Journal of Medical Systems (2019) 43: 69
https://doi.org/10.1007/s10916-019-1193-9

PATIENT FACING SYSTEMS

Analysis of the Factors Related to the Effectiveness of Transcranial Current Stimulation in Upper Limb Motor Function Recovery after Stroke: a Systematic Review

María Antonia Fuentes Calderón [1] · Ainhoa Navarro Miralles [2] · Mauricio Jaramillo Pimienta [3] · Jesús María Gonçalves Estella [3] · María José Sánchez Ledesma [1,4]

Received: 8 January 2019 / Accepted: 30 January 2019 / Published online: 8 February 2019

Abstract

Transcranial direct current stimulation is one of the non-invasive techniques whose main mechanism of action is based on its modulation of cortical excitability. The objective of this study is to analyze the variables (i.e, demographics, clinicals, stimulation parameters) that could influence into the responses during rehabilitation of the upper extremity in patients with stroke. Our systematic review has been performed by searching full-text articles published from January 2008 to December 2018 in Embase, Medline, PubMed and Cochrane Library databases. Studies with adult patients with ischemic or hemorrhagic stroke at any stage of evolution were included. We compared interventions with any type of transcranial direct current stimulation (anodal, cathodal or bihemispheric, also known as dual) regarding improvement of upper extremity motor function. We included 14 studies with 368 patients, of whom almost 89% have ischemic etiology and more than half are males. Most patients were considered subacute or chronic, while only two studies were selected with patients in the acute phase. Different methods of using transcranial direct current stimulation with several complementary therapies were identified, such as virtual reality, robot therapy, Occupational Therapy, Physiotherapy, Constraint Induced Movement Therapy or Peripheral Nerve Stimulation. In conclusion, there is not significant evidence due to heterogeneity of clinical data and therapies. Clinical studies with greater number of participants and protocols standardized could outline this assessment in future studies.

Keywords Transcranial direct current stimulation · Stroke · Upper extremity · Rehabilitation · Systematic review

Introduction

Post-stroke sensorimotor dysfunction occurs in more than half of the cases with neurological deficits, causing a restriction in the autonomous performance of Activities of Daily Living (ADL's) and thus entailing a deterioration in the quality of the patient's life [1, 2]. Recently, numerous strategies oriented to increase the effectiveness of traditional therapies aimed at achieving functional recovery have been developed. Accordingly, robotics [3], Virtual Reality (VR) [4], and non-invasive brain stimulation techniques, including both transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), are being used more frequently [5, 6]. In the last few years, the evidence supporting the effectiveness of these methods applied individually [7, 8] or in combination with other techniques with similar mechanisms of action, has increased [9, 10]. Nevertheless, more studies are needed to investigate the effectiveness of complementary techniques such as tDCS and VR, among other possible options [11–13].

On the other hand, the increasing importance of neuroplasticity and changes in brain activity by rehabilitation techniques, has led to functional recovery through other

This article is part of the Topical Collection on *Patient Facing Systems*

✉ María Antonia Fuentes Calderón
marianrhb@gmail.com

[1] Departament of Surgery, University of Salamanca, Alfonso X el Sabio s/n, 37007 Salamanca, Spain

[2] Official College of Physiotherapists, Departament of Physiotherapy, Alicante, Spain

[3] Departament of Neurosurgery, Universitary Hospital of Salamanca, Paseo de San Vicente, 58-182, 37007 Salamanca, Spain

[4] VisualMed Systems Group, University of Salamanca, Patio Escuelas 1, 37008 Salamanca, Spain

pathways that go beyond reconditioning or physical recovery [14]. In this way, the target of the rehabilitation activity is the brain itself. Thus arise, techniques that seek to synchronize brain activity with sensory and motor function [15, 16].

tDCS generates neural action potentials from an electric current stimulation. Its mechanism is not completely clear although it is believed to induce changes in the resting potential of the neuronal membrane [17]. These changes are specific to the applied polarity, so that the anodal stimulation causes depolarization (increase excitability) while the cathodal causes a hyperpolarization (decrease excitability) of the neuronal membrane potential [18].

In recent years, several systematic reviews and meta-analysis [8, 19–21] have shown positive effects of tDCS on upper extremity (UE) motor recovery in patients who are in the chronic phase of stroke. Some of the clinical trials report a decrease in spasticity after the stimulation sessions [11, 22, 23], but this parameter it is not measured consistently, so it would be interesting to investigate it.

The aim of this study is to achieve a systematic review analyzing the factors which could influence the performance of responses to recovery of the UE in patients with stroke, taking into account demographic variables such as age and sex; clinical aspects including etiology and time since stroke; as well as parameters related to stimulation technique itself; such as the number of sessions, the duration of stimulation, the electrodes position and size.

Material and methods

We conducted a systematic search of full text articles written in English and published between January 2008 and December 2018 in the following electronic databases: Medline, Embase, PubMed and Cochrane Library. Combination of keywords with the use of 'AND' were used for the search and MeSH term used for 'upper extremity'.

> Search: *transcranial direct current stimulation [Title/Abstract] AND stroke [Title/Abstract] AND Upper Extremity [Mesh, Title/Abstract]. Filters: published in the last 10 years*

The inclusion criteria for articles include: randomized, double or single blind with patients over 18 years old who have experienced one or more strokes with ischemic or hemorrhagic etiology, and in acute, subacute or chronic phase, with impaired UE motor or sensorimotor function. The variables collected include number of patients, age and gender and clinical data such as etiology and time since stroke onset. The results on the mobility of the UE affection are subsequent to the application of any form of tDCS (anodal, cathodal, dual or sham) [24], with or without complementary therapies such as VR [25], RT [20, 26], Constraint Induced Movement Therapy (CIMT) [27, 28], Peripheral Nerve Stimulation (PNS) [9, 29], Occupational Therapy (OT) [30, 31] or Physiotherapy (PT) [32]. The scales chosen for the UE functionality assessment were Fugl-Meyer Assessment (FMA) [33], Wolf Motor Function Test (WMFT) [34] or Action Research Arm Test (ARAT) [35].

During the process of studies' selection (Fig. 1), one of the authors (AN) excluded incomplete texts, duplicates and irrelevant studies after titles and abstracts reading. We retrieved the full text of the 83 articles selected with the inclusion criteria, and with scientific relevance and were classified as relevant, possibly relevant or irrelevant. Two authors (AN, MAF) decided whether publications potentially relevant fit PICOS strategy (Patient, Intervention, Comparison, Outcome, Study design) [36] to solve our research question. We excluded studies classified as irrelevant and we analyzed the quality of all trials classified as relevant or possibly relevant via Jadad scores [37]. Disagreements were solved among all authors of the review. Finally, two authors (AN, MAF) extracted independently the results of the studies selected for the qualitative analysis.

Results

After making the studies' selection process (Fig. 1) [38] according to the criteria described previously, we extracted 14 publications whose demographic analysis is contained in Table 1. We collected a total of 368 patients with stroke, of whom almost 89% have ischemic etiology and more than half are males. The average age is 59.2. In two studies [39, 40], with a total of 36 patients, we found interventions in the acute phase, while the rest of publications, are in the subacute [12, 41–43], or chronic phase [11, 44–48] and other two [49, 50] mixed patients in the subacute and chronic phase; with a total of 193 patients in the subacute phase and 139 in the chronic.

In terms of parameters used for tDCS stimulation (Table 2), the interventions offer between 5 and 30 sessions of anodal, cathodal or dual stimulation with a variable duration from 10 to 40 min, while sham stimulation varied from 10 s to 1 min, except in one study in which 20 min of stimulation was applied [41]. The intensity oscillated between 1 and 2 mA and the size of the electrodes ranged from 16.3cm^2 to 35cm^2.

All studies except one [43], agree that the application of tDCS is effective, taking into account the scores of the motor function assessments. In all collected results from the FMA [11, 12, 39, 41–50], except Lee and Chun [40], which assesses the functionality in the ADL's. However, we cannot compare the studies to each other due to the heterogeneity of the results, that is recruiting patients in a broad age range, diverse lesion location and etiology; and the variability in terms of the methods of collecting the results from the scales. In some

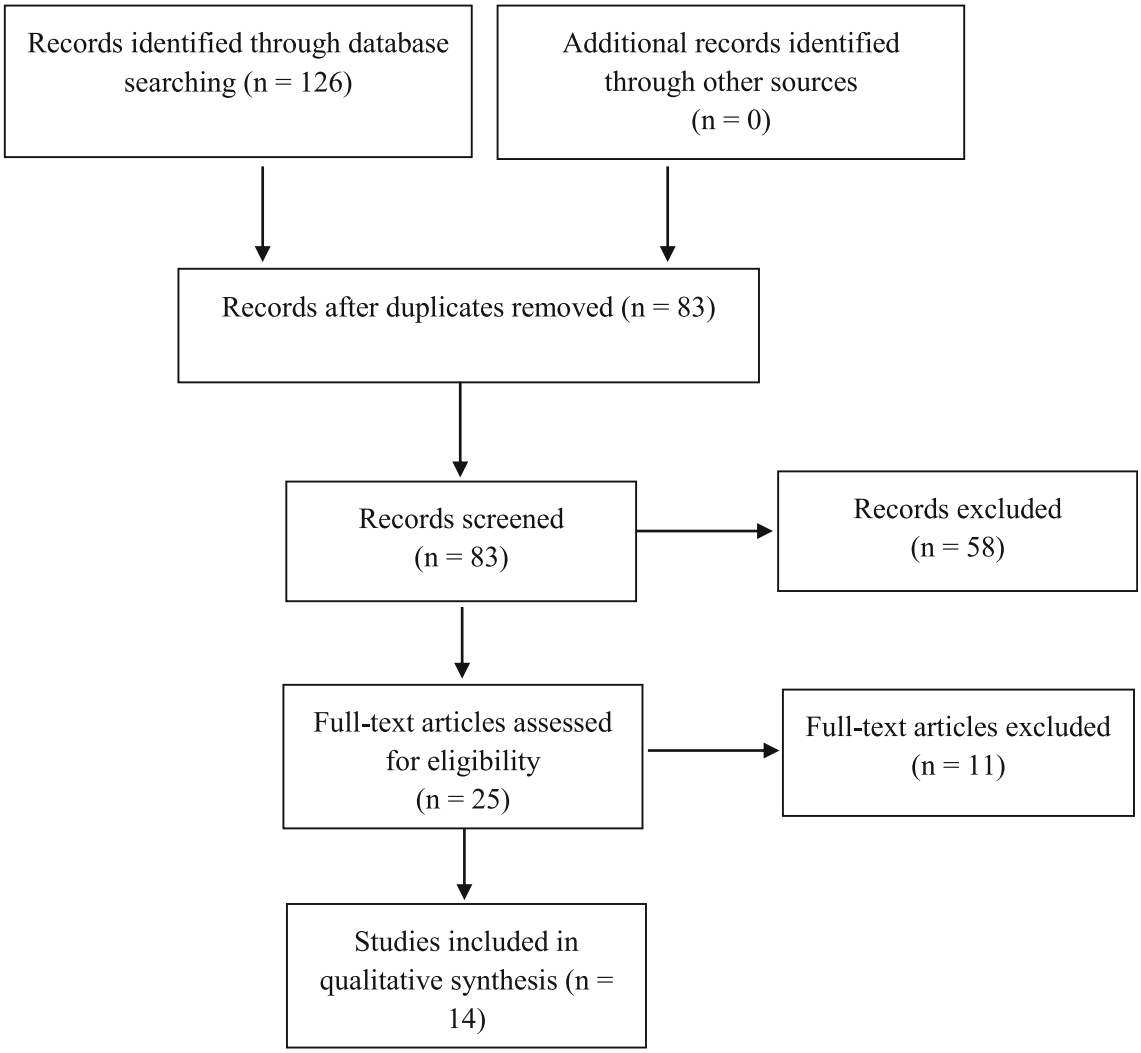

Fig. 1 PRIMSA flowchart

cases, we found the average score obtained from the motor function assessment, and in other cases we found the scores of each patient individually [42, 44].

Discussion

There is no doubt that studies published after the application of tDCS with or without additional treatment report positive effects in the rehabilitation of patients with stroke in both acute and long-term [51–54]. In this sense, it would be necessary to expand the number of randomized trials of assessable quality to avoid biases. From the review of the articles selected in our study, we consider some factors that might influence over the effectiveness of tDCS in any of its variants, anodal, cathodal or dual.

Firstly, demographic variables such as the patient's age and sex, as well as the clinical data on etiology, time of evolution and lesion location, are factors to emphasize. Nowadays, it is accepted that stroke is the first cause of death in women and the third in males as well as the first cause of disability in the adult [55]. This information about patients is collected, broadly speaking, in all studies included in this work [11, 12, 39–50], but only a minority mentioned that it would be important to take them into account [39, 40, 42, 43, 50]. On the other hand, none of them sets out more specific analyses.

As for the data associated with the pathology, it has been observed that there is a controversy in relation to the time limits that define the shape of the stroke in relation to the terms that define the type of stroke by time evolution. That is, the studies analyzed considered as acute stroke, when the elapsed time reaches up to 10 days or 2 weeks after stroke [39, 40]; subacute between 2 weeks and 6 months [12, 41–43, 49, 50]; and chronic, from 8 weeks or since 6 months after stroke onset [11, 41, 44, 46, 47, 49, 50]. Without doubt this variability poses a major difficulty when comparing the results, so it would be necessary to standardize these basic concepts and to develop studies with patients who are clearly at the same time of evolution, in order to obtain more valuable results.

Table 1 Demographic details, etiology and post stroke delay

Study	*N*	Sex (M/F)	Age (mean)	Etiology (I/H)	Post stroke delay
Lindenberg et al. (2010)	20	15/5	34.6–77.8 (58.7)	I	Chronic
Kim et al. (2010)	18	13/5	34–77 (57.2)	I	Subacute
Bolognini et al. (2011)	14	5/9	26–75 (46.7)	12/2	Chronic
Hesse et al. (2011)	96 (85)	59/32	39–79 (64.9)	I	Subacute
Nair et al. (2011)	14	9/5	40–76 (58.5)	I	Chronic
Fusco et al. (2014)	11	5/6	33–77 (58.3)	I	Subacute
Joung Lee and Chun (2014)	59	31/28	– (61.3)	35/24	Subacute
Viana et al. (2014)	20	16/4	– (55.5)	I	Chronic
Sattler et al. (2015)	20	14/6	37–82 (65.1)	I	Acute
Triccas et al. (2015)	22	13/9	37–83 (63.4)	17/5	Subacute, chronic
Ilic et al. (2016)	26	17/9	48–67 (60.1)	I	Chronic
Straudi et al. (2016)	23	12/11	– (58.2)	19/4	Subacute, chronic
Rabadi et al. (2017)	16	16/0	– (62)	I	Acute
Takebayashi et al. (2017)	20	14/6	– (59.3)	14/6	Chronic

F female, *H* hemorrhagic stroke, *I* ischemic stroke, *M* male

Related to stimulation technique, we also observed notable differences between the publications since there is no protocol for the parameters used with tDCS, in terms of intensity, number of sessions and electrodes position, and there are disagreements between which is the best type of stimulation or position for the electrodes on each situation to achieve the best results and to maintain of the long-term benefits. For instance, Nair et al. [48], applied tDCS cathodal over M1 unaffected, intensity at 1 mA, for 30 min, 5 consecutive days in patients with ischemic chronic stroke and moderate UE dysfunction, to the time they receive OT rehabilitation treatment. The benefits obtained persist for at least 1 week after the end of the intervention. However, in the study by Lindenberg et al. [44], the parameters differ in that patients receive bihemispheric stimulation and the intensity is 0.5 mA higher.

In contrast, Ilic et al. [45] report that after 10 sessions of 20 min anodal stimulation in M1 affected at 2 mA intensity, the maintenance of the mobility effectiveness and function of the UE is observed up to 1 month later. Unlike in previous studies, the stimulation is performed prior to the OT rehabilitation treatment, so that could be another factor that act over the technique effectiveness.

The greatest long-term benefit with an intervention of tDCS cathodal and OT in ischemic subacute stroke was observed by Kim et al. [42], with a duration of up to 6 months. Another study that follows in maintenance of gains is Hesse et al. [41], which reaches to 3 months. There are no significant differences between age, sex, etiology, time of stroke evolution and severity of UE impairment among the patients of both studies. The treatment covers 20 sessions more than Kim et al. [42] including, in addition, RT.

Therefore, in patients with ischemic subacute stroke, stimulation with tDCS anodal or cathodal along with RT, would not provide greater long-term benefits than tDCS cathodal with OT. Otherwise, Straudi et al. [50] study the effectiveness of the combination of dual-tDCS with RT for 10 sessions, for the rehabilitation of the paretic arm in patients with subacute and chronic stroke, whose results showed slightly relevant changes, but they claim that dual-tDCS was more suitable for chronic stroke with a subcortical lesion and less effective for subjects in a subacute phase or with cortical stroke. Moreover, Triccas et al. [49], concludes that the use of anodal-tDCS with RT is more effective in the subacute phase of stroke than in the chronic one. In addition, tDCS should be applied before the motor training task to avoid the activation of the mechanism for homeostatic regulation [56, 57]. In this way, the role of the tDCS with complementary therapies that include functional tasks would turn or decrease the cortical excitability to optimize the process of learning prior to the activity execution [56].

Associating tDCS with a complementary technique, could have a synergistic effect that would contribute to a greater benefit in the rehabilitation of the UE than the application of each of them individually. It is observed that VR provides feedback in real time, which increases the intensity of the activity and the duration of task-oriented training, promoting the function of the UL [12, 52, 53]. Thus, the first study carried out with a combination of tDCS and VR in Lee and Chun [12], with a sample of patients with subacute stroke, corroborates the functional improvement in the UE also detected in the study of Viana et al. [11], which collected patients with chronic stroke. This is interesting, because 6 months after suffering brain damage, spontaneous recovery is unlikely [58, 59]. In addition, the recovery of UE function in patients with long-term stroke using robotics favors joint mobility and provides a greater increase in social participation compared to

Table 2 Intervention parameters

Study	Intervention	Stimulation	Duration	Intensity	Size	N° sessions
Lindenberg et al. (2010)	PT/OT	dual-tDCS/sham	30 min/30s	1.5 mA	16.3 cm^2	5
Kim et al. (2010)	OT	anodal/cathodal/sham	20 min/20 min/1 min	2 mA	25 cm^2	10
Bolognini et al. (2011)	CIMT	dual-tDCS/sham	40 min/10 s	2 mA	35 cm^2	14
Hesse et al. (2011)	RT	anodal/cathodal/sham	20 min/20 min/20 min	2 mA	35 cm^2	30
Nair et al. (2011)	OT	cathodal/sham	30 min/30 min	1 mA	–	5
Fusco et al. (2014)	PT/OT	cathodal/sham	10 min/10 min	1.5 mA	35 cm^2	10
Joung Lee and Chun (2014)	VR, OT	cathodal	20 min	2 mA	25 cm^2	15
Viana et al. (2014)	VR	anodal/sham	13 min/30s	2 mA	35 cm^2	15
Sattler et al. (2015)	PNS	anodal/sham	13 min/1 min	1.2 mA	35 cm^2	5
Triccas et al. (2015)	RT	anodal/sham	20 min/10 s	1 mA	35 cm^2	18
Ilic et al. (2016)	OT	anodal/sham	20 min/1 min	2 mA	25 cm^2	10
Straudi et al. (2016)	RT	dual-tDCS/sham	30 min/30 s	1 mA	35 cm^2	10
Rabadi et al. (2017)	PT/OT	cathodal/sham	30 min/30s	1 mA	35 cm^2	10
Takebayashi et al. (2017)	CIMT, PNS	anodal/cathodal	20 min/20 min	1 mA	–	10

CIMT Constraint Induced Movement Therapy, *OT* Occupational Therapy, *PNS* peripheral nerve stimulation, *PT* physiotherapy, *RT* robot therapy, *tDCS* transcranial direct current stimulation; *VR* virtual reality

conventional therapies [60]. However, this type of treatment is even more passive than the VR therapy, since robotics and exoskeletons can improve UE overall UE mobility but not manual dexterity [61].

When establishing a suited stimulation protocol, it is necessary to keep in mind that the mechanism of cortical reorganization after stroke is a dynamic process that differs depending on the location of the injury, the evolution time and severity of the damage [62]. This neuroplastic process does not always facilitate motor recovery. In fact, there could be maladaptive consequences that may interfere with the spontaneous recovery in the acute and subacute stage [63]. Contralesional hyperexcitability begins 1 week after stroke onset and lasts up to 4 months [64]. In case of the primary sensorimotor cortex (S1 M1), a study with functional Magnetic Resonance Imaging (fMRI) [65] shows the evolution from the activation of the contralesional hemisphere 20 days after the stroke onset to hyperactivation of ipsilesional hemisphere 4 months later, concurrent with the recovery. In most severe cases, there is a hyperactivation of both hemispheres at the same time. In this way, to re-establish the interhemispheric balance in this case, it seems appropriate to apply a stimulation protocol with dual-tDCS [66], as referred to in Bolognini et al. [47], in which a significant improvement is observed in chronic stroke patients compared to a control group after 14 sessions of 40 min of bihemispheric stimulation, during CIMT. Accordingly, Takebayashi et al. [46] describe better results in the experimental group compared to the control group, but in this case, dual-tDCS is applied first, followed by PNS and CIMT. tDCS is known to potentiate the benefits in motor function induced by CIMT, either before or during the therapy [46, 47, 67], although it remains unclear which of the two options provides the greatest benefits in the case of chronic stroke or if there are differences comparable depending on the ischemic or hemorrhagic etiology.

Two of the studies found [42, 44], show the demographic and clinical data of each patient individually, which has allowed us to compare if there is any relationship between these factors, the type of stimulation applied and the improvement in the UE mobility. None of them are double blind, what could be a risk of bias. In Kim et al. [42], the greatest benefit was in a female, 34 years old, with subcortical subacute ischemic stroke which received anodal tDCS for 20 min during 10 sessions at 2 mA, followed by a male, 68 years old, with a cortical subacute ischemic stroke, who received cathodal tDCS with the same dosage. In this study, both patients received OT sessions at the same time during treatment and the follow-up, which lasts up to 6 months, where the results have statistical significance just in the cathodal group. Here we find other probable biases, because these benefits may be masked by a possible spontaneous recovery and its maintenance due to OT sessions. Moreover, the best score collected in the study by Lindenberg et al. [44] is a male, 52 years old, with cortical chronic ischemic stroke who received dual-tDCS for 30 min during 5 consecutive sessions at 1.5 mA with PT/OT at the same time of the stimulation. This patient scored higher on the FMA scale post-intervention and follow-up than another male, who received the same treatment, was younger, the time after stroke onset is 11 months older, the lesion size was similar, but the damage at the corticospinal tract was bigger. This can lead us to think that regardless of the age of the patient, the effectiveness of the technique depends on the state of the corticospinal tract and the time of stroke evolution. In addition, OT rehabilitation sessions after the intervention with

tDCS is favorable for the maintenance of the profits obtained. All the patients mentioned have ischemic etiology, but in Fuentes et al. [52], they obtained close results to the previous study using anodal tDCS with VR for 20 min during 25 sessions at 2 mA in a male, 38 years old, with hemorrhagic subcortical chronic stroke. He received 25 sessions of PT after the intervention plan and FMA scores decreased slightly at the end. So, it would be interesting to analyze cerebral reorganization after a stroke to know the differences during the process between ischemic and hemorrhagic etiology.

The evidence indicates that there is a greater effect of non-invasive stimulation with dual-tDCS in patients in the chronic phase of stroke [44, 47, 50]; with the use of cathodal tDCS on unaffected hemisphere in patients with subacute stroke [12, 42, 43, 48, 52]; and we have not found in our review any differences among the results with anodal or cathodal stimulation in the acute phase [39, 40]. From our point of view, performing neuroimaging (fMRI, PET scan) and electrophysiological studies (EEG) might help to know the status of the brain activation and to be able to choose what type of stimulation is the most appropriate according to the time of evolution.

Conclusions

There was clinical heterogeneity among the included studies concerning age of participants, time since stroke; type, duration and intensity of stimulation, location of the electrodes, severity impairment at baseline and concurrent therapies. This may be because the optimal stimulation protocol is not yet established. Confirming the performance protocols with tDCS for the rehabilitation of UE in patients with stroke, taking into account factors such as age, sex, stroke etiology and location could have a great economic and psychosocial impact, reducing the duration of rehabilitation. It will be necessary to study the durability of the effects of tDCS, evaluating the maintenance and prognosis of neurological improvement over time with and without complementary therapies, as well as analyzing the change in cortical excitability using standardized protocols with neuroimaging (fMRI, PET) or electrophysiological assessment (EEG) before and after the stimulation. All in all, this will make it possible to verify the neurophysiological changes in an objective manner to apply these techniques with scientific evidence.

Compliance with Ethical Standards

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Timmermans, A. A., Lemmens, R. J., Monfrance, M. et al., Effects of task-oriented robot training on arm function, activity and quality of life in chronic stroke patients: Randomized controlled trial. *J. Neuroeng. Rehabil.* 11:45, 2014. https://doi.org/10.1186/1743-0003-11-45.
2. Wu, C. Y., Huang, P. C., Chen, Y. T., Lin, K. C., and Yang, H. W., Effects of mirror therapy on motor and sensory recovery in chronic stroke: A randomized controlled trial. *Arch. Phys. Med. Rehabil.* 94:1023–1030, 2013. https://doi.org/10.1016/j.apmr.2013.02.007.
3. Grimm, F., Naros, G., and Gharabaghi, A., Closed-loop task difficulty adaptation during virtual reality reach-to-grasp training assisted with an exoskeleton for stroke rehabilitation. *Front Neurosci.* 10:518, 2016. https://doi.org/10.3389/fnins.2016.00518.
4. Layer, K. E., Thomas, G. S., Deutsch, J. E., and Crotty, M., Virtual reality for stroke rehabilitation. *Cochrane Database Syst. Rev.* 11, 2017. https://doi.org/10.1002/14651858.CD008349.pub4.
5. McDonell, M. N., and Stinear, C. M., TMS measures of motor cortex function after stroke: A meta-analysis. *Brain Stimul.* 10(4): 721–734, 2017. https://doi.org/10.1016/j.brs.2017.03.008.
6. Fleming, M. K., Rothwell, J. C., Sztriha, L., Teo, J. T., and Newham, D. J., The effect of transcranial direct current stimulation on motor sequence learning and upper limb function after stroke. *Clin. Neurophysiol.* 128(7):1389–1398, 2017. https://doi.org/10.1016/j.clinph.2017.03.036.
7. Grefkes, C., and Fink, G. R., Noninvasive brain stimulation after stroke: It is time for large randomized controlled trials. *Curr. Opin. Neurol.* 29(6):714–720, 2016. https://doi.org/10.1097/WCO.0000000000000395.
8. Elsner, B., Kwakkel, G., Kugler, J., and Mehrholz, J., Transcranial direct current stimulation (tDCS) for improving capacity in activities and arm function after stroke: A network meta-analysis of randomized controlled trials. *J. Neuroeng. Rehabil.* 14(1):95, 2017. https://doi.org/10.1186/s12984-017-0301-7.
9. Menezes, I. S., Cohen, L. G., Mello, E. A. et al., Combined brain and Pheripheral nerve stimulation in chronic stroke patients with moderate to severe motor impairment. *Neuromodulation* 21(2): 176–183, 2018. https://doi.org/10.1111/ner.12717.
10. Simonetti, D., Zollo, L., Milighetti, S. et al., Literature review on the effects of tDCS coupled with robotic therapy in post stroke upper limb rehabilitation. *Front. Hum. Neurosci.* 11:268, 2017. https://doi.org/10.3389/fnhum.2017.00268.
11. Viana, R. T., Laurentino, G. E. C., Souza, R. J. et al., Effects of the addition of transcranial direct current stimulation to virtual reality therapy after stroke: A pilot randomized controlled trial. *Neurorehabilitation* 34(3):437–446, 2014. https://doi.org/10.3233/nre-141065.
12. Lee, S. J., and Chun, M. H., Combination transcranial direct current stimulation and virtual reality therapy for upper extremity training in patients with subacute stroke. *Arch. Phys. Med. Rehabil.* 95(3): 431–438, 2014. https://doi.org/10.1016/j.apmr.2013.10.027.
13. Kim, Y. J., Ku, J., Cho, S. et al., Facilitation of corticospinal excitability by virtual reality excercise following anodal transcranial direct current stimulation in healthy volunteers and subacute stroke patients. *J. Neuroeng. Rehabil.* 11:124, 2014. https://doi.org/10.1186/1743-0003-11-124.
14. Dobkin, B. H., and Dorsch, A., New evidence for therapies in stroke rehabilitaiton. *Curr. Atheroscler. Rep.* 15(6):331, 2013. https://doi.org/10.1007/s1183-013-0331-y.

15. Lewis, P. M., Thomson, R. H., Rosenfeld, J. V., and Fitzgerald, P. B., Brain neuromodulation techniques: A review. *Neuroscientist* 22(4):406–421, 2016. https://doi.org/10.1177/1073858416646707.
16. Gassert, R., and Volker, D., Rehabilitation robots for the treatment of sensoriomotor deficits: A neurophysiological perspective. *J. NeuroEng. Rehabil.* 5(1):46, 2018. https://doi.org/10.1186/s12984-018-0383-x.
17. Kropotov, J.D., Transcranial direct current stimulation. In: *Functional neuromarkers for psychiatry*, 273–280, 2016. https://doi.org/10.1016/B978-0-12-410513-3.00018-8
18. Roche, N., Geiger, M., and Bussel, B., Mechanisms underlying transcranial direct current stimulation in rehabilitation. *Ann. Phys. Rehabil. Med.* 58(4):214–219, 2015. https://doi.org/10.1016/j.rehab.2015.04.009.
19. Buttler, A. J., Shuster, M., O'Hara, E. et al., A meta-analysis of the efficacy of anodal transcranial direct current stimulation for upper limb motor recovery in stroke survivors. *J. Hand Ther.* 26(2):162–170, 2013. https://doi.org/10.1016/j.jht.2012.07.002.
20. Triccas, L. T., Burridge, J. H., Hughes, A. M. et al., Multiple sessions of transcranial direct current stimulation and upper extremity rehabilitation in stroke: A review and meta-analysis. *Clin. Neurophysiol.* 127(1):945–955, 2016. https://doi.org/10.1016/j.clinph.2015.04.067.
21. Kandel, M., Beis, J. M., Le Chapelain, L., Guesdon, H., and Paysant, J., Non-invasive cerebral stimulation for the upper limb rehabilitation after stroke: A review. *Ann. Phys. Rehabil. Med.* 55:657–680, 2012. https://doi.org/10.1016/j.rehab.2012.09.001.
22. Levin, M. F., Baniña, M. C., Frenkel-Toledo, S. et al., Personalized upper limb training combined with anodal-tDCS for sensorimotor recovery in spastic hemiparesis: Study protocol for a randomized controlled trial. *Trials* 19(1):7, 2018. https://doi.org/10.1186/s13063-017-2377-6.
23. Del Felice, A., Daloli, V., Masiero, S., and Manganotti, P., Contralesional cathodal versus dual transcranial direct current stimulation for decreasing upper limb spasticity in chronic stroke individuals: A clinical and neurophysiological study. *J. Stroke Cerebrovasc. Dis.* 25(12):2932–2941, 2016.
24. Thair, H., Holloway, A. L., Newport, R., and Smith, A. D., Transcranial direct current stimulation (tDCS): A beginner's guide for design and implementation. *Front. Neurosci.* 11:641, 2017. https://doi.org/10.3389/fnins.2017.00641.
25. Laver, K. E., George, S., Thomas, S., Deutsch, J. E., and Crotty, M., Virtual reality for stroke rehabilitation. *Cochrane Database Syst. Rev.* 9(2):1–107, 2015.
26. Triccas, L. T., Burridge, J. H., Hughes, A. M. et al., A qualitative study exploring views and experiences of people with stroke undergoing transcranial direct current stimulation and upper limb robot therapy. *Top. Stroke Rehabil.* 20:1–9, 2018. https://doi.org/10.1080/10749357.2018.1493072.
27. Kwakkel, G., Verbeek, J. M., van Wegen, E. H., and Wolf, S. L., Constraint-induced movement therapy after stroke. *Lancet Neurol.* 14(2):224–234, 2015. https://doi.org/10.1016/S1474-4422(14)70160-7.
28. Thrane, G., Friborg, O., Anke, A., and Indredavik, B., A meta-analysis of constraint-induced movement therapy after stroke. *J. Rehabil. Med.* 46(9):833–842, 2014. https://doi.org/10.2340/16501977-1859.
29. Carrico, C., Chelette, K. C., Westgate, P. M. et al., Randomized trial of peripheral nerve stimulation to enhance modified constraint-induced therapy after stroke. *Am. J. Phys. Med. Rehabil.* 95(6):397–406, 2016. https://doi.org/10.1097/PHM.0000000000000476.
30. Govender, P., and Kalra, L., Benefits of occupational therapy in stroke rehabilitation. *Expert. Rev. Neurother.* 8:1013–1019, 2007. https://doi.org/10.1586/14737175.7.8.1013.
31. Steultjens, E. M., Dekker, J., and Bouter, L. M., Occupational therapy for stroke patients: A systematic review. *Stroke* 34(3):676–687, 2003. https://doi.org/10.1161/01.STR0000057576.77308.30.
32. Wattchow, K. A., McDonnell, M. N., and Hillier, S. L., Rehabilitation interventions for upper limb function in the first four weeks following stroke: A systematic review and meta-analysis of the evidence. *Arch. Phys. Med. Rehabil.* 99(2):367–382, 2018. https://doi.org/10.1016/j.apmr.2017.06.014.
33. Gladstone, D. J., Danells, C. J., and Black, S. E., The fugl-meyer assessment of motor recovery after stroke: A critical review of its measurement properties. *Neurorehabil. Neural Repair* 16(3):232–240, 2002. https://doi.org/10.1177/154596802401105171.
34. Woodbury, M., Velozo, C. A., Thompson, P. A. et al., Measurement structure of the Wolf Motor function test: Implications for motor control theory. *Neurorehabil. Neural Repair* 24(9):791–801, 2010. https://doi.org/10.1177/1545968310370749.
35. Van der Lee, J. H., De Groot, V., Beckerman, H. et al., The intra- and interrater reliability of the action research arm test: A practical test of upper extremity function in patients with stroke. *Arch. Phys. Med. Rehabil.* 82:14–19, 2001. https://doi.org/10.1053/apmr.2001.18668.
36. Da Costa Santos, C. M., Pimenta, A. M., and Nobre, M. R., The PICO strategy for the research question contruction and evidence search. *Rev. Latino-Am Enfermagem* 15:3, 2007. https://doi.org/10.1590/S0104-11692007000300023.
37. Clark, H. D., Wells, G. A., Huët, C. et al., Assessing the quality of randomized trials: Reliability of the Jadad scale. *Control. Clin. Trials* 20(5):448–452, 1999. https://doi.org/10.1016/S0197-2456(99)00026-4.
38. Moher, D., Liberati, A., Tetzlaff, J., and Altman, D. G., Preferred Reportin items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med.* 6(7):31000097, 2009. https://doi.org/10.1371/journal.pmed1000097.
39. Sattler, V., Acket, B., Raposo, N. et al., Anodal tDCS combined with radial nerve stimulation promotes hand motor recovery in the acute phase after ischemic stroke. *Neurorehabil. Neural Repair*:1–12, 2015. https://doi.org/10.1177/1545968314565465.
40. Rabadi, M. H., and Aston, C. E., Effect of transcranial direct current stimulation on severely affected arm-hand motor function in patients after an acute ischemic stroke. *Am. J. Phys. Med. Rehabil.* 96:00–00, 2017. https://doi.org/10.1097/PHM.0000000000000823.
41. Hesse, S., Waldner, A., Mehrholz, J. et al., Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: An exploratory, randomized multicenter trial. *Neurorehabil. Neural Repair* 25(9):838–846, 2011. https://doi.org/10.1177/1545968311413906.
42. Kim, D. Y., Lim, J. Y., Kang, E. K. et al., Effect of transcranial direct current stimulation on motor recovery in patients with subacute stroke. *Am. J. Phys. Med. Rehabil.* 89(11):879–886, 2010. https://doi.org/10.1097/PHM.0b013e3181f70aa7.
43. Fusco, A., Assenza, F., Iosa, M. et al., The ineffective role of cathodal tDCS in enhancing the functional motor outcomes in early phase of stroke rehabilitation: An experimental trial. *Biomed. Res. Int.*:1–9, 2014. https://doi.org/10.1155/2014/547290.
44. Lindenberg, R., Renga, V., Zhu, L. et al., Bihemispheric brain stimualtion facilitates motor recovery in chronic stroke patients. *Neurology* 71(24):2176–2184, 2010. https://doi.org/10.1212/wnl.0b013e318202013a.
45. Ilic, N. V., Dubljanin-Raspapovic, E., Nedeljkovic, U. et al., Effects of anodal tDCS and occupational therapy on fine motor skill deficits in patients with chronic stroke. *Restor. Neurol. Neurosci.* 34(6):935–945, 2016. https://doi.org/10.3233/rnn-160668.
46. Takebayashi, T., Takahashi, K., Moriwaki, M. et al., Improvement of upper extremity deficit after constraint-induced movement therapy combined with and without preconditioning stimulation using

dual-hemisphere transcranial direct current stimulation and peripheral neuromuscular stimulation in chronic stroke patients: A pilot randomized controlled trial. *Front. Neurol.* 8:568, 2017. https://doi.org/10.3389/fneur.2017.00568.

47. Bolognini, N., Vallar, G., Casati, C. et al., Neurophysiological and behavioral effects of tDCS combined with constraint-induced movement therapy in Poststroke patients. *Neurorehabil. Neural Repair* 25(9):819–829, 2011. https://doi.org/10.1177/1545968311411056.
48. Nair, D. G., Renga, V., Lindenberg, R. et al., Optimizing recovery potential through simultaneous occupational therapy and non-invasive brain-stimulation using tDCS. *Restor. Neurol. Neurosci.* 29:411–420, 2011. https://doi.org/10.3133/RNN-2011-0612.
49. Triccas, L. T., Burridge, J. H., Hughes, A. et al., A double-blinded randomised controlled trial exploring the effect of anodal transcranial direct current stimulation and uni-lateral robot therapy for the impaired upper limb in sub-acute and chronic stroke. *NeuroRehabilitation* 37(2):181–191, 2015. https://doi.org/10.3233/nre-151251.
50. Straudi, S., Fregni, F., Martinuzzi, C. et al., tDCS and robotics on upper limb stroke rehabilitaiton: Effect modification by stroke duration and type of stroke. *Biomed. Res. Int.*:1–8, 2016. https://doi.org/10.1155/2016/5060127.
51. Kang, N., Summers, J. J., and Cauraugh, J. H., Transcranial direct current stimulation facilitates motor learning post-stroke: A systematic review and meta-analysis. *J. Neurol. Neurosurg. Psychiatry* 87(4):345–355, 2016. https://doi.org/10.1136/jnnp-2015-311242.
52. Fuentes, M. A., Borrego, A., Latorre, J., Colomer, C., Alcañiz, M., Ledesma, M. J., and LLorens, R., Combined transcranial direct current stimulation and virtual reality-based paradigm for upper limb Rehabilitaiton in individuals with restricted movements. A feasibility study with a chronic stroke survivor with severe hemiparesis. *J. Med. Syst.* 42:87, 2018. https://doi.org/10.1007/s10916-018-0949-y.
53. Dehem, S., Giliaux, M., Lejeune, E. et al., Effectiveness of a single session of dual-transcranial direct current stimulation in combination with upper limb robotic-assisted rehabilitaiton in chronic stroke patients: A randomized double-blind cross-over study. *Int. J. Rehabil. Res.* 41:138–145, 2018. https://doi.org/10.1097/MRR.0000000000000274.
54. Sparing, R., and Mottaghy, M., Noninvasive brain stimulation with transcranial magnetic or direct current stimulation (TMS/tDCS) - from insights into human memory to therapy of its dysfunction. *Methods* 44:329–337, 2008. https://doi.org/10.1016/j.ymeth.2007.02.001.
55. Yaghi, S., Pilot, M., Song, C. et al., Ischemic stroke risk after acute coronary syndrome. *J. Am. Heart Assoc.* 5(7):e002590, 2016. https://doi.org/10.1161/jaha.115.002590.
56. Cabral, M. E., Baltar, A., Borba, R. et al., Transcranial direct current stimulation: Before, during, or after motor training? *NeuroReport* 26(11):618–622, 2015. https://doi.org/10.1097/wnr.0000000000000397.
57. Giacobbe, V., Krebs, H. I., Volpe, B. T. et al., Transcranial direct current stimulation (tDCS) and robotic practice in chronic stroke: The dimension of timing. *NeuroRehabilitation* 33(1):49–56, 2013. https://doi.org/10.1017/cbo9780511736216.013.
58. Bayona, N. A., Bitensky, J., Salter, K., and Teasell, R., The role of task-specific training in rehabilitation therapies. *Top. Stroke Rehabil.* 12(3):58–65, 2005. https://doi.org/10.1310/BQM5-6YGB-MVJ5-WVCR.
59. Barker, R. N., Gill, T. J., and Brauer, S. G., Factor contributing to upper limb recovery after stroke: A survey of stroke survivors in Queensland Australia. *Disabil. Rehabil.* 29(13):981–989, 2007. https://doi.org/10.1080/09638280500243570.
60. Lo, A. C., Guarno, P. D., Richards, L. G. et al., Robot-assisted therapy for long-term upper-limb impairment after stroke. *N. Engl. J. Med.* 362(19):1772–1783, 2010. https://doi.org/10.1056/nejmx110075.
61. Lambercy, O., Doyat, L., Johnson, V. et al, Development of a robot-assisted rehabilitation therapy to train hand function for activities of daily living. In: *10th international conference on rehabilitation robotics*, 2007. https://doi.org/10.1109/icorr.2007.4428498
62. Grefkes, C., and Ward, N. S., Cortical reorganization after stroke: How much and how functional? *Neuroscientist* 20(1):56–70, 2014. https://doi.org/10.1177/1073858413491147.
63. Schlaug, G., and Renga, V., Transcranial direct current stimulation: A noninvasive tool to facilitate stroke recovery. *Expert Rev. Med. Devices* 5:759–768, 2008. https://doi.org/10.1586/17434440.5.6.759.
64. Schiene, K., Bruehl, C., Zilles, K. et al., Neuronal hyperexcitability and reduction of GABAA-receptor expression in the surround of cerebral photothrombosis. *J. Cereb. Blood Flow Metab.* 16:906–914, 1996. https://doi.org/10.1097/00004647-199609000-00014.
65. Tombari, D., Loubinoux, I., Pariente, J. et al., A longitudinal fMRI study: In recovering and then in clinically stable sub-cortical stroke patients. *Neuroimage* 23:827–839, 2004. https://doi.org/10.1016/j.neuroimage.2004.07.058.
66. Stinear, C. M., Barber, P. A., Smale, P. R. et al., Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain* 130(1):170–180, 2007. https://doi.org/10.1093/brain/awl333.
67. Bonaiuti, D., Rebasti, L., and Sioli, P., The constraint induced movement therapy: A systematic review of randomised controlled trials on the adult stroke patients. *Eura. Medicophys.* 43:139–146, 2007. https://doi.org/10.1161/01.str.0000143320.64953.c4.