fluid. Cytotoxic edema is the result of the metabolic derangements within the cells that lead to failure of membrane ion regulation and to subsequent changes in osmolality (8,14).

Many efforts have been made in order to develop therapeutic agents that protect the brain from the aforementioned acute damage. However, their benefits have proven difficult to demonstrate conclusively (33,34), and motor and neurobehavioral deficits are commonly seen in TBI survivors. For this reason there is an ongoing need to explore novel techniques that may be advantageous in this setting.

SUBACUTE AND CHRONIC CHANGES AFTER TBI

The Role of Brain Plasticity in TBI Recovery

Plasticity can be defined as an ongoing, intrinsic property of the nervous system, whereby changes in the afferent input or the efferent demands of a neural network lead to systemic reorganization that might be demonstrable from molecular and cellular to anatomical and behavioral levels (35). This dynamic process plays a crucial role in neural development and homeostasis (36), as well as in the response after damage to the peripheral or central nervous system. In the setting of brain injury, plasticity can be viewed as a mechanism to compensate for the injury and reestablish function.

Brain plasticity may be neuronal or nonneuronal, and the former may be synaptic or non-synaptic (37). Thus, modulation of synaptic transmission (38) is only one of many mechanisms of brain plasticity (39). Others include changes in the integrative properties of individual neurons (40) and neuronal networks (41), neurotransmitters and ions (42,43), gap junctions (44), and glial cells (45,46), all of which can ultimately result in anatomical and functional modifications (47). From a functional point of view, neuroplasticity may be regarded as activity- or time-dependent (48). The former refers to an increase in neuronal firing that can be demonstrated during performance of a specific task, whereas the latter refers to "a precisely-timed relationship between neuronal activation within a network," indicating cooperation between neurons (37).

Recovery of function after TBI involves three stages. First, activation of cell repair, which mediates resolution of edema and inflammation and takes place mainly over the first three weeks after brain

injury (49). The second stage consists of functional cell plasticity, involving modifications in the properties of previously existing neuronal networks and, ultimately, anatomical plasticity which leads to the formation of new connections (50). After the acute stage, plasticity and remyelination are the most important factors, and are most prominent within the first three months after the insult (51,52). Therefore, the greatest recovery occurs in the acute and subacute setting.

Subacute Period

Following subsidence of inflammation and edema, functional cell plasticity, the second stage involved in the recovery of function after brain injury, refers to plastic changes that may be rapid but relatively transient. Changes in the amount of excitation or inhibition induced by modulation of neuronal traffic represent the fastest of such processes, and are therefore critical for short-term plasticity (53). These changes are responsible for decreasing γ-aminobutyric acid (GABA) interneuron-mediated tonic inhibition (54), therefore allowing neural networks to become active (55,56). Using animal models, it has been demonstrated that TBI induces working memory deficits lasting for about one month post-injury, a process that is associated with increased levels of glutamic acid decarboxylase 67, the enzyme that catalyzes the decarboxylation of glutamate to GABA, and reverted by its blockage. This provides evidence that such deficits, seen in the subacute period after the injury, may be induced by excessive GABA-mediated inhibition (57).

Changes in the strength of specific synapses represent another rapid mechanism for brain plasticity (55). Repetitive neuronal firing can modify the properties of synaptic transmission, and successive action potentials targeting the presynaptic membrane are capable of increasing or decreasing postsynaptic activity. Thus, synaptic strength is activity-dependent and is stimulated at specific synapses during the process of memory formation (58,59).

In addition to promoting memory and learning, activity-dependent synaptic plasticity can also have a role in the recovery after brain injury, accounting for its direct rehabilitation applications. Animal studies using both healthy and brain injury models have demonstrated the remarkable effects of exercise training on synaptic activity, resulting in significant improvements in object recognition (60) and spatial learning (61), as well as in acquisition of motor skills (62–64), to mention a few examples. Evidence from human studies specifically focused on brain injury has yielded similar results, which can have important implications for motor (65) and cognitive (66) recovery. It is therefore important to understand the factors associated with activity-dependent plasticity as to maximize its behavioral gains during rehabilitation.

The abovementioned principles constitute the basis for the phenomena of long-term potentiation (LTP) and long-term depression (LTD), two extremely relevant concepts in neuroscience given their ability to explain the mechanisms of synaptic memory, as proposed by Hebb in 1949 (67).

LTP was first discovered in the dentate gyrus (68) and then demonstrated in the motor cortex (69). This phenomenon refers to a long-lasting increase in the strength of excitatory glutamatergic synapses, taking place after brief high-frequency stimulation. That is, it results in a durable effect following delivery of a stimulus that, under different circumstances, would only induce a short-term effect with a rapid return to baseline (58). Importantly, LTP is input-specific, and changes can be induced in a particular set of synapses within a neuron without affecting others (70). LTD refers to the opposite mechanism (71,72), and together they play an important role in attention (73), memory and learning (74,75). In addition to previous synaptic history and learning, factors such as development, ageing, stress, disease, and brain injury have been shown to modify LTP and LTD (76).

The mechanisms for LTP and LTD induction are mainly related to modulation of the number and conductance of AMPA receptors, mediated by calcium influx via ionotropic NMDA glutamatergic receptors (38,70,77). A comprehensive review of the molecular basis of LTP and LTD is provided elsewhere (70).

TBI can affect LTP and LTD in different ways. It is well known that TBI can lead to the development of late posttraumatic seizures (LPTS), with an incidence ranging from 5 to 18.9% in civilians, and up to 32–50% in military populations (78). In this setting, seizures may be due to hyperexcitability, likely related to excessive LTP at glutamatergic synapses (70). On the other hand, LTP and LTD in humans have also been shown to be persistently suppressed by GABA-mediated inhibition resulting from single and repeated concussive injuries, a process known to cause long-lasting motor and cognitive deficits (79). Excessive LTD has been reported in animal models of major depression (80) and may be a contributing factor to its development after TBI.

Chronic Changes

Both LTP and LTD are thought to be intermediate stages that can later be complemented by anatomical changes (81,82). In humans, these changes primarily involve ipsilateral brain regions, with contralateral areas also being engaged in cases of severe damage (83). When such processes take place, a longer lasting and more secure plastic change is ensured. Evidence of such structural modifications can be demonstrated both microscopically (remodeling of dendritic spines [84], axonal sprouting [85], neosynaptogenesis [86], and even neurogenesis [87,88]) and macroscopically (89). Even mild TBI can damage hippocampal anatomy (90,91), particularly in the dentate gyrus (76), providing another explanation for the memory deficits seen as a sequel of brain injury. A brief overview of the pathophysiological changes occurring at different stages after TBI is provided in Figure 1.

Adaptive vs. Maladaptive Plasticity

Despite the crucial role of plasticity in promoting recovery after brain injury, such changes are not always favorable and could in turn lead to maladaptive outcomes. Spasticity after stroke (37), pathological pain (92,93), schizophrenia (94,95), and dystonia (96) are all examples of pathological plastic changes. In the setting of TBI, such maladaptive plasticity could cause dysfunctional motor and cognitive recovery, in some cases leading to the development of Alzheimer's disease (97,98). Similarly, collateral sprouting may give rise to the development of seizure foci (99) or to the spread of epilepsy from a primary focus to synaptically related brain regions (100,101).

Understanding of the functional or dysfunctional nature of neuroplasticity, along with the specific pathophysiological processes occurring at different time points after TBI, provides a clear rationale for their therapeutic modulation. In such a way, functionally maladaptive changes can be suppressed while enhancing favorable outcomes, leading to a better recovery of motor and cognitive function and helping decrease the burden of disabling sequelae. Given the fact that activity-dependent plasticity is modulated by task performance, and since time-related plasticity is responsible for inducing specific network changes, techniques that artificially couple neuronal discharges to modify their functional or structural connec-

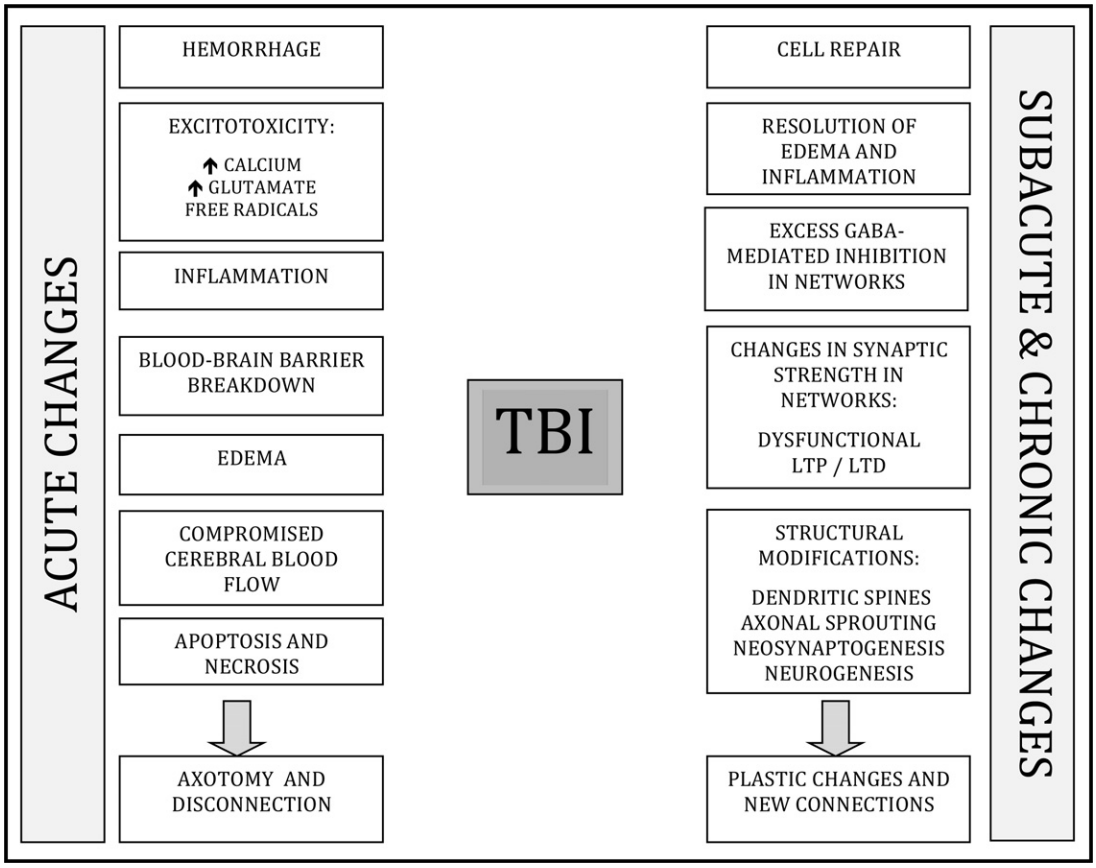

Figure 1. Overview of the acute, subacute, and chronic changes following TBI. TBI, traumatic brain injury; LTP, long-term potentiation; LTD, long-term depression.

tivity can modulate the way neuroplasticity takes place (102). Due to its ability to modulate both activity- and time-related plasticity, NBS represents a promising therapeutic intervention in the setting of TBI.

PHYSIOLOGIC EFFECTS OF NBS

Transcranial Magnetic Stimulation (TMS)

TMS, introduced in 1985 (103), is an NBS technique based on the principle of electromagnetic induction. By passing a very brief and large electric current though a coil held over the scalp, a rapidly changing magnetic field is created which then penetrates relatively unimpeded through the skull and secondarily induces electric currents in particular brain regions. When a single TMS pulse is applied, the resulting electric current can be of sufficient magnitude to depolarize cortical neurons, either through a direct effect on their axon hillock, or indirectly by depolarizing interneurons (104). The induced electrical stimulus can simultaneously activate many different populations of neurons, mainly in the neocortex, some of which project axons to or from the site of stimulation. Therefore, varying effects can be induced on the cerebral cortex and in functionally related brain regions via synaptic spread. Factors such as coil orientation and baseline cortical activity influence the effects of TMS (105,106), and patient-specific factors such as anatomical or neurophysiologic derangements can have similar consequences. In fact, Wagner et al. have modeled TMS-induced current distribution in brain models with cortical stroke lesions, showing that current distribution becomes less predictable and that the peak of current is found over the edges of the lesion (107).

Short-Term Physiologic Effects of Repetitive TMS (rTMS)

When the aforementioned pulses are applied in trains, this modality is termed rTMS. rTMS can be further classified as "conventional," when all the pulses are delivered at constant intervals, or as "patterned" when brief rTMS bursts at a high inner frequency are interleaved by short pauses of no stimulation (108). Examples of patterned rTMS include theta burst (TBS) and quadripulse stimulation.

Different neuronal populations show different thresholds to electrical stimulation, allowing for some selectivity in their activation depending on the rTMS parameters used (105). In most cases (109), conventional rTMS frequencies between 0.2 and 1 Hz (i.e., *low-frequency* rTMS) tend to cause a decrease in cortical excitability (110), probably due to preferential stimulation of GABAergic neurons (111), while frequencies ≥5 Hz (i.e., *high-frequency* rTMS) have the opposite effect (112). The inhibitory effects of rTMS can be enhanced when low-frequency pulses are preceded by a brief high-frequency priming and vice versa (113). Moreover, rTMS has been shown to induce changes in regional CBF in a stimulation-dependent manner, with low-frequency rTMS decreasing it and high-frequency rTMS increasing it, probably as a response to changes in cortical excitability (104,114). One important aspect is that during application of rTMS there is a disruption of activity, and it is after stimulation when the neuromodulatory effects of rTMS, inducing an increase or a decrease in cortical excitability, can usually be observed.

TBS, a protocol where trains of three 50-Hz stimuli are delivered regularly five times per second, can also show distinct effects on cortical excitability. When trains are administered continuously

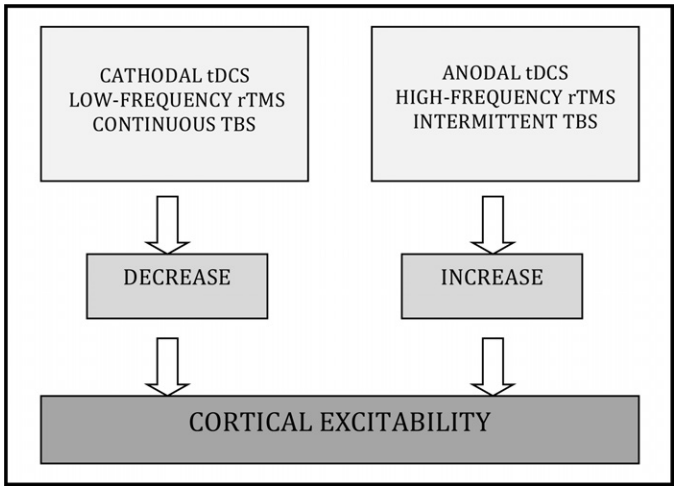

Figure 2. Net effects of different NBS techniques on cortical excitability. NBS, noninvasive brain stimulation; tDCS, trancranial direct current stimulation; rTMS, repetitive transcranial magnetic stimulation; TBS, theta burst stimulation.

(cTBS), a decrease in cortical excitability is observed, which also seems to be mediated mainly by stimulation of GABAergic neurons (115). If intermittent (iTBS) trains are applied, the net result is an increased excitability (116). Figure 2 shows a simplified representation of the net effect of complex inhibitory and excitatory interactions in the area of stimulation, and potentially in other CNS regions part of a distributed network.

For both conventional and patterned rTMS, short-term effects of stimulation appear to be caused by modifications in neural excitability brought about by ionic changes around active neurons, or in stimulation-induced storage of charge. The electric field induced in brain tissue causes a flow of ions that consequently modifies the electric charge stored on both sides of the cell membrane, inducing neuronal depolarization or hyperpolarization (108). Reafferent feedback to the site of stimulation by its target structures may also play an important role (105). The effects of TMS primarily target the axonal-soma and axonal-bouton boundaries, as well as fiber bends of individual cells (117).

Long-Term Physiologic Effects of rTMS

After a period of stimulation that usually ranges between 10 and 15 min (118), the facilitatory or inhibitory effects of rTMS can be observed (112), usually lasting for about ten more minutes after the end of the intervention (119). However, such effects are of greater magnitude following repeated sessions (120) and may persist for several weeks (121). These long-lasting effects seen after repeated stimulation can prove to be crucial for the potential therapeutic role of rTMS, since they indicate that this technique is able to induce an environment supportive of neural plasticity.

Even though the mechanisms responsible for inducing the long-term effects of TMS are yet to be fully understood, evidence from pharmacological studies suggests that they could be related to the modulation of NMDA glutamatergic receptors, depending upon stimulation parameters (122,123), a process comparable to the induction of LTP and LTD. Hence, high- or low-frequency rTMS can be used to induce LTP or LTD, respectively. This effect can be demonstrated in the actual target site for stimulation, as well as in remote functionally or anatomically related brain regions (124).

Induction of immediate early genes associated with neuronal activation (such as *c-fos*) (125–127) and neurotrophic factors (such as brain-derived neurotrophic factor) (128) is also amenable to modulation by rTMS, suggesting these as potential mechanisms for the long-term effects of this NBS method. Induction of the former is most prominent after chronic stimulation, and this effect is not accompanied by evidence of reactive gliosis or cell damage (126).

TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS)

Modification of brain function by means of electrical currents was first described more than 200 years ago (129) and extensively studied in animal models in the 1950s and 1960s (130–134). Based on these observations, tDCS was developed as an NBS technique that consists of placing two relatively large rubber electrodes (25–35 cm^2) on the scalp, in order to allow a weak direct current to flow from anode to cathode. Although there is shunting of current in the overlying tissues, the electrical stimulus that reaches the brain is of enough intensity to modify the level of spontaneous neuronal excitability and activity by changing the resting membrane potential (135,136). Thus, tDCS serves as a neuromodulatory NBS intervention, as opposed to neurostimulatory techniques capable of inducing action potentials by rapid depolarization of neuronal membrane, such as TMS (136).

Common tDCS parameters include current intensities between 1 and 2 mA, which are often applied for 10 to 20 min (136). Current density, the quotient of current strength and electrode size, is responsible for determining the efficacy of tDCS for inducing acute changes in membrane polarity (136). Despite having similar neurophysiologic effects, the mechanisms underlying tDCS-induced excitability changes during stimulation differ from its aftereffects (137). Therefore, they will be discussed separately.

Short-Term Physiologic Effects of tDCS

Studies performed in human subjects have demonstrated that tDCS of the primary motor (M1) and visual cortices modifies cortical excitability in a polarity-dependent manner: whereas anodal stimulation increases it, cathodal stimulation decreases it (138–142). These effects are shown in Figure 2. When tDCS is applied for a sufficient period of time, modifications in cortical excitability can outlast the stimulation period and seem to last longer than those induced by conventional rTMS. In fact, it has been reported that 13 min of a single session of tDCS can affect cortical excitability for approximately 90 min (139), and the effects of consecutive sessions can last for weeks (143).

The sole mechanism mediating the acute effects of both anodal and cathodal tDCS appears to involve changes in transmembrane proteins and hydrogen ions that induce modifications in membrane potential (140), predominantly affecting interneurons (137,144). Immediate effects of anodal tDCS are decreased by sodium and calcium channel blockers (145), but are not affected by NMDA-, $GABA_A$-, nor glutamate-dependent mechanisms (144–146). Effects of cathodal tDCS do not appear to be mediated by NMDA nor GABA either (147). However, as opposed to anodal tDCS, the effects of cathodal stimulation on cortical excitability are not affected by sodium or calcium channel blockers (145), maybe as a result of inactivation of voltage-gated channels due to neuronal hyperpolarization (137). Thus, effects of both anodal and cathodal tDCS during stimulation appear to be mediated by modification of resting membrane potential, without affecting synaptic plasticity significantly.

Long-Term Physiologic Effects of tDCS

Non-synaptic processes involving changes in neuronal membrane function are also one of the proposed mechanisms for tDCS aftereffects. Similar to what occurs during stimulation, exposure to constant electric fields could induce ionic changes and modifications in transmembrane proteins, which in turn cause long-lasting changes of neural membrane function (148). However, as opposed to the immediate effects of tDCS, synaptic mechanisms may also play a role in the induction of its aftereffects.

Membrane depolarization seems to be a necessary step for the induction of anodal tDCS long-term effects, as shown by their abolishment after administration of sodium or calcium channel blockers (137,145). Furthermore, the long-term effects of anodal tDCS appear to depend at least in part on synaptic modulation (137,149), involving both $GABA_A$ergic and glutamatergic synapses (137,144,150). Long-term effects of cathodal tDCS are mediated by glutamatergic but not GABAergic synapses (145), and likely affect intracortical interneurons (137,144).

The aftereffects of tDCS may comprise LTP- and LTD-like mechanisms, which are crucial for synaptic modulation (151). As mentioned previously, LTP depends on the activation of NMDA receptors by glutamate. The fact that NMDA antagonists abolish the aftereffects of tDCS provides evidence that tDCS and LTP share common features (152), and suggests that the induction and maintenance of changes in excitability and neuroplasticity after this intervention are all mediated by the glutamatergic system (153). Consequently, anodal tDCS could induce LTP through increased presynaptic activity and postsynaptic depolarization. On the other hand, cathodal stimulation may be able to contribute to the development of LTD-like phenomena, and also help to promote neuroplastic changes.

NBS AS A THERAPEUTIC TOOL IN TBI

TBI may lead to a variety of neurobehavioral consequences that may appear in the first days after the insult and continue to show in the following months (2). These may include seizures (154,155), headache (156), movement disorders, motor impairment, language and visual deficits, sleep (157), memory (158,159), and attention disorders as well as concentration impairment (160). The course of recovery is complex and the time needed to recover from these sequelae may last months to years (2), sometimes without achieving a complete return to baseline function. The different mechanisms that underlie the complications of TBI create a window for specific interventions at different time periods.

Approaches for targeting the consequences of TBI fall within two major categories: first, those aimed at limiting the extent of the initial injury in order to minimize further neurological deficits; and second, strategies that promote reorganization of neural networks, allowing for relearning of functions that have already been affected or lost (161). One feasible therapeutic strategy in this setting consists of modifying cortical excitability for an adequate period of time, which may in turn: 1) help counteract the acute inflammatory phenomena of TBI; 2) modulate adaptive organization allowing for the formation of functionally appropriate neural connections; and 3) enhance behavioral recovery.

In this context, we will now discuss the theoretical basis for the therapeutic use of NBS after TBI. However, it should be noted that due to the scarce number of publications addressing this issue, as well as due to the incomplete understanding of the mechanisms underlying TBI, the following recommendations should only be used to encourage further research in this field. The broad clinical spectrum, the diffuse nature of the lesions, and the difficulty assessing the degree of anatomical and functional damage to the brain following TBI make it hard to predict the functional outcomes of NBS. The study of such interventions in animal models will be crucial in order to explore the most appropriate stimulation protocols in each setting, allowing them to be translated into clinical trials in the near future.

Acute Injury

As we have discussed, the processes responsible for recovery and relearning after TBI are time-dependent. Therefore, different pathophysiological mechanisms will predominate at different stages, which have to be adequately targeted by therapeutic interventions. Hence, the techniques and parameters used must be carefully tailored in order to address the underlying mechanisms of brain damage.

In the acute setting, one suitable approach would be the inhibition of excessive glutamatergic activity through the use of interventions that have a suppressive effect on cortical excitability. In this regard, cathodal tDCS, low-frequency rTMS, and cTBS may prove to be useful. In fact, there is direct evidence demonstrating the modulatory effects of daily low-frequency rTMS sessions on the glutamatergic and GABAergic systems in murine models (162).

The use of NBS could also help to enhance the resolution of the inflammatory processes and decrease the extent of brain damage occurring acutely after TBI, as suggested by animal studies where rTMS was able to revert biomarkers indicative of oxidative stress and apoptosis following brain injury (163). However, given the relatively focal nature of most NBS techniques, their efficacy in the setting of the widespread phenomena of TBI might be limited. In order to clarify this, it is necessary to further explore the use of this intervention in animal models. Furthermore, it needs to be underscored that as rTMS leads initially to a disruption of activity and potentially to an increase in activation of neural elements, even the rTMS protocols associated with a decrease of cortical excitability might be deleterious. In this context tDCS would be a more appropriate tool as this technique involves subthreshold stimulation.

Despite the potentially limited role of NBS in reducing the acute inflammatory processes, it may prove useful in initially modulating plastic changes as to avoid maladaptive consequences. Animal studies have demonstrated prominent axonal sprouting and synaptogenesis just days after brain injury (164), providing a window for intervention. For example, cTBS targeting the uninjured hemisphere and iTBS of the lesioned side have both shown to increase cortical excitability in the injured hemisphere in acute stroke patients (165), leading to a favorable therapeutic effect.

Subacute and Chronic Period

Induction of long-lasting effects on neural tissue requires previous changes in synaptic strength and ultimately anatomical modifications, as previously discussed. Given the fact that long-term modifications in synaptic strength via LTP/LTD may lead to such anatomical changes, modulation of the former via NBS represents a reasonable therapeutic intervention (166) in the setting of TBI.

As we mentioned in a previous section, one of the changes that may be seen in the subacute period after TBI is an excessive GABA-mediated inhibition, which can persistently silence certain neural networks (54) and affect LTP/LTD (79). These defective plasticity mechanisms can be associated with the development of cognitive derangements (involving attention [73], memory and learning [74,75]), as well as predisposing to motor deficits (79).

Pharmacological reversal of excessive GABAergic inhibition has already been shown to facilitate recovery of motor function in stroke models (167). Thus, interventions such as high-frequency rTMS or anodal tDCS may potentially be used to increase cortical excitability and counteract GABAergic inhibition and excessive LTD. Even though these paradigms have not yet been tested in TBI survivors, high-frequency rTMS delivered to the parietal and prefrontal cortices has proven to increase neural efficiency related to working memory in healthy subjects (168–170). Moreover, anodal tDCS to the left dorsolateral prefrontal cortex (DLPFC) may improve certain aspects of working memory performance in the same population (171,172), as well as in stroke patients (173).

Given the important role of the DLPFC, particularly in the right hemisphere, in modulating attention and memory as well as due to its strong connections with the reticular formation, a study performed a protocol of patterned rTMS to the right DLPFC, using 30 sessions of paired stimuli interleaved by periods of no stimulation in a man in a vegetative state following severe TBI (174). Neurobehavioral assessments and evoked potentials showed positive findings, suggesting a beneficial effect on neural conduction. However, this patient was within the window of spontaneous recovery. Therefore, the intervention may not be responsible for this improvement, and further evidence is needed to support the potential of rTMS to promote recovery in persons with disordered consciousness due to severe TBI.

Although the use of interventions with an overall excitatory effect may seem most appropriate during the subacute period, in some circumstances the use of inhibitory NBS interventions may be desirable, as is the case for counteracting excess LTP at glutamatergic synapses, which leads to the development of LPTS (70).

Modulation of interhemispheric balance of activity across the left and right DLPFC using combinations of NBS parameters has shown clinical significance in the treatment of depression as well as in the modification of risk-taking behaviors, two common consequences of TBI (175–177). Although most evidence comes from trials that included subjects without structural brain abnormalities, modulation of DLPFC activity has also been reported to elicit antidepressant effects in a stroke patient (178), thereby providing encouraging results for its use in patients with structural lesions. Also in stroke patients, restoration of interhemispheric equilibrium by targeting other areas, such as low-frequency rTMS to the unaffected parietal cortex, has proved effective for attention deficits like unilateral neglect (179,180).

Motor learning has also proved to be amenable to modulation by NBS, thereby favoring adaptive plastic changes. In broad terms, approaches that enhance excitability of the M1 contralateral to the training hand tend to result in an improvement of motor learning in healthy subjects (181). This effect has been observed with high-frequency rTMS (112,182), as well as with anodal tDCS (183,184), while cathodal tDCS failed to induce an improvement (185). Interestingly, low-frequency rTMS applied ipsilateral to the training hand can increase motor cortical excitability of the opposite M1 (186,187). These excitability changes may result in different outcomes depending on the complexity of the task performed (181,188), sometimes showing no improvement in performance (189).

Moreover, NBS has demonstrated its ability to induce plastic changes in disease-specific settings, such as in stroke, resulting in favorable effects. In chronic stroke patients, low-frequency rTMS and cathodal tDCS to the contralesional hemisphere are able to increase motor cortex excitability in the side of the lesion (143,190) by decreasing transcallosal inhibition from the uninjured hemisphere (191). Likewise, excitatory stimulation of the lesioned side using iTBS or anodal tDCS has shown similar results in the setting of chronic stroke (192,193). Given these findings, the therapeutic use of NBS could potentially be translated to TBI.

As previously mentioned, immediate early genes such as *c-fos* are linked to neuronal activation. Significant increases in their expression occur rapidly after strong stimuli such as epilepsy or ischemia, increasing within 30 min and returning to baseline levels within three to six hours (126,194). Therefore, if the effects of rTMS are dependent on gene expression, the time window in relation to events that determine gene expression may be critical. However, it is still unknown whether this could determine a window of opportunity for the use of NBS approaches in TBI.

Coupling NBS and Physical Therapy

Motor training involving skill learning (as opposed to simple exercises) induces plastic changes in the CNS via increased synaptogenesis, LTP/LTD-like mechanisms, and reorganization in the thalamus and the M1 motor maps (62,195,196). Changes in motor cortical representations induced by constraint-induced movement therapy (CIMT) in chronic stroke patients (65) are an example of the benefits of such interventions on motor recovery. In TBI patients, physical exercise can improve motor and cognitive outcomes (66), likely due to similar phenomena.

Given that NBS and motor learning seem to share similar mechanisms for inducing neuroplasticity, their individual therapeutic effects may be enhanced by their combination. While NBS delivered prior to a given task may prime neuronal networks in the cortex, stimulation delivered simultaneously with the task may recruit specific sets of synapses involved with its performance. NBS may even be administered after the intervention and facilitate consolidation of newly acquired patterns (39). Such approaches have the benefit of favoring plasticity in certain neuronal networks, therefore maximizing relearning mechanisms while decreasing the likelihood of developing maladaptive changes.

Animal studies and clinical trials focused on the use of these interventions after TBI are scarce, and most of our current knowledge derives from those addressing stroke. After ischemic stroke, animal studies have shown that electrical cortical stimulation combined with rehabilitative training induces structural neuroplasticity, improving functional outcomes (197).

These observations have been translated to humans in a small number of trials involving subacute and chronic stroke, where physical therapy was coupled with high-frequency rTMS of the injured hemisphere (198) or low-frequency stimulation of the contralesional side (199), showing clinically significant improvements over sham stimulation. Similarly, CIMT coupled with active tDCS, where cathodal tDCS of the intact M1 and anodal stimulation of the affected M1 were provided simultaneously, showed a significant reduction in transcallosal inhibition from the undamaged to the affected hemisphere in chronic stroke patients and provided greater gains in motor function as compared with CIMT coupled with sham stimulation (200). However, a recent study where subacute stroke patients with severe upper limb paresis were randomized to receive either anodal tDCS of the affected hemisphere, cathodal tDCS of the uninjured side, or sham stimulation combined with robotic assistive device training, showed similar degrees of improvement in motor function in all groups, suggesting that the anatomic pattern, the severity of paresis, and the type of physical therapy may all influence the success of treatment (201).

Optimal protocols for interventions coupling NBS and physical therapy are yet to be defined. Factors such as the technique of NBS used and its parameters, the target area, the type of physical training performed, and its timing in relation to stimulation (151) can all influence the therapeutic outcomes, and will have to be individually tailored based on considerations such as the time elapsed after brain injury and the specific anatomic and neurophysiologic derangements of each patient. Therefore, the need for further research in the field is emphasized.

SAFETY CONSIDERATIONS

Due to specific characteristics of this group of patients, some particular safety considerations regarding the use of NBS in TBI should be noted. First, given their high incidence of LPTS, one of the potential issues that may arise relates to the likelihood of triggering seizures associated with the stimulation. The other involves the effects of NBS in individuals with skull defects and skull plates, two common findings among TBI survivors.

A large number of subjects and patients have undergone rTMS since the publication of the 1998 safety guidelines (202) with very few seizure-related events reported (108). This provides support for the safety of this intervention among different populations when such guidelines are followed. In fact, the crude per-subject risk to develop a seizure among healthy subjects undergoing high-frequency rTMS has been estimated to be <1%, with a 1.4% rate for epileptic patients. Cases of status epilepticus have never been described in this setting (108,203). To date, tDCS has not been reported to induce seizures in animals (204) nor humans (205), and this possibility seems to be relatively unlikely (136). However, few data exist specifically addressing the safety of rTMS and tDCS in TBI survivors. Given the underlying structural damage and the increased propensity to seizures in this population, further studies providing evidence on safety parameters are necessary. One might, however, be clinically cautious in those who have had craniectomy and subsequent cranioplasty.

Skull defects are capable of modifying the intensity and distribution of electrical currents delivered by tDCS. Brain modeling studies have reported that, while small defects located midway between the electrodes do not alter current distribution or magnitude significantly, large increases in current intensity can be seen when one of the electrodes overlies a moderate-sized defect (206). In the case of titanium plates, current is shunted away and stimulates brain tissue underlying the edges of the plate (206). These findings demonstrate that the main issue in patients with skull defects or skull plates relates to changes in current distribution. Therefore, in order to find optimal approaches for such patients, individualized models are needed.

Evidence from *ex vivo* studies demonstrates that displacement and heating of titanium plates during low-frequency rTMS are minimal and unlikely to cause damage to the surrounding tissue (207). Based on these data, this type of stimulation was used for the control of intractable seizures in a series of six patients with titanium skull plates (208). At least four daily sessions were administered, all of them delivered over the craniotomy area and the seizure focus. Each session consisted of 1800 pulses at 1 Hz, with a stimulation intensity ranging from 55 to 100% machine output. None of the patients experienced any adverse effects. Seizure frequency improved in four of them, while remaining unchanged in the other two.

As of today, the presence of metallic devices in close proximity to the discharging coil, such as cochlear implants, medication pumps, or deep brain stimulation systems, remains the only absolute contraindication to TMS (108). In fact, there is evidence from *ex vivo* studies suggesting that TMS-induced voltage might affect deep brain stimulation leads and cause tissue damage (209). Although this technique may be safe in TBI patients with skull plates, the wide diversity of brain lesions that can be found in such individuals mandates further safety studies before large-scale clinical studies can be undertaken.

CONCLUDING REMARKS

The complex pathophysiology underlying TBI, together with the diversity of phenomena that predominate at different time points and the unique characteristics of each patient, make it necessary to develop individualized therapeutic approaches. They would help enhance recovery and decrease the burden of disabling sequelae after the injury.

Plasticity, an innate property of the brain, is responsible for the changes occurring not only in the lesioned site but also in distant areas, and takes place in the subacute and chronic periods after the initial insult. Although these changes can be responsible for inducing functional recovery, they might also lead to additional injury and negative outcomes. It is therefore critical to identify potential adaptive and maladaptive plastic changes in order to enhance the former while suppressing the latter.

Over the past two decades, a large number of studies have been published demonstrating the remarkable ability of two NBS methods, rTMS and tDCS, to induce neuroplastic changes. In addition to their inherent therapeutic potential, they may also be coupled with other interventions such as physical or behavioral therapy, therefore targeting specific neural networks and potentiating each other's effects. However, further research specifically focused on TBI is needed in order to understand the mechanistic interaction between the aforementioned techniques, as well as to establish their safety and define optimal stimulation parameters.

Acknowledgements

The authors wish to thank Ms. Laura Sherman for her editorial support during preparation of this manuscript, and the reviewers for their insightful feedback and comments.

Authorship Statements

Drs. Villamar and Santos Portilla conducted a review of the literature and prepared the manuscript, with important intellectual input provided by Drs. Zafonte and Fregni. All authors approved the final manuscript.

How to Cite this Article:

Villamar M.F., Santos Portilla A., Fregni F., Zafonte R. 2012. Noninvasive Brain Stimulation to Modulate Neuroplasticity in Traumatic Brain Injury.
Neuromodulation 2012; 15: 326–338

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COMMENTS

In this paper, the authors provide a glimpse into the largely uncharted territory of non-invasive brain stimulation (NBS) as a treatment for individuals who sustain traumatic brain injury. At present, there is no definitive evidence that any intervention can favorably alter the course of recovery from TBI. The authors provide a clear rationale for the use of NBS techniques and discuss the challenges and potential benefits of this emerging technology.

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The article by Villamar et al. reviews the potential therapeutic role of noninvasive brain stimulation (NBS) in traumatic brain injury (TBI) recovery. They begin by providing a concise overview of the pathophysiology of TBI with particular emphasis on neuroplasticity. The role of long-term potentiation (LTP) and long-tern depression (LTD) in the mechanism of neuroplasticity is described. Furthermore, the consequences of both adaptive and maladaptive neuroplasticity in TBI recovery are underscored. Next, the neurophysiological effects of NBS are described in detail and it is proposed that NBS may modulate neuroplasticity via induction of LTP/LTD. With this background, they postulate that NBS may facilitate TBI recovery via modulation of neuroplasticity.

Considering the complexity of both TBI and NBS, the authors are to be congratulated for their succinct and systematic review. Appropriately, they highlight some of the limitations of NBS in TBI. In particular, due to the diffuse anatomical and functional nature of TBI, targeting applicable neuro-systems with NBS techniques will be challenging. However, the authors advocate targeting areas with known anatomical-functional correlates to ameliorate sub-symptoms within TBI. Furthermore, selection of optimal NBS parameters, timing of administration, and safety considerations (such as induction of seizures) in TBI are addressed. The manuscript is a hypothesis-driven and provides the scientific foundation to undertake future preliminary research in the therapeutic potential of NBS in TBI recovery.

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Non-invasive brain stimulation (NBS) has both diagnostic and therapeutic potential in traumatic brain injury (TBI). A large body of NBS literature exists spanning several decades in humans and animal models, both in health and disease, yet TBI has been seldom studied. The few existing studies have demonstrated that NBS is useful to understand TBI pathophysiology, and have raised the possibility for NBS as a treatment adjunct. The review paper titled 'Noninvasive brain stimulation to modulate neuroplasticity in traumatic brain injury' by Villamar et al, provides a timely and important discussion on a potentially useful application of NBS, based on a synthesis of available data. In addition, the paper proposes theoretical benefits and risks according to known pathophysiology.

A variety of single and paired-pulse transcranial magnetic stimulation (TMS) techniques have been developed to painlessly and safely probe intracortical, corticocortical (intrahemispheric as well as interhemispheric) and corticospinal networks in humans. TMS has been used to assay local and network excitability of the brain following stroke, representing the sum of complex and interacting pathologic processes, as well as adaptive physiological processes. The net change in excitability identified by TMS relates well to dysfunction and thus sets the stage for excitability modulating protocols to improve function. These therapeutic protocols include TMS delivered repetitively (rTMS, repeated pulses causing synaptic activity in cortex) and transcranial direct current stimulation (tDCS, a low-level continuous unidirectional current reaching the cortex). Here, cortical excitability is modified—outlasting the stimulation period for several tens of minutes, and thus has the potential to positively influence altered brain excitability. When acting to restore cortical excitability associated with neurologic dysfunction, NBS has been shown to have clinical benefit in several classes of neurologic conditions (both acute damage and degenerative disease), suggesting a potential benefit for TBI. However, further controlled studies are needed with clearly defined and hypothesis-driven interventions, in well-characterized patients. Studies in animal models will be particularly appealing to systematically explore the most appropriate stimulation protocols with different lesion types and temporal recovery profile.

The authors suggest that therapeutic approaches might fall within two categories; (1) those aimed at limiting the extent of the initial injury in order to minimize further neurological deficits; and (2) strategies that promote reorganization of neural networks. Each of these could be useful in maximizing function following acute traumatic injury.

Single or paired-pulse investigative TMS is generally not considered a major risk in the days to weeks post brain lesion. This may not be true for protocols with therapeutic intent (designed to have a lasting effect), which may pose a safety risk depending on the injury physiology and stimulation characteristics. For example, promoting increased excitability may seem most appropriate during the sub-acute period, however in some circumstances the use of inhibitory NBS interventions may be desirable, such as for counteracting the excessive glutamatergic activity thought to underlie development of seizures. They suggest that even inhibitory rTMS protocols might increase activation of neural elements, having a deleterious effect. In this case tDCS might be warranted as a more benign alternative, albeit differently acting. Other safety issues discussed include the effects of skull defects or plates that modify the intensity and distribution of electrical currents.

The authors touch on the interesting areas for future study in TBI including: augment learning and memory, recovery from disordered consciousness, and using NBS in combination with other therapies, such as physical therapies. A recommendation is put forward for further research using NBS in TBI patients, to give specific attention to the type of stimulation (mode, parameters) according to the goal of the physiological interaction, and thus elucidate possible time-windows for specific interventions.

Villamar and colleagues provide valuable insight for TBI clinicians and NBS researchers on safety and efficacy considerations that may shape future studies as the field of NBS in TBI unfolds. The heterogeneity of traumatic brain injuries and the complex pathophysiology that varies with time since injury, make it unlikely that any specific NBS protocol will be beneficial for all TBI patients. If individualized treatments are developed targeting known pathophysiology, we stand the best chance of enhancing recovery and decreasing the magnitude of disabling sequelae after the injury.

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Comments not included in the Early View version of this paper.

