International
Journal of Neurorehabilitation

Yin and Slavin, Int J Neurorehabilitation Eng 2015, 2:1
DOI: 10.4172/2376-0281.1000151

Review Article Open Access

A Review of Neuromodulation in the Neurorehabilitation

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Abstract

For many years, invasive neuromodulation has been used in neurorehabilitation, mainly in treatment of movement disorders and various psychiatric conditions. Use of deep brain stimulation and other implanted electrical stimulators is being explored in other conditions, such as stroke, traumatic brain injury and spinal cord injury. This paper provides a review of the possible role of Neuromodulation in neurorehabilitation and highlights some of its applications for patients with various neurological conditions. Since most of the existing findings are based on animal studies, preliminary data, case reports and poor-controlled studies, further investigations including research and clinical trials are necessary to increase the applications of neurostimulation in the field of neurorehabilitation.

Keywords: Neuromodulation; Neurorehabilitation; Stroke; Traumatic brain injury; Spinal cord injury; Epilepsy

Introduction

Neurorehabilitation is a complicated medical process; its goal is to help patients to recover from injuries or abnormalities in the Central Nervous System [CNS], and to compensate for functional deficits if possible. Neurorehabilitation offers a series of therapies, including physical, occupational, speech, psychological therapies and so on with a focus on improving the patients' health. The field of neurorehabilitation is relatively new, and some cutting edge therapies, including neuromodulation, that may be potentially beneficial topatients withCNS injuries or other disorders, are currently being investigated. The brain operates through signal processing within neural networks [1,2]. The advances in the understanding of brain circuitry, together with the development of neurostimulation technologies have prompted us to explore the potential of electrical stimulation of the nervous system to promote functional recovery in patients with CNS disorders through activation of neuronal structures and alteration or inhibition of pathological pattern of neuronal activity. Over the past several decades, electrical neurostimulation of deep cerebral structures hasbeen proven a clinically effective therapy in the treatment of movement disorders with a remarkable safety profile [3,4]. Neurostimulation approach in patients with movement disorders has shed light on the possibility of correcting abnormal networks. The neurostimulation technology has been also applied to psychiatric disorders and chronic pain. The objective of this review is to explore the use of neurostimulation in treatment of stroke, traumatic brain injury, spinal cord injury and epilepsy. A thorough search of the literature was conducted in preparation of this review.

Neuromodulation for Brain Injury Caused By Stroke And Trauma

The incidence rate of Traumatic Brain Injury [TBI] is 558 per 100,000 people [5], and that of stroke is 67-70 per 100,000 [6]. Brain injury caused bytrauma and stroke remains a significant public health problem with devastating consequences, and is a leading cause of disability and death in the world. New therapeutic strategies are needed for treatment of neurological functional deficits followingtraumatic or ischemic brain injury. Neuromodulation approach has been employed to treat stroke and TBI in animal models [7-11] and clinical studies [12-14], with preliminary data showing that neurostimulation may lead to functional improvement in the setting of brain injuries. A few animal studies in non-human primates have observed thatcortical stimulationenhances functional recovery and cortical plasticity after neural injury induced by stroke [7-9]. Cortical stimulation during rehabilitation constantly improves motor function in ratsfollowing motor cortex injury [10-11].

Motor Cortex Stimulation

A small randomized clinical trial [n=24] found that Motor Cortex Stimulation [MCS] lead to motor and functional improvements [difference of Fugl-Meyer motor scores in estimated means = 3.8, p = .042] in stroke patients, and the effect was maintained during 6-month follow-up period [12]. In a multicenter safety and efficacy study, MCSresulted in improvementsin upper-extremity function during 3 weeks or 6 weeks [13, 14] of the rehabilitation. MCS for 3 weeks during stroke rehabilitation also led to improvement inpincer movement of the previously paretic hand in a hemi-paretic stroke patient [13]. Moreover, MCS resulted in 40%–50% improvement of pain caused by brain injury in approximately 50% of patients [15]. Table 1 shows clinical data of different studies. However, the limitations of these studies on MCS include small sample size and short follow up. Overall, the long-term effect of MCS is uncertain, as no study has explored that.The mechanismsby which such improvements occur are not clear.The improvements may be a result of increased dendritic plasticity and decreased astrogliosis in the perilesional cortex and the contralesional anterior horn of the cervical spinal cord as shown by an immunohistochemical study[16]. Another study indicated motor cortex stimulation after pyramidotomy could increase the length of axons from theprimary motor cortex to the spinal cord, as well as to the red nucleus and cuneate nucleus [17]. Increased axonal outgrowthwith stimulation may be due to a release of neurotrophins, such as brain-derived neurotrophic factor, and increased motor activityof the subjects [7].

Deep Brain Stimulation

DBS has been explored on patients with Persistent Vegetative State [PVS] or minimally conscious state [MinCS] following traumatic brain injury.In the late 1960-s, Hassler et al described the concept of using

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Received December 09, 2014; **Accepted** February 28, 2015; **Published** March 06, 2015

Citation: Yin D, Slavin KV (2015) A Review of Neuromodulation in the Neurorehabilitation. Int J Neurorehabilitation 2: 151. doi:10.4172/2376-0281.1000151

Clinical data of different studies									
Type of Neurostimulation	**Authors**	**Ref #**	**Types of Study**	**Sample Size**	**Study Population**	**Groups**	**Outcome Measures**	**Results and Outcome Data**	**Follow up**
Mortor Cortex Stimulation	Huang et al	12	Small phase II pilot study	24	Ischemic stroke patients	Stimulation with rehabilatation vs rehabilation alone	Upper extremity Fugl-Meyer score	Improvement in upper extremity motor control in the investigational group	6 months
Mortor Cortex Stimulation	Brown et al	13	Nonblinded trial and safety study	10	Ischemic stroke patients	Stimulation with rehabilatation vs rehabilation alone	Upper extremity Fugl-Meyer score	signoficant improvement in upper extremity motor control in stimulation plus rehabilitation	12 weeks
Mortor Cortex Stimulation	Levy et al	14	Safety and efficacy study	24	Ischemic stroke patients	Stimulation with rehabilatation vs rehabilation alone	Upper extremity Fugl-Meyer score, Arm motor ability test	67%, Improvement in upper extremity motor control.	4 weeks
Deep Brain Stimulation	Hassler et al	18	Case report	1	Post-traumatic apallic syndrome	N/A	Behavioural and EEG measurement	Behavioural and EEG arousal.	N/A
Deep Brain Stimulation	Cohadon et al	19	Clinical study	25	Post-traumatic vegetative state	DBS treated group only	Changes in clinical feathres and overall behaviour	Recovery of some degree of consciousness in 13 cases.	1 to 12 years
Deep Brain Stimulation	Katayama et al	20	Case series	8	Patients in PVS	DBS treated group only	Pain-related P250	The Pain-related P250 transiently increased in 4 patients.	> 6 months
Deep Brain Stimulation	Yamamoto et al	21	Case series	21	Patients in PVS	DBS treated group only	Neurological and electophysiological evaluation	Eight patients emerged from PVS.	> 10 years
Deep Brain Stimulation	Yamamoto et al	22	Case series	26	Patients in PVS or MCS	DBS treated group only	Neurological and electophysiological evaluation	Eight patients emerged from PVS, and 4 from the bedridden state.	> 10 years
Deep Brain Stimulation	Yamamoto et al	23	Case series	107	Patients in PVS	21 DBS treated vs 86 non-treated group	Auditory brainstem response, somatosensory evoked potential and pain-related P250	Eight DBS-treated patients emerged from PVS and obey verbal commands; No patients with DBS recovered.	> 10 years
Deep Brain Stimulation	Schiff et al	24	Case report	1	Patients in MCS	DBS treated group only	Qualitative changes in behaviour	behavioural improvements (command following, verbalization and inconsistent communication)	6 months
Spinal Cord Stimulatuin	Hosobuchi	40	Case series	10	Stroke and carotid stenosis	5 cervical SCS vs 5 thoracic SCS	Cerebral blood flow	Cervical SCS significantly increased CBF, thoracic SCS had no effect on CBF	N/A
Spinal Cord Stimulatuin	Yamamoto et al	43	Case series	10	Patients in MCS	SCS treated group only	electrophysiological evaluations and SPECT	Seven patients recovered from MCS following SCS; Cervical SCS increased CBF by 22.2%	> 1 year
Spinal Cord Stimulatuin	Kanno et al	44	Prospective uncontrolled study	214	Patients in PVS	SCS treated group only	Efficacy scale, detecting signs of awareness of self and surrounding and SPECT	Excellent and positive results were obtained in 54% of patients	3.5 months

Table 1: Clinical data of different studies. PVS, persistent vegetative state; MCS, minimally conscious state; DBS, deep brain stimulation; SCS, spinal cord stimulation; CBF, cerebral blood flow.

DBS to treat disorder of consciousness [18], and then in early 1990-s, two groups used this technique in a larger series of patients with vegetative state [19,20].In one case-series study, DBS of the midbrain reticular formation or central thalamus was conducted in patients with MinCS 4- 8 months post-injury. They received continuous stimulation for 10 years. Eight of the 21 patients emerged from a vegetative state and were able to follow verbal instructions [21-23]. A case study observed improvements in the level of arousal, limb movement and verbalization after DBS to the central thalamus [24]. However, one has to be cautious to differentiate the effectiveness of DBS from spontaneous recovery following injury [25]. Sen et al also pointed out that differentiating between the PVS and MinCS may be important in determining the possible benefit of DBS therapy since either state may result from a traumatic brain injury and both have profound functional

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consequences [26]. It is not clear if PVS and MinCS respond differently to DBS. It is possible that patients with MinCS would respond better as areas of essential cortical functioning were relatively preserved [24,26].

Furthermore, in one case report and one small case series study, DBS in the Ventralis Intermedius[VIM] nucleus of the thalamus, Ventralis Oral is Anterior and Posterior [VOA/VOP] and Globus Pallidus internus [GPi] has been used to treat posttraumatic tremor with good response [27,28]. A few small case series studies suggest that DBS of the Ventro Postero Lateral nucleus of the thalamus [VPL] and GPi can reduce symptoms of posttraumatic dystonia, which results in overall symptomatic improvement [29-31]. In addition, DBS of Subgenual Cingulate Cortex [SCC] is currently under investigation for the treatment of depression, a common neuropsychological disorder following TBI [7].

Spinal Cord Stimulation

Multiple animal studieshave shown augmentation of Cerebral Blood Flow [CBF] with Cervical Spinal Cord Stimulation[SCS][32-39]. The effect of SCS on increase in CBF in human brain was first reported in 1985 [40]. An interesting concept of "redistribution of CBF" rather than an absolute change in CBF during SCS was introduced in 1995 [41,42]. Further case series studies have shown cervical SCS could increase CBF, and improve upper-extremity motor function and communication skills in patients with MinCS resulted from TBI and stroke [7,43]. A single-group study reported improvements in awareness in 54% [109/201] of people with stroke or TBI after cervical SCS [44]. The treatment effect may be achieved by enhancing cerebral hemodynamics via autonomic nervous system and the release of hormonal factors [45]. Moreover, based on the thorough literature review, it has been proposed that SCS targeting the lower cervical segments may prevent Subarachnoid Hemorrhage [SAH]-related delayed vasospasm [46-48]. Furthermore, once the vasospasm is present,patients may still receive additional benefit and possibly improve clinical outcome by CBF augmentation and treatment of thevasospasm through stimulation of the cervical spinal cord.

Transcranial Magnetic Stimulation And Transcranial Direct-Current Stimulation

Transcranial Magnetic Stimulation [TMS] and transcranial Direct-Current Stimulation [tDCS] are two non-invasive neuromodulatory therapies, which can modulate neuroplasticity and cortical hyperexcitability[49-51].Their therapeutic value is unclear. Some studies, including randomized double-blind studyand sham stimulation-controlled trial, have assessed their effects on motor function in people with stroke and TBI. The findings have been inconsistent [51-54].

Neuromodulation for Spinal Cord Injury

Traumatic Spinal Cord Injury[SCI] is estimated to affect approximately 300,000 individuals in the United States, and more than 2.5 million worldwide [55], with estimated cost over $9 billion annually in the United States alone [56]. SCI often leads to serious neurological sequelae and medical complications. Therefore, more efforts in medical practice development are needed to improve the quality of life of patients with SCI.It has been reported that SCS in lumbosacral segments helped restore voluntary control of locomotion in paralyzed rats after SCI[57].A study using closed-loop neuromodulation to treat rats with complete SCI found that it improved the locomotion and enabled animals to perform more than 1,000 successive steps without failure and to climb staircases of various heights and lengths with precision and fluidity [58]. Another similar study on rats, however, found no treatment effect [59]. A case study reported that SCS enabled a paraplegic man [C7-T1 subluxation] to produce some leg movements and to stand during stimulation [60]. The author pointed out that even after a severe low cervical SCI, the neural networks remaining within the lumbosacral segments can be reactivated into functional states so that they can recognize specific details of ensembles of sensory input delivered by SCS to the extent that it [SCS] may serve as the source of neural control [60]. While this suggests that SCS can activate spared neural circuits and promote plasticity, there is no evidence that it would lead to functional gains and physical improvements after SCS.

Neuromodulation for Epilepsy

Epilepsy affects 1% of population in the world, and 30-40% of cases are medically refractory [61-65]. Management of patients who have recurrent seizures and did not respond to medication or surgery is challenging. A number of double-blind randomized controlled trials have confirmed the therapeutic effects of Vagus Nerve Stimulation [VNS] for epilepsy [66-69]. A recent European long-term study [n=347] showed a 50% reduction in seizure frequency for up to 43.8% of patients[66]. Greater treatment effect has been observed with higher VNS settings [66]. A review study also found DBS effective in reducing seizure frequency [70]. The target areas of DBS for treatment of epilepsy include Anterior Nucleus [AN] of thalamus [71-73], centro median nucleus [CM] of thalamus [74, 75], Sub Thalamic Nucleus [STN] [76,77], Caudate Nucleus[75], cerebellum [78]and hippocampus [79]. Closed loop brain stimulation has recently been used for treatment of epilepsy. One type of this stimulation is a Responsive Neurostimulation System [RNS][Responsive Neurostimulation System, Neuropace, Mountain view, CA] that delivers stimuli only when abnormal electrocortico graphic activity of a seizure is detected [80]. Another type is a recording pulse generator unit [Medtronic, Minneapolis, MN][81] that deliver bidirectional stimulation. The RNS is approved by FDA for clinical use in the USA [82, 83], and the DBS – by the regulatory agencies in Canada, Europe, Australia, and elsewhere [61]. However,DBS is still in its early stage as a therapy for epilepsy.

Discussion

Overall, advances in neuromodulation may offer new therapeutic interventions for patients with stroke, traumatic brain injury, spinal cord injury and epilepsy by counteract the abnormal network in the brain. The emerging neuromodulation therapy for patients with these conditions is still facing great challenges. Since most of the existing findings are based on animal studies, preliminary data, case reports andpoor-controlled studies, and short follow up, further investigations including research and clinical trials are necessary to increase the applications of neurostimulation in the field of neurorehabilitation.

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