

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 to patients with CNS 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 has been 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 by trauma 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 following traumatic 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 that cortical stimulation enhances functional recovery and cortical plasticity after neural injury induced by stroke [7-9]. Cortical stimulation during

rehabilitation constantly improves motor function in rats following 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, MCS resulted in improvements in 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 in pincer 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 mechanisms by 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 the primary motor cortex to the spinal cord, as well as to the red nucleus and cuneate nucleus [17]. Increased axonal outgrowth with stimulation may be due to a release of neurotrophins, such as brain-derived neurotrophic factor, and increased motor activity of 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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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 rehabilitation vs rehabilitation 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 rehabilitation vs rehabilitation alone	Upper extremity Fugl-Meyer score	significant 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 rehabilitation vs rehabilitation 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 electrophysiological 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 electrophysiological 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 1990s, 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

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 Vento 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 studies have 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 the vasospasm 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 study and 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, Neupace, Mountain view, CA] that delivers stimuli only when abnormal electrocorticographic 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 and poor-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.

References

1. Morcom AM, Johnson W (2015) Neural reorganization and compensation in aging. *J Cogn Neurosci* 20:1-11.
2. Depue BE, Orr JM, Smolker HR, Naaz F, Banich MT (2015) The Organization of right prefrontal networks reveals common mechanisms of inhibitory regulation across cognitive, emotional, and motor processes. *Cereb Cortex* 26:2424-2433
3. Ostergard T, Miller JP (2014) Deep brain stimulation: new directions. *J Neurosurg Sci* 58:191-198
4. Okun MS (2014) Deep-brain stimulation-entering the era of human neural-network modulation. *N Engl J Med* 15:1369-1373.
5. Leibson CL, Brown AW, Ransom JE, Diehl NN, Perkins PK, et al. (2011) Incidence of traumatic brain injury across the full disease spectrum: a population-based medical record review study. *Epidemiology* 22:836-844.

6. Rothwell PM, Coull AJ, Silver LE et al. (2005) Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet* 366:1773-1783.
7. Shin SS, Dixon E, Okonkwo DO, Richardson RM (2014) Neurostimulation for traumatic brain injury. *J Neurosurg* 121:1219-1231.
8. Kleim JA, Bruneau R, VandenBerg P, MacDonald E, Mulrooney R, et al. (2003) Motor cortex stimulation enhances motor recovery and reduces peri-infarct dysfunction following ischemic insult. *NeurolRes* 25:789-793.
9. Plautz EJ, Barbay S, Frost SB, Friel KM, Dancause N, et al. (2003) Post-infarct cortical plasticity and behavioral recovery using concurrent cortical stimulation and rehabilitative training: a feasibility study in primates. *Neurol Res* 25:801-810.
10. Teskey GC, Flynn C, Goertzen CD, Monfils MH, Young NA (2003) Cortical stimulation improves skilled forelimb use following a focal ischemic infarct in the rat. *NeurolRes* 25:794-800.
11. Yoon YS, Yu KP, Kim H, Kim HI, Kwak SH, et al. (2012) The effect of electric cortical stimulation after focal traumatic brain injury in rats. *Ann RehabilMed* 36:596-608.
12. Huang M, Harvey RL, Stoykov ME, Ruland S, Weinand M, et al. (2008) Cortical stimulation for upper limb recovery following ischemic stroke: a small phase II pilot study of a fully implanted stimulator. *Top Stroke Rehabil* 15:160-172.
13. Brown JA, Lutsep HL, Weinand M, Cramer SC (2006) Motor cortex stimulation for the enhancement of recovery from stroke: a prospective, multicenter safety study. *Neurosurgery* 58:464-473.
14. Levy R, Ruland S, Weinand M, Lowry D, Dafer R, et al. (2008) Cortical stimulation for the rehabilitation of patients with hemiparetic stroke: a multicenter feasibility study of safety and efficacy. *J Neurosurg* 108:707-714.
15. Fontaine D, Hamani C, Lozano A (2009) Efficacy and safety of motor cortex stimulation for chronic neuropathic pain: critical review of the literature. *Clinical article. J Neurosurg* 110:251-256.
16. Zheng J, Liu L, Xue X, Li H, Wang S, et al. (2013) Cortical electrical stimulation promotes neuronal plasticity in the perischemic cortex and contralesional anterior horn of cervical spinal cord in a rat model of focal cerebral ischemia. *Brain Res* 1504:25-34.
17. Carmel JB, Kimura H, Berrol LJ, Martin JH (2013) Motor cortex electrical stimulation promotes axon outgrowth to brain stem and spinal targets that control the forelimb impaired by unilateral corticospinal injury. *Eur J Neurosci* 37:1090-1102.
18. Hassler R, Ore GD, Dieckmann G, Bricolo A, Dolce G (1969) Behavioural and EEG arousal induced by stimulation of unspecific projection systems in a patient with post-traumatic apallid syndrome. *ElectroencephalogrClinNeurophysiol* 27:306-310.
19. Cohadon F, Richer E (1993) Deep cerebral stimulation in patients with post-traumatic vegetative state. 25 cases. *Neurochirurgie* 39:281-292.
20. Katayama Y, Tsubokawa T, Yamamoto T, Hirayama T, Miyazaki S, et al. (1991) Characterization and modification of brain activity with deep brain stimulation in patients in a persistent vegetative state: pain-related late positive component of cerebral evoked potential. *Pacing ClinElectrophysiol* 14:116-121.
21. Yamamoto T, Katayama Y (2005) Deep brain stimulation therapy for the vegetative state. *NeuropsycholRehabil*. 15:406-413.
22. Yamamoto T, Kobayashi K, Kasai M, Oshima H, Fukaya C, et al. (2005) DBS therapy for the vegetative state and minimally conscious state. *ActaNeurochirSuppl* 93:101-104.
23. Yamamoto T, Katayama Y, Kobayashi K, Oshima H, Fukaya C, et al. (2010) Deep brain stimulation for the treatment of vegetative state. *Eur J Neurosci* 32:1145-1151.
24. Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, et al. (2007) Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature* 448:600-603 (Erratum in *Nature* 2008, 452:120).
25. Schiff ND (2012) Moving toward a generalizable application of central thalamic deep brain stimulation for support of forebrain arousal regulation in the severely injured brain. *Ann N Y AcadSci* 1265:56-68.
26. Sen AN, Campbell PG, Yadla S, Jallo J, Sharan AD (2010) Deep brain stimulation in the management of disorders of consciousness: a review of physiology, previous reports, and ethical considerations. *Neurosurg Focus* 29 (E14):1-6.
27. Foote KD, Seignourel P, Fernandez HH, Romrell J, Whidden E, et al. (2006) Dual electrode thalamic deep brain stimulation for the treatment of posttraumatic and multiple sclerosis tremor. *Neurosurgery* 58:280-286.
28. Lim DA, Khandhar SM, Heath S, Ostrem JL, Ringel N, et al. (2007) Multiple target deep brain stimulation for multiple sclerosis related and poststroke Holmes' tremor. *StereotactFunctNeurosurg* 85:144-149.
29. Carvalho KS, Sukul VV, Bookland MJ, Koch SA, Connolly PJ (2014) Deep brain stimulation of the globus pallidus suppresses post-traumatic dystonic tremor. *J ClinNeurosci* 21:153-155.
30. Lohrer TJ, Hasdemir MG, Burgunder JM, Krauss JK (2000) Long-term follow-up study of chronic globus pallidus internus stimulation for posttraumatic hemidystonia. *J Neurosurg* 92:457-460.
31. Sellal F, Hirsch E, Barth P, Blond S, Marescaux C (1993) A case of symptomatic hemidystonia improved by ventroposterolateral thalamic electrostimulation. *MovDisord* 8:515-518.
32. Ebel H, Schomäcker K, Balogh A, Volz M, Funke J, et al. (2001) High cervical spinal cord stimulation (CSCS) increases regional cerebral blood flow after induced subarachnoid haemorrhage in rats. *Minim Invasive Neurosurg* 44:167-171.
33. Gurelik M, Kayabas M, Karadag O, Goksel HM, Akyuz A, et al. (1995) Cervical spinal cord stimulation improves neurological dysfunction induced by cerebral vasospasm. *Neuroscience* 134:827-832.
34. Isono M, Kaga A, Fujiki M, Mori T, Hori S (1995) Effect of spinal cord stimulation on cerebral blood flow in cats. *StereotactFunctNeurosurg* 64:40-46.
35. Lee JY, Huang DL, Keep R, Sagher O (2008) Effect of electrical stimulation of the cervical spinal cord on blood flow following subarachnoid hemorrhage. *J Neurosurg* 109:1148-1154.
36. Patel S, Huang DL, Sagher O (2003) Sympathetic mechanisms in cerebral blood flow alterations induced by spinal cord stimulation. *J Neurosurg* 99:754-761.
37. Patel S, Huang DL, Sagher O (2004) Evidence for a central pathway in the cerebrovascular effects of spinal cord stimulation. *Neurosurgery* 55:201-206.
38. Sagher O, Huang DL (2000) Effects of cervical spinal cord stimulation on cerebral blood flow in the rat. *J Neurosurg* 93(Suppl. 1):71-76.
39. Yang X, Farber JP, Wu M, Foreman RD, Qin C (2008) Roles of dorsal column pathway and transient receptor potential vanilloid type 1 in augmentation of cerebral blood flow by upper cervical spinal cord stimulation in rats. *Neuroscience* 152:950-958.
40. Hosobuchi Y (1985) Electrical stimulation of the cervical spinal cord increases cerebral blood flow in humans. *ApplNeurophysiol* 48:372-376.
41. Mazzone P, Pisani R, Nobili F, Arrigo A, Rosadini G (1995) Assessment of regional cerebral blood flow during spinal cord stimulation in humans. *StereotactFunctNeurosurg* 64: 197-201.
42. Mazzone P, Rodriguez G, Arrigo A, Nobili F, Rosadini G (1996) Cerebral haemodynamic changes induced by spinal cord stimulation in man. *Ital J NeurolSci* 17: 55-57.
43. Yamamoto T, Katayama Y, Obuchi T, Kobayashi K, Oshima H, et al. (2012) Spinal cord stimulation for treatment of patients in the minimally conscious state. *Neurol Med Chir (Tokyo)* 52:475-481.
44. Kanno T, Morita I, Yamaguchi S, Yokoyama T, Kamei Y, et al. (2009) Dorsal column stimulation in persistent vegetative state. *Neuromodulation*. 12:33-38.
45. Visocchi M, Della Pepa GM, Esposito G, Tufo T, Zhang W, et al. (2011) Spinal cord stimulation and cerebral hemodynamics: Updated Mechanism and Therapeutic Implications. *StereotactFunctNeurosurg* 89:263-274.
46. Goellner E, Slavin KV (2009) Cervical spinal cord stimulation may prevent cerebral vasospasm by modulating sympathetic activity of the superior cervical ganglion at lower cervical spinal level. *Medical hypothesis* 73:410-413.
47. Slavin KV, Vannemreddy PSSV, Goellner E, Alaraj AM, Aydin S, et al. (2011) Use of cervical spinal cord stimulation in treatment and prevention of arterial vasospasm after aneurysmal subarachnoid hemorrhage: Technical details. *The Neuroradiology Journal* 24:131-135.
48. Slavin KV (2014) Spinal stimulation for pain: Future applications. *Neurotherapeutics* 11:535-542.
49. Fregni F, Boggio PS, Valle AC, Rocha RR, Duarte J, et al. (2006) A sham-

- controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. *Stroke* 37:2115–2122.
50. Khedr EM, Ahmed MA, Fathy N, Rothwell JC (2005) Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. *Neurology* 65:466–468.
51. Mansour CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, et al. (2005) A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. *Neurology* 64:1802–1804.
52. Kim YH, You SH, Ko MH, Park JW, Lee KH, et al. (2006) Repetitive transcranial magnetic stimulation-induced corticomotor excitability and associated motor skill acquisition in chronic stroke. *Stroke* 37:1471–1476.
53. Takeuchi N, Tada T, Tushima M, Chuma T, Matsuo Y, et al. (2008) Inhibition of the unaffected motor cortex by 1 Hz repetitive transcranial magnetic stimulation enhances motor performance and training effect of the paretic hand in patients with chronic stroke. *J RehabilMed* 40:298–303.
54. Malcolm MP, Triggs WJ, Light KE, Gonzalez Rothi LJ, Wu S, et al. (2007) Repetitive transcranial magnetic stimulation as an adjunct to constraint-induced therapy: an exploratory randomized controlled trial. *Am J Phys Med Rehabil* 86:707–715.
55. National Spinal Cord Injury Statistical Center (2013) Spinal cord injury facts and figures at a glance. *J. Spinal Cord Med* 36:1–2.
56. DeVivo MJ (2012) Epidemiology of traumatic spinal cord injury: trends and future implications. *Spinal Cord* 50:365–372.
57. Van Den Brand R, Heutschi J, Barraud Q, DiGiovanna J, Bartholdi K, et al. (2012) Restoring voluntary control of locomotion after paralyzing spinal cord injury. *Science* 336:1182–1185.
58. Wenger N, Moraud EM, Raspopovic S, Bonizzato M, DiGiovanna J, et al. (2014) Closed-loop neuromodulation of spinal sensorimotor circuits controls refined locomotion after complete spinal cord injury. *SciTranslMed* 6:255ra133.
59. Lee CH, Hyun SJ, Yoon CY, Lim JY, Jahng TA, et al. (2012) Neuroprotective effects of sacral epidural neuromodulation following spinal cord injury: an experimental study in rats. *J Korean NeurosurgSoc* 52:509–512.
60. Harkema S, Gerasimenko Y, Hodes J, Burdick J, Angeli C, et al. (2011) Effect of Epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. *Lancet* 377:1938–1947.
61. Laxpati NG, Kasoff WS, Gross RE (2014) Deep brain stimulation for the treatment of epilepsy: circuits, targets and trials. *Neurotherapeutics* 11:508–526.
62. WHO. Epilepsy.
63. Kwan P, Sperling MR (2009) Refractory seizures: Try additional antiepileptic drugs (after two have failed) or go directly to early surgery evaluation? *Epilepsia* 50:57–62.
64. Wiebe S, Blume WT, Girvin JP, Eliasziw M. (2001) A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 345:311–318.
65. Sander JW (2003) The epidemiology of epilepsy revisited. *CurrOpinNeurol* 16:165–170.
66. Orosz I, McCormick D, Zampono N, Varadkar S, Feucht M, et al. (2014) Vagus nerve stimulation for drug-resistant epilepsy: A European long-term study up to 24 months in 347 children. *Epilepsia* 55:1576–1584.
67. A randomized controlled trial of chronic vagus nerve stimulation of medically intractable seizures. The Vagus Nerve Stimulation Study Group. *Neurology* 45:224–230.
68. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, et al. (1998) Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology* 51:48–55.
69. Klinkenberg S, Aalbers MW, Vles JS, Cornips EM, Rijkers K, et al. (2012) Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. *Dev Med Child Neurol* 54:855–861.
70. Lega BC, Halpern CH, Jaggi JL, Baltuch GH (2010) Deep brain stimulation in the treatment of refractory epilepsy: update on current data and future directions. *Neurobiol Dis* 38: 354–360.
71. Andrade DM, Zumsteg D, Hamani C, Hodaie M, Sarkissian S, et al. (2006) Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy. *Neurology* 66: 1571–1573.
72. Lee KJ, Shon YM, Cho CB (2012) Long-term outcome of anterior thalamic nucleus stimulation for intractable epilepsy. *StereotactFunctNeurosurg* 90: 379–385.
73. Fisher R, Salanova V, Witt T, Worth R, Henry T, et al. (2010) Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 51: 899–908.
74. Velasco AL, Velasco F, Jimenez F, Velasco M, Castro G, et al. (2006) Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox-Gastaut syndrome. *Epilepsia* 47: 1203–1212.
75. Chkhenkeli SA, Sramka M, Lortkipanidze GS, Rakviashvili TN, Bregvadze ESh, et al. (2004) Electrophysiological effects and clinical results of direct brain stimulation for intractable epilepsy. *ClinNeuroNeurosurg* 106: 318–329.
76. Handforth A, DeSalles AA, Krahl SE (2006) Deep brain stimulation of the subthalamic nucleus as adjunct treatment for refractory epilepsy. *Epilepsia* 47: 1239–1241.
77. Chabardes S, Kahane P, Minotti L, Koudsie A, Hirsch E, et al. (2002) Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. *Epileptic Disord* 4: S83–S93.
78. Velasco F, Carrillo-Ruiz JD, Brito F, Velasco M, Velasco AL, et al. (2005) Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. *Epilepsia* 46: 1071–1081.
79. Boon P, Vonck K, De Herdt V, Van Dycke A, Goethals M, et al. (2007) Deep brain stimulation in patients with refractory temporal lobe epilepsy. *Epilepsia* 48: 1551–1560.
80. Morrell MJ (2011) RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* 77: 1295–1304.
81. Stypulkowski PH, Stanslaski SR, Denison TJ, Giftakis JE (2013) Chronic evaluation of a clinical system for deep brain stimulation and recording of neural network activity. *StereotactFunctNeurosurg* 91:220–232.
82. Bergey GK, Morrell MJ, Mozrahi EM, Goldman A, King-Stephens D, et al. (2015) Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology* 84: 810–817
83. Heck CN, King-Stephens D, Massey AD, Nair DR, Jobst BC, et al. (2014) Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. *Epilepsia* 55:432–441.