Neuromodulation in rehabilitation after traumatic brain injury

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Abstract

Standard rehabilitation approaches that target functional recovery following focal brain damage have limited utility in severe traumatic brain injury.The characteristic dual nature of brain injury, which combines diffuse and focal damage, makes anatomo-clinical correlations exceptionally challenging and limits the success of conventional rehabilitation. Neuromodulation approach represents the class of therapies thatcan help restore function or relieve symptoms that have a neurological basis through the use of devices to stimulate nerves – with pharmaceutical agents, electrical signals, or other forms of energy – by modulating abnormal neural pathway behaviour caused by the disease process. Different neuromodulation methods are described in this paper.

Keywords: traumatic brain injury, neuromodulation, deep brain stimulation, non-invasive brain stimulation

Mogućnosti neuromodulacije u rehabilitaciji nakon ozljede mozga

Sažetak

Standardni rehabilitacijski pristup funkcijskom oporavku nakon žarišne ozljede mozga je ograničene koristi kod teške traumatske ozljede mozga. Karakteristično dvojaka priroda ozljede mozga, koja kombinira difuzno i fokalno oštećenje, stvara iznimno zahtjevan anatomsko-klinički suodnos i

ograničava uspješnost konvencionalne rehabilitacije. Neuromodulacijski pristup predstavlja vrstu terapije kojom se pomaže u obnavljanju funkcije ili ublaženju neuroloških simptoma, korištenjem uređaja za stimulaciju živčanog tkiva – lijekovima, električnim signalima ili drugim oblicima energije – modulirajući abnormalno djelovanje neuralnih putova, nastalo u procesu bolesti. U radu su opisane različite neuromodulacijske metode.

Ključne riječi: traumatska ozljeda mozga, neuromodulacija, stimulacija dubokih moždanih jezgra, neinvazivna stimulacija mozga

Introduction

Traumatic brain injury (TBI) is a nondegenerative and noncongenital insult to the brain from an external mechanical force, possibly leading to permanent or temporary impairment of cognitive, physical, and psychosocial functions, with an associated diminished or altered state of consciousness (1). Traumatic brain injury occurs across the lifespan, but is most common among active and otherwise healthy teenagers and young adults (2). The consequences are staggering and include a broad spectrum of cognitive, behavioral, and sensorimotor disabilities which dramatically reduce the quality of life, necessitate long-term care and create a worldwide public health problem (3).

Standard rehabilitation approaches that target functional recovery following focal brain damage have limited utility in severe TBI. The characteristic dual nature of injury, which combines diffuse and focal damage, makes anatomo-clinical correlations exceptionally challenging and limits the success of conventional rehabilitation (4).

The International Neuromodulation Society (INS) defines therapeutic neuromodulation as:

"the alteration of nerve activity through the delivery of electrical stimulation or chemical agents to targeted sites of the body" (5).

In appropriate patients, this growing class of therapies which is in common use since the 1980s, can help restore function or relieve symptoms that have a neurological basis. Neuromodulation devices stimulate nerves – with pharmaceutical agents, electrical signals, or other forms of energy – by modulating abnormal neural pathway behaviour caused by the disease process (6). Neuromodulation presents any method used with non-invasive or invasive approach, aimed to influence on adaptation, plasticity, structural change of

central (CNS) or peripheral nerve sistem (PNS).Variety of methods are used in different stages after neuronal injury, with different goals of therapies, that work on level of structure, activity and participation.

Deep brain stimulation in therapy of disorders of consciousness after traumatic brain injury

Some patients after anoxic or traumatic brain injury demonstrate preserved normal circadian rhythm, but absence of self-awareness and absent response from environment (7 - 9). They remain with completelly or partially preserved autonomic functions of hypothalamus and brainstem, which is due to local (billateral) injury of thalamic and subthalamic – as well rostro-caudal regions. It is well known that neurons of those structures play role in maintaining and regulation of sleep– wake mechanism and awareness. Nevertheless neurons in centro-thalamic region are extremelly sensitive to mechanism of diffuse axonal injury and hypoxic / anoxic injury

Current use of deep brain stimulation is evidently in use in neurology, psychiatry and neurosurgery. Most succesfull use is described in treatment of extrapiramidal movement disorders and obsesive-compulsive disorders. Unconfirmed success of therapy is reported in treatment of minimal conscious state and unresponsive wakefullness syndrome after TBI, where it is still „off-label therapy".

Implantation of deep brain stimulation is a neurosurgical procedure under 3D stereotactic guidance with implantation of two wired electrodes with four stimulation electrodes each in the region of subthalamic nuclei. Wired electrodes are subcutaneously connected with the stimulator placed infraclaviculary (10).

Regarding the data from existing literature, DBS method seems to be far from reccomended for general use in patients in UWS or / and MCS after TBI. Even when clinical status in different patients seem to be similar, their basal brain activity is un-doubtfully different.

Prior to consideration about the DBS, assesment of cortico-thalamic and cortico – mesencephalic connectivity with neurophysiology diagnostic and neuro imaging is reccomended (SSEP, ABR, EEG, PET, f-MRI). We are still not aware of any reliable prognostic factors that could predict the outcome with DBS therapy.

Table 1: Literature overview of the DBS trials in states of disorders of consciousness after TBI

Trial	Method	Results
Hassler et al. (11)	19 days of stimulation of R pallidum and L latero-polar thalamic nuclei in male patient 5 months after TBI	Raised wakefulness, spontaneous left limbs movement, turning to objects and subjects as well beginning of non-functional vocalisation. Additionally: EEG changes in term of decreased delta activity L temporal, asimetry reduction and partial restorement of alpha rhytm Majority of effects diminished soon after the stimulation was switched off
Sturm et al. (12)	Stimulation of polar reticular subtalamic nuclei in male patient after stroke in mesencephalic region – with subsequent condition described as "intermediate between coma and apalic syndrome".	More reliable folowing to comands, longer awakeness periods, improved oral communication, more efficient oral intake. Patient died two months after permanent DBS system implantation
Tsubokawa et al. (13)	Eight patients in UWS of at least six months duration. Three patients after TBI, two after anoxic injury and three after spontaneous CVI (ICH and / or SAH). System for permanent stimulation of RF and non-specific subthalamic nuclei was implanted in all patients.	Six months after DBS: Two patients after CVI regained effective oral communication, following of comands, proper emotional response and oral intake. One patient after CVI showed partial and inconsistent following of commands, full object eye-tracking and spontaneous limb movement. In five patients (including all after TBI), there was no improvement in neurological condition or level of awareness.
Schiff et al. (14)	Implantation of permanent DBS of subthalamic pf nuclei in a patient six months after TBI Primary parameter: „JFK – Coma recovery scale – revised" during double blind "on" and "off" stimulation for period of six months. Secondary parameter: object naming, following motorical commands, oral intake.	Significant correlation between „on" period and qualitative changes in patient`s behaviour – prolonged eye opening periods, following commands, trying of functional use of objects and verbalisation

Trial	Method	Results
Yamamoto et al. (15)	Study group: 21 patients in UWS (AAN criteria), four to eight months after TBI or stroke (9 stroke, 9 TBI, 3 anoxic BI) Average age 44 yrs (range 19-72) Control group consisted of 86 patients in UWS (AAN criteria) of various aetiologies Methods: In two patients DBS electrodes were implanted in the region of mesencephalo-RF and 19 patients in the subthalamic CM-pf nuclei of dominant haemisphere	All 86 patients in control group remained in UWS. 21/21 patients in study group showed early arousal immediately after switching the system „on" in term of: eye opening with dilated pupils, raise of heart frequency and arterial pressure as well mouth opening. 8/21 patients emerged from UWS, and could communicate with some speech or other responses, but needed some assistance with their everyday life in bed. Even after long-term rehabilitation, their state of being bedridden remained unchanged in seven of these eight cases. The other case became able to live in a wheelchair. The remaining 13/21 cases were unable to communicate at all and failed to emerge from the UWS.
Chudy et al. (16)	Study group: 7 patients in UWS and 4 patients in MCS. The stimulation sites in all patients were centromedian-parafascicular nucleus complex.Patients were stimulated during the day for 30 min every three hours with different intensity and frequency parameters	Two patients in MCS regained consciousness, independent walking without help, become able to speak, showing impressive speech comprehension, but needed some assistance with their everyday life. Other nine patients remained bedridden and their status remained unchanged but showed improvement in Rappaport Coma/Near coma scale.

Non invasive brain stimulation (NIBS)

Different forms of noninvasive brain stimulation techniques are potentially promising for diagnostic and therapeutic use, particularly in modulating processes of cortical reorganization and hence to enable functional restoration after TBI. Available evidence is sparse, but the present understanding about the pathophysiology of post-traumatic brain damage and the mechanisms of action of various noninvasive brain stimulation methods justifies exploration of new interventions that may forestall the functional impact of TBI. Non-invasive brain stimulation are techniquestailored to modulate individual plastic changes associatedwith neurological diseases might enhance clinical benefits and minimize adverse effects. In this review,we discuss the use of

two noninvasive brain stimulation techniques: repetitive transcranial magnetic stimulation (r-TMS) andtranscranial direct currentstimulation (tDCS), which are aimed to modulate activity in the targeted cortex orin a dysfunctional network, to restore an adaptive equilibrium in a disrupted network for best behavioral outcome, and to suppress plastic changesforfunctional advantage. Other, but less evidence based medicine supported methods of NIBS are Transcranial near- infrared stimulation (t-NIRS) and therapy with Low level laser therapy (LLLT).

Electromagnetic brain stimulation was first investigated in the late 19th century (17). It was not until the mid-1980s, however, that Barker andcolleagues introduced transcranial magnetic stimulation (18), having solved the technical challenges involved in bridging the scalp and skull with a magnetic field pulse of sufficient strength and rapid enough change over time. Repetative TMS is a neurostimulatory and neuromodulatory application, whereas tDCS is a purely neuromodulatory intervention. TMS uses the principle of electromagnetic induction to focus induced currents in the brain (19). Single pulses of current can be of sufficient magnitude to depolarize neuronstransiently, but when these currents are applied repetitively—an approach known as rTMS—they can modulate cortical excitability, decreasing or increasing it - depending on the parameters of stimulation, beyond the duration of the train of stimulation (20).

Repetitive transcranial magnetic stimulation (rTMS)

Repetitive trains of magnet stimulation applied to targeted brain regions can suppress or facilitate cortical processes, depending upon stimulation parameters. In most instances, continuous low frequency (≤1Hz) rTMS decreases the excitability of the underlying cortex while bursts of intermittent high frequency (≥5Hz) rTMS enhance it (21).

Induction of „modulation" across cortico-subcortical and cortico-cortical networks by means of trans-synaptic spread, results in distant but specific changes in brain activity along functional networks (22, 23).

Transcranial direct current stimulation (t-DCS):

With t-DCS low-level current flows from the positive electrode - anode, to the negative electrode – cathode.It increases the regional activity by the anode, while decreasing the activity underneath the cathode. The process may be referred to as cathodal or anodal tDCS depending on the electrode placed over the region being modulated.

Non invasive brain stimulation
– potential therapeutical applications in brain injury rehabilitation

Available evidence of the use of NIBS is sparse, but the present understanding about the pathophysiology of post-traumatic brain damage and the mechanisms of action of various noninvasive brain stimulation methods justifies exploration of new interventions that may forestall the functional impact of TBI.

Hand motor dysfunction following brain damage can be improved via direct enhancement of the perilesional activity in the affected primary motor cortex or the premotor cortex in the precentral gyrus using high frequency rTMS or anodal TDCS. The alternative approach is to decrease the excessive activation of unaffected motor cortex using low frequency rTMS or cathodal TDCS to modify the imbalance in transcallosal motor activity, which results from the loss of inhibitory projections from the damaged area and decreased use of the affected hand. Behavioral gains from rTMS/tDCS protocols may be maximized when brain stimulation is coupled with carefully designed occupational/physical therapy. It has been reported that tDCS is possible to enhance the effects of upper extremity robotic motor training in TBI patients with no skull defects (25 – 30).

Alternativelly enhancing right or left dorsolateral prefrontal cortex may prove effective for improving working memory and/or executive dysfunctions in TBI and stroke patients (31 -35). High frequency rTMS (5Hz) to primary motor cortex increases cortical excitability as well as the excitability of spinal motor neurons to Ia afferent inhibitory input, resulting in improvements in clinical spasticity of different CNS aetiologies, predominantly after spinal cord injury, multiple sclerosis and stroke. Accordingly to this data, TBI related spasticity may also benefit from this approach (36 - 38).

For improving gait after TBI, repeated sessions of rTMS have been proposed as a preventive treatment for limb disuse following brain injury.Stimulating the lower limb motor cortex region using high frequency rTMS may enhance gait rehabilitation in combination with gait therapy following TBI (39).Recently, the study of Madhavan et al. reported, that tDCS has been succesfull to enhance fine motor control of the paretic ankle and improve hemiparetic gait patterns (40). In this context, we might envision and understand that coupling brain stimulation approaches with robot-assisted gait training is the choise in the future.

Precautions for non-invasive stimulation in TBI patients:

Although TMS-induced seizures are self-limited and do not tend to recur, this risk could bring practical implications in a seizure-prone population, especially in patients with moderate to severe TBI. In the region of fractures and craniectomies of skull, the conductance and magnitude of the electric current being induced in cortical regions may be different. A recent tDCS modeling study highlighted that skull injuries significantly change the distribution of the current induced (41).

Conclusion

Neuromodulation as brain stimulation techniques harbor the promise of therapeutic utility, particularly to guide processes of cortical reorganization and enable functional restoration in TBI. Available evidence is sparse, but the present understanding about the pathophysiology of post-traumatic brain damage and the mechanisms of action of various neuromodulation methods justifies exploration of new interventions that may forestall the functional impact of TBI. Future lines of safety research and well-designed clinical trials in TBI are warranted to ascertain the capability of neuromodulation to promote recovery and minimize disability.

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