European Review for Medical and Pharmacological Sciences 2018; 22: 7385-7392

The effect of transcranial direct current stimulation combined with functional task training on motor recovery in stroke patients

M. ALSHARIDAH[1], F. AL-HUSSAIN[2], M. IQBAL[3], A. HAMZA[4], W.-K. YOO[5,6], S. BASHIR[7]

[1]Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia
[2]Department of Neurology, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia
[3]Department of Physiology, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia
[4]Department of Electrical Engineering, National University of Computer and Emerging Sciences, Lahore, Pakistan
[5]Department of Physical Medicine and Rehabilitation, Division of Neuroscience Center, Hallym, University Sacred Heart Hospital, Anyang, South Korea
[6]Hallym Institute for Translational Genomics and Bioinformatics, Hallym University College of Medicine, Anyang, South Korea
[7]Department of Neurophysiology, Neuroscience Center, King Fahad Specialist Hospital Dammam, Dammam, Riyadh, Saudi Arabia

Abstract. – The field of neuromodulation encompasses a wide spectrum of interventional technologies that modify pathological activity within the nervous system to achieve a therapeutic effect. Therapy including transcranial direct current stimulation (tDCS) has all shown promising results across a range of neurological and neuropsychiatric disorders. This article reviews the state-of-the-art of neuromodulation for stroke and discusses the opportunities and challenges available for clinicians and researchers interested in advancing neuromodulation therapy. The annual worldwide incidence of stroke ranges from 27.5 to 63 individuals per 100,000. Stroke, a major cause of adult disability, has devastating effects on patients and their caregivers, which has a tremendous socioeconomic impact on families and healthcare systems around the world. There are only a few treatments available for the improvement of motor function in stroke patients. The majority of these treatments are based on functional motor learning (ML) strategies. Both the mechanisms underlying stroke recovery and the effectiveness of neurorehabilitation interventions still remain poorly understood for widespread implementation, although it strongly depends on the quality of rehabilitation service to reach maximal post-stroke recovery.

Key Words:
Neuromodulation, Neuroengineering, Transcranial direct current stimulation.

Introduction

Stroke is the third leading cause of death and, in many surviving patients, is the devastating endpoint of cerebrovascular disease. The impacts of acquired brain injuries such as stroke on individuals, families, and society continue to increase due to both the aging general population and the increasing length of post-insult survival. Stroke-related neurologic deficits, including motor function deficits, are often persistent and exert a negative effect on the patients' quality of life[1,2].

Understanding the Stroke Recovery Mechanism Based on Brain Plasticity is Critical for Developing New Therapeutic Approaches

Brain plasticity is a broad term for the property of the human brain to adapt to environmental pressure, experiences, and challenges including brain damage[3-5]. Brain plasticity occurs at many levels from molecular to system including cortical reorganization. The time after a stroke, the location of the lesion, the lesion volume, the integrity of corticospinal tracts (CST) and cortical and subcortical connections are the main factors influencing stroke outcome[6]. In general, each hemisphere of the brain undergoes neuroplasticity

Corresponding Author: Shahid Bashir, Ph.D; e-mail: sbashir10@gmail.com

changes by means of regeneration by axonal and dendritic sprouting and/or reorganization within cortical motor areas, e.g., by the modulation of synaptic plasticity, the remapping of functional representations by a diminution of GABAergic inhibition or increased NMDA receptor binding that is redirected from lesioned areas onto ipsilesional unaffected areas surrounding the lesion or homologous areas within the unaffected (contralesional) hemisphere[6,7]. Recent research indicates that noninvasive brain stimulation (NIBS) techniques such as transcranial direct current stimulation (tDCS) can enhance motor function recovery in chronic stroke patients. Two potential roles have been described for tDCS in stroke recovery: (1) the inhibition (i.e., downregulation) of the healthy hemisphere; or (2) an enhancement of the excitability of the lesioned hemisphere. The downregulation of the contralesional hemisphere can lead to improve motor performance in the affected limb, which is thought to act via a reduction in interhemispheric inhibition of the lesioned side of the brain. Much of the spontaneous recovery from the stroke after the acute phase involves plastic changes in the brain[8-10].

The Measurement of Indicators of Cortical Physiology and Corticospinal Tract Integrity is Important in Terms of Planning an Effective Treatment

The advances in technologies enabling non-invasive exploration of the human brain have increased our understanding of brain reorganization after ischemic stroke[11,13]. This kind of therapeutic approach relies solely on the functional and physiological status of each hemisphere and the balance between the two hemispheres, which implies the importance of this physiological measure on planning an effective treatment strategy. Diffusion tensor imaging tractography (DTI) is a recently developed technique that enables non-invasive visualization of fiber tracts in the human brain *in vivo*, and is likely to have an impact on the future design and choice of rehabilitation methods for individual patients[11,14-15]. This imaging technique has advantages in delineating the white matter integrity, which has clinical importance as it broadened the possibility to check the individual motor tract precisely. Especially, the corticospinal tract is most important descending motor tract for functional recovery, which is known to be related to selective and voluntary control of individual muscles[16]. Measurements of corticospinal tract volume and each diffusion metrics including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD), will give us insight into its pathological status of the lesion causing the inter-individual variability in the efficacy of therapeutic interventions. Non-invasive brain stimulation (NIBS) techniques such as TMS and tDCS have recently been reintroduced in neuroscience research due to their potential for both the investigation of causal brain-behavior relationships and for the rehabilitation of many diseases. It is worth noting that progress in neuroscience often depends on the convergence of evidence from multiple methods, because each individual technique has unique limitations, there is a clear theoretical advantage in combining different approaches[17,18].

Development of a Novel Therapeutic Approach Combining Motor Learning and Neuromodulation with Shared and Similar Mechanisms

It is known that coupling cortical stimulation with motor learning can enhance motor recovery. As described above, both strategies for enhancing motor recovery – motor learning and cortical stimulation – are associated with similar mechanisms of action, i.e., an increase in the local excitability of the affected motor cortical area (possibly via synaptic strengthening) coupled with a corresponding decrease in the contralateral healthy hemisphere. To date, a few animal and human studies support this suggestions[12,19]. Although, there is sufficient evidence to support the significant influence of NIBS in inducing neuroplasticity changes that are reflected in observable behavioral changes, the exact mechanism of action of NIBS in producing this neuromodulator is not completely clear. Therefore, recent efforts to combine NIBS and neuroimaging in experimental paradigms have been undertaken to provide a more methodical characterization of neuroplasticity modulation by NIBS through the use of brain network analysis techniques[20,21]. The brain has the characteristic of plasticity and is, thus, capable of major functional reorganization after injury. Using functional neuroimaging techniques, several studies have reported that cortical activation can change according to the clinical recovery of hand function over time in stroke patients. The elucidation of the changes in cortical activation coinciding with clinical recovery is important for brain rehabilitation because such information can be used to develop or

evaluate treatment methods in brain-injured patients[22-24]. Recent investigations[13,25] have demonstrated that cortical brain stimulation with invasive and non-invasive brain stimulation improves motor function in stroke patients. An animal and a human study both indicated that epidural stimulation of the motor cortex resulted in motor function enhancement after stroke. The rTMS effect on motor learning paradigm was proven in healthy subjects and stroke patients. It is important to note that stimulating the primary motor cortex did not only affect the neuronal activity at that site, but the activity throughout the entire motor network related to motor learning[26]. Both mechanisms of action of neuromodulation and exercise in improving motor function in stroke are related to a change in local brain activity. Previous studies have suggested that these effects are associated with plastic changes such as long-term potentiation (LTP) and depression (LTD) in rTMS[27-29]. Similarly, it has been shown that tDCS induces a modulatory effect on cortical excitability that depends on the direction of the current; for example, cathodal tDCS decreases cortical excitability, and anodal tDCS increases cortical excitability[30,31]. The after-effects of tDCS have also been linked to changes in synaptic strengthening, as demonstrated in pharmacological studies[32,33]. An important finding is that the effects of brain stimulation on cortical excitability last beyond the period of stimulation; when applied for several consecutive days, these effects can last for several weeks. Additionally, several consecutive stimulation sessions of tDCS induce behavioral effects that last up to 3 months[34,35].

Current Rehabilitation Therapy Approaches

The primary goal of the rehabilitation approaches is training patients to approximate the partially lost motor function closely to the previous healthy condition. If it is not possible, then the other strategic approaches such as substitution for its absence by using the other limb or a device can be used[36]. Therefore, the ideal rehabilitation therapy may evolve over the course of recovery, and different strategies may be needed according to the time since the brain insult (BI), to the injury characteristics and to the potential plasticity. Finally, prolonged and sustained interventions are likely the underlying cause of the higher level of recovery observed in some patients. If so, identification of the correct intervention and sustained persistence will be crucial. However, currently, the majority of post-stroke patients receive only a few weeks to a few months of rehabilitation[37-39]. Some of the earliest observational studies of BI patients suggested that motor disabilities were largely the result of disuse[40]. Another technique to increase paretic arm activity in chronic stroke patients involves bilateral arm training with a custom-built arm trainer[41]. In this researches, patients participated in three 20-minute sessions per week of bilateral repetitive pushing and pulling movements for 6 weeks. The results revealed increased function and increased strength and an active range of motion; however, the lack of a control group prevents any extrapolation of the specificity of this type of training. Bilateral movements likely allow facilitation of the paretic arm through spared ipsilateral CM projections, indirect ipsilateral corticospinal pathways or ipsilateral corticospinal pathways from the unaffected hemisphere[42]. Again, the lack of clear evidence that this approach results in functional improvements that are superior to conventional physiotherapy limits the clinical relevance of these studies. In line with this strategy for searching effective rehabilitative intervention, the Constraint-induced Movement Therapy (CIMT) became as a useful technique for effectively induce activation in the peri-lesion area, which is proven by functional imaging. A common characteristic of behavioral rehabilitation approaches, with or without technology support, is that functional gains are usually associated with the amount of cortical excitability within the lesioned and non-lesioned motor-related cortical areas. Study showed that CIMT therapy leads to an increase in the motor mapping area size as indexed by TMS, which supports the notion that CIMT leads to an increase in corticospinal excitability in the affected primary motor cortex[43]. In other words, it implies that the significance of the Ipsilesional corticospinal tract integrity would be critical in building up the enhancement of the functional motor recovery[44,45] (Table I). Achieving maximal post-stroke recovery strongly depends on the quality of rehabilitation. As recovery processes are reflected and adjusted by cortical reorganization, it is important to guide these plastic changes so as to restore natural movement sequences. Therefore, physiotherapists have a great impact on the outcome of rehabilitative training. However, there are three limiting factors in this context: (1) a physiotherapist has limited time to devote to each patient; (2) movements practiced under the supervision of physiotherapists are generally not

Table I. Stroke recovery studies that used transcranial direct current stimulation.

Authors	Protocol thereby	Patients number and diagnosis	Age (mean ± SD)	Time post stroke	Description of the intervention	Neurophysiological indicators
Ochi et al[46]	– Anodal tDCS + BmanuTrack RT – Cathodal tDCS + BmanuTrack RT .	2 Groups: 9 patients for each Chronic: 11 hemorrhagic, 7 ischemic stroke	61.1 ± 10.0 years .	4.4 years	1 mA anodal tDCS during first 10 min of RT, 1 mA cathodal tDCS during first 10 min of RT, 10 days multiple sessions spaced out by 2-days rest	–
Ang et al[47]	Bilateral Real Sham tDCS+MI-BCI with robotic feedback	2 Groups: 10 patients for real group: 9 patients for sham group. Chronic stroke: 13 ischemic, 9 hemorrhagic: 18 subcortical 1 cortical.	Group A (real): 52.1 ± 11.7 Group B (Sham): 56.3± 9.5	9 Months	Group A: 10 sessions of 20 min of bilateral tDCS (1 mA) before 1 h of MI-BCI with upper limb robotic feedback for 2 weeks Group B: 10 Sessions of 20 min of sham tDCS (1 mA) before 1 h of MI-BCI with upper limb robotic feedback for 2 weeks	MI-BCI screening
Powel et al[48]	Anodal tDCS deliverd before PNS or after PNS combined with robotic thereby	2 Groups: 4 patients for tDCS before PNS, 6 patients for tDCS after PNS group Chronic stroke: 7 ischemic 3 hemorrhagic: 6 left side lesion, 4 right side lesion.	Group A (before PNS): 61.0 ± 6.63 Group B (after PNS) 60.5 ± 2.95	4.5 Years	Group A: 10 daily sessions of 20 min of anodal tDCS (2 mA). Before 2 h of PNS followed by 2 h of RT. Group B: 10 daily sessions of 20 min of anodal tDCS (2 mA). After 2 h of PNS followed by 2 H of RT.	Motor map Volume of FMS, SIS, ipsilesional hemisphere, COG.
Straudi et al[49]	Anodal and cathodal Real /Sham tDCS+ReoGo System RT	2 groups: 12 patients for real group, 11 patients for Sham group 9 subacute: 6 cortical and 3 subcortical (9 ischemic 2 hemorrhagic) 14 Chronic: 8 cortical and 6 subcortical (10 ischemic and 2 hemorrhagic)	Group A (real): 52 ± 16 years. Group B (sham): 64.3 ± 9.7 years.	Sub-acute stork: < 6 months Chronic stroke: > 6 months	Group A: 30 min of RT with anodal-and cathodal real tDCS (1.0mA). Group B: 30 min of RT with anodal-and cathodal sham tDCS during first 30 s, 10 session for 2 weeks (5 session per week).	–

tDCS = Transcranial Direct Current Stimulation; RT = Robotic Training; TMS = Transcranial Magnetic Stimulation; MEP = Motor Evoked Potential; FMS = Fugl-Meyer-Score ; MAS = Modified Ashowrth Scale; BI = Barthel Index; B&B = Box and block test; MRC = Medical Research Council; MAL= Motor Activity Log ; FCR = Flexor Carpi Radialis; SD = Standard deviation; MI-BCI = Motor Imagery-Brain Computer Interface ; COG = Center Of the Gravity lesion; SIS = Stroke Impact Scale.

completely optimized for an individual patient; and (3) treatment is not standardized and, therefore, the effects are heterogeneous. To ameliorate these problems, robotic devices such as the LOKOMAT and ARMIN were developed (for the lower and upper extremities, respectively). The combination of individualized support and repetitive training increases motivation and has a net positive effect on rehabilitation[46].

Coupling Cortical Stimulation with Motor Learning With the Armeo System

We suggest that coupling transcranial direct current stimulation with functional task training will enhance the effect on motor recovery in BI survivors. The learning of new skills (that is accompanied by behavioral changes) is linked to changes in neuronal activity and excitability[51]. A possible mechanism is through changes in synaptic strength, for example, through N-methyl-D-aspartate (NMDA) receptor-modulated long-term potentiation (LTP)[52,53]. Successful manipulation of cortical excitability to improve learning processes has been demonstrated in humans in neuro-pharmacological investigations, with TMS, and with differentiation of adjacent or contralateral body parts[54-56]. tDCS presents an interesting alternative to these approaches, because it is non-invasive, painless (compared to TMS), and without serious side effects (compared to pharmacological agents). In addition, tDCS has an important theoretical advantage as it modifies spontaneous neuronal activity and therefore can increase activity in a more physiological manner. tDCS also offers a valuable practical advantage as investigators and study subjects can be reliably blinded, thus allowing well-controlled trials[57,58]. Studies showed that anodal tDCS of the human motor cortex elicits prolonged increases in cortical excitability, probably by sub-threshold neuronal membrane depolarization.[59] Moreover, it has been shown that the evoked after-effects are NMDA receptor dependent, and thus may share some similarities with the LTP thought to underlie learning processes. Hence, anodal tDCS has the potential to improve learning by increasing cortical excitability and modulating neurotransmitter dependent plasticity in the brain[11,61]. Furthermore, it has been shown that tDCS can enhance motor learning in healthy subjects, and stroke patients.[62,63] These findings have been confirmed, and extended to language in normal subjects and in patients with aphasia[63,64].

Conclusions

The human brain continues to adjust throughout life and this neuroplasticity is particularly important for recovery of neurological disorders such as stroke. Neurorehabilitation programs improve function partly by enhancing cortical reorganization, which is greatly dependent on various factors including remaining corticospinal integrity. Both non-invasive neuromodulation and exercise are based on similar physiological mechanism, i.e. Long-term potentiation, which induces a potent change in cortical excitability and plasticity in the motor network. For maximizing the efficacy of the rehabilitative interventions, one need to be aware of the basic mechanisms on which each therapeutic interventions based on and how one can combine each of this intervention leading to functional recovery in stroke patients.

Acknowledgements

The authors extend their appreciation to the Deanship of Scientific Research, King Saud University for funding this work through the research group no. (RGP- 1438-008).

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Mebius MJ, Kooi EMW, Bilardo CM, Bos AF. Brain injury and neurodevelopmental outcome in congenital heart disease: a systematic review. Pediatrics 2017; 140: e20164055.
2) Chang FH, Chen CY, Liang WM, Lin MR. Validating the quality of life after brain injury through rasch analysis. J Head Trauma Rehabil 2016; 32: E11-E18.
3) McComas AJ, Sica RE, Upton AR, Aguilera N. Functional changes in motoneurones of hemiparetic patients. J Neurol Neurosurg Psychiatry 1973; 36: 183-193.
4) Jorgensen HS, Kammersgaard LP, Houth J, Nakayama H, Raaschou HO, Larsen K, Hübbe P, Olsen TS. Who benefits from treatment and rehabilitation in a stroke Unit? A community-based study. Stroke 2000; 31: 434-439.
5) Johansson BB. Current trends in stroke rehabilitation. A review with focus on brain plasticity. Acta Neurol Scand 2011; 123: 147-159.
6) Johansson BB. Brain plasticity and stroke rehabilitation. The Willis lecture. Stroke 2000; 31: 223-230.

7) Komitova M, Johansson BB, Eriksson PS. On neural plasticity, new neurons and the postischemic milieu: an integrated view on experimental rehabilitation. Exp Neurol 2006; 199: 42-55.

8) Pavlova EL, Lindberg P, Khan A, Ruschkowski S, Nitsche MA, Borg J. Transcranial direct current stimulation combined with visuo-motor training as treatment for chronic stroke patients. Restor Neurol Neurosci 2017; 35: 307-317.

9) Rocha S, Silva E, Foerster A, Wiesiolek C, Chagas AP, Machado G, Baltar A, Monte-Silva K. The impact of transcranial direct current stimulation (tDCS) combined with modified constraint-induced movement therapy (mCIMT) on upper limb function in chronic stroke: a double-blind randomized controlled trial. Disabil Rehabil 2016; 38: 653-660.

10) Bolognini N, Vallar G, Casati C, Latif LA, El-Nazer R, Williams J, Banco E, Macea DD, Tesio L, Chessa C, Fregni F. Neurophysiological and behavioral effects of tDCS combined with constraint-induced movement therapy in poststroke patients. Neurorehabil Neural Repair 2011; 25: 819-829.

11) Mehrholz J, Pohl M, Platz T, Kugler J, Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. Cochrane Database Syst Rev 2015; 11: CD006876.

12) Ellis MD, Lan Y, Yao J, Dewald JPA. Robotic quantification of upper extremity loss of independent joint control or flexion synergy in individuals with hemiparetic stroke: a review of paradigms addressing the effects of shoulder abduction loading. J Neuroeng Rehabil 2016; 13: 95.

13) Giszter SF. Motor primitives--new data and future questions. Curr Opin Neurobiol 2015; 33: 156-165.

14) Richards LG, Stewart KC, Woodbury ML, Senesac C, Cauraugh JH. Movement-dependent stroke recovery: a systematic review and meta-analysis of TMS and fMRI evidence. Neuropsychologia 2008; 46: 3-11.

15) Stark A, Meiner Z, Lefkovitz R, Levin N. Plasticity in cortical motor upper-limb representation following stroke and rehabilitation: two longitudinal multijoint FMRI case-studies. Brain Topogr 2012; 25: 205-219.

16) Leclercq D, Delmaire C, de Champfleur NM, Chiras J, Lehericy S. Diffusion tractography: methods, validation and applications in patients with neurosurgical lesions. Neurosurg Clin N Am 2011; 22: 253-268.

17) Todder D, Grisaru N, Kaplan Z. Noninvasive brain stimulation in neuropsychiatric disorders. Harefuah 2016; 155: 753-756.

18) Zhao H, Qiao L, Fan D, Zhang S, Turel O, Li Y, Li J, Xue G, Chen A, He Q. Modulation of brain activity with noninvasive transcranial direct current stimulation (tDCS): clinical applications and safety concerns. Front Psychol 2017; 8: 685.

19) Beer RF, Dewald JP, Dawson ML, Rymer WZ. Target-dependent differences between free and constrained arm movements in chronic hemiparesis. Exp Brain Res 2004; 156: 458-470.

20) Alia C, Spalletti C, Lai S, Panarese A, Lamola G, Bertolucci F, Vallone F, Di Garbo A, Chisari C, Micera S, Caleo M. Neuroplastic changes following brain ischemia and their contribution to stroke recovery: novel approaches in neurorehabilitation. Front Cell Neurosci 2017; 11: 76.

21) Caleo M. Rehabilitation and plasticity following stroke: insights from rodent models. Neuroscience 2015; 311: 180-194.

22) Daly JJ, Ruff RL. Construction of efficacious gait and upper limb functional interventions based on brain plasticity evidence and model-based measures for stroke patients. ScientificWorld Journal 2007; 20: 2031-2045.

23) Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J. Interventions for improving upper limb function after stroke. Cochrane Database Syst Rev 2014; 11: CD010820.

24 Cauraugh JH, Summers JJ. Neural plasticity and bilateral movements: a rehabilitation approach for chronic stroke. Prog Neurobiol 2005; 75: 309-320.

25) Arya KN, Pandian S. Interlimb neural coupling: implications for poststroke hemiparesis. Ann Phys Rehabil Med 2014; 57: 696-713.

26) Hill AT, Fitzgerald PB, Hoy KE. Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. Brain Stimul 2016; 9: 197-208.

27 Clayton E, Kinley-Cooper SK, Weber RA, Adkins DL. Brain stimulation: neuromodulation as a potential treatment for motor recovery following traumatic brain injury. Brain Res 2016; 1640(Pt A): 130-138.

28) Harvey RL, Nudo RJ. Cortical brain stimulation: a potential therapeutic agent for upper limb motor recovery following stroke. Top Stroke Rehabil 2007; 14: 54-67.

29) Levy R, Ruland S, Weinand M, Lowry D, Dafer R, Bakay R. Cortical stimulation for the rehabilitation of patients with hemiparetic stroke: a multicenter feasibility study of safety and efficacy. J Neurosurg 2008; 108: 707-714.

30) Ludemann-Podubecka J, Bosl K, Rothhardt S, Verheyden G, Nowak DA. Transcranial direct current stimulation for motor recovery of upper limb function after stroke. Neurosci Biobehav Rev 2014; 47: 245-259.

31) Zimerman M, Heise KF, Hoppe J, Cohen LG, Gerloff C, Hummel FC. Modulation of training by single-session transcranial direct current stimulation to the intact motor cortex enhances motor skill acquisition of the paretic hand. Stroke 2012; 43: 2185-2191.

32) Lang N, Siebner HR, Chadaide Z, Boros K, Nitsche MA, Rothwell JC, Paulus W, Antal A. Bidirectional modulation of primary visual cortex excitability: a combined tDCS and rTMS study. Invest Ophthalmol Vis Sci 2007; 48: 5782-5787.

33) Di Lazzaro V, Profice P, Pilato F, Dileone M, Oliviero A, Ziemann U. The effects of motor cortex rTMS on corticospinal descending activity. Clin Neurophysiol 2010; 121: 464-473.

34) A Caipa, M Alomar, S Bashir. TMS as tool to investigate the effect of pharmacological medications on cortical plasticity. European review for medical and pharmacological sciences. 2018; 22:844-852.

35) Kourtis D, Seiss E, Praamstra P. Movement-related changes in cortical excitability: a steady-state SEP approach. Brain Res 2008; 1244: 113-120.

36) Rabadi MH, Aston CE. Effect of transcranial direct current stimulation on severely affected arm-hand motor function in patients after an acute ischemic stroke: a pilot randomized control trial. Am J Phys Med Rehabil 2017; 96 (10 Suppl 1): S178-S184.

37) Song LP, Wang Q, Zhang T. The importance of early rehabilitation for the traumatic brain injury patients based on rehabilitation medicine. Zhonghua Yi Xue Za Zhi 2017; 97: 1604.

38) Horn SD, Corrigan JD, Dijkers MP. Traumatic brain injury rehabilitation comparative effectiveness research: introduction to the traumatic brain injury-practice based evidence archives supplement. Arch Phys Med Rehabil 2015; 96: S173-177.

39) Brasure M, Lamberty GJ, Sayer NA, Nelson NW, Macdonald R, Ouellette J, Wilt TJ. Participation after multidisciplinary rehabilitation for moderate to severe traumatic brain injury in adults: a systematic review. Arch Phys Med Rehabil 2013; 94: 1398-1420.

40) Montagna M, Cerri G, Borroni P, Baldissera F. Excitability changes in human corticospinal projections to muscles moving hand and fingers while viewing a reaching and grasping action. Eur J Neurosci 2005; 22: 1513-1520.

41) Monfils MH, Plautz EJ, Kleim JA. In search of the motor engram: motor map plasticity as a mechanism for encoding motor experience. Neuroscientist 2005; 11: 471-483.

42) Butefisch CM, Khurana V, Kopylev L, Cohen LG. Enhancing encoding of a motor memory in the primary motor cortex by cortical stimulation. J Neurophysiol 2004; 91: 2110-2116.

43) Houweling S, van Dijk BW, Beek PJ, Daffertshofer A. Cortico-spinal synchronization reflects changes in performance when learning a complex bimanual task. NeuroImage 2010; 49: 3269-3275.

44) Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in people after stroke. Cochrane Database Syst Rev 2016; 3: CD009645.

45) Floel A, Hummel F, Duque J, Knecht S, Cohen LG. Influence of somatosensory input on interhemispheric interactions in patients with chronic stroke. Neurorehabil Neural Repair 2008; 22: 477-485.

46) S Bashir, A Caipa, EB Plow. Assessment of behavioral tasks performed by hemiplegic patients with impaired dexterity post stroke. European review for medical and pharmacological sciences. 2017; 21:2443-2451.

47) Ang KK, Guan C, Phua KS, Wang C, Zhao L, Teo WP, Chen C, Ng YS, Chew E. Facilitating effects of transcranial direct current stimulation on motor imagery brain-computer interface with robotic feedback for stroke rehabilitation. Arch Phys Med Rehabil 2015; 96: S79-S87.

48) Powell ES, Carrico C, Westgate PM, Chelette KC, Nichols L, Reddy L, Salyers E, Ward A, Sawaki L. Time configuration of combined neuromodulation and motor training after stroke: a proof-of-concept study. NeuroRehabilitation 2016; 39: 439-449.

49) Straudi S, Fregni F, Martinuzzi C, Pavarelli C, Salvioli S, Basaglia N. tDCS and robotics on upper limb stroke rehabilitation: effect modification by stroke duration and type of stroke. Biomed Res Int 2016; 2016: 5068127.

50) Housman SJ, Scott KM, Reinkensmeyer DJ. A randomized controlled trial of gravity-supported, computer-enhanced arm exercise for individuals with severe hemiparesis. Neurorehabil Neural Repair 2009; 23: 505-514.

51) Antal A, Terney D, Kuhnl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. J Pain Symptom Manage 2010; 39: 890-903.

52) O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. A report of a Cochrane systematic review and meta-analysis. Eur J Phys Rehabil Med 2011; 47: 309-326.

53) Kratz O, Studer P, Barth W, Wangler S, Hoegl T, Heinrich H, Moll GH. Seizure in a nonpredisposed individual induced by single-pulse transcranial magnetic stimulation. J ECT 2011; 27: 48-50.

54) Tang Q, Li G, Liu T, Wang A, Feng S, Liao X, Jin Y, Guo Z, He B, McClure MA, Xing G, Mu Q. Modulation of interhemispheric activation balance in motor-related areas of stroke patients with motor recovery: systematic review and meta-analysis of fMRI studies. Neurosci Biobehav Rev 2015; 57: 392-400.

55) Sun L, Yin D, Zhu Y, Fan M, Zang L, Wu Y, Jia J, Bai Y, Zhu B, Hu Y. Cortical reorganization after motor imagery training in chronic stroke patients with severe motor impairment: a longitudinal fMRI study. Neuroradiology 2013; 55: 913-925.

56) Gor-Garcia-Fogeda MD, Molina-Rueda F, Cuesta-Gomez A, Carratala-Tejada M, Alguacil-Diego IM, Miangolarra-Page JC. Scales to assess gross motor function in stroke patients: a systematic review. Arch Phys Med Rehabil 2014; 95: 1174-1183.

57) Pollock A, Baer G, Campbell P, Choo PL, Forster A, Morris J, Pomeroy VM, Langhorne P. Physical rehabilitation approaches for the recovery of function and mobility following stroke. Cochrane Database of Syst Rev 2014; 22: CD001920.

58) Kim JH, Sim WS, Won BH. Effectiveness of elastic band-type ankle-foot orthoses on postural control

in poststroke elderly patients as determined using combined measurement of the stability index and body weight-bearing ratio. Clin Interv Aging 2015; 10: 1839-1847.

59) Tyson SF, Kent RM. Effects of an ankle-foot orthosis on balance and walking after stroke: a systematic review and pooled meta-analysis. Arch Phys Med Rehabil 2013; 94: 1377-1385.

60) Mehrholz J, Thomas S, Werner C, Kugler J, Pohl M, Elsner B. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev 2017; 5: CD006185.

61) Di Lazzaro V, Rothwell JC. Corticospinal activity evoked and modulated by non-invasive stimulation of the intact human motor cortex. J Physiol 2014; 592: 4115-4128.

62) Di Lazzaro V, Ziemann U. The contribution of transcranial magnetic stimulation in the functional evaluation of microcircuits in human motor cortex. Front Neural Circuits 2013; 7: 18.

63) Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving aphasia in patients with aphasia after stroke. Cochrane Database Syst Rev 2015; 5: CD009760.

64) Brady MC, Kelly H, Godwin J, Enderby P, Campbell P. Speech and language therapy for aphasia following stroke. Cochrane Database Syst Rev 2016; 6: CD000425.