Video Article

The Combined Use of Transcranial Direct Current Stimulation and Robotic Therapy for the Upper Limb

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Abstract

Neurologic disorders such as stroke and cerebral palsy are leading causes of long-term disability and can lead to severe incapacity and restriction of daily activities due to lower and upper limb impairments. Intensive physical and occupational therapy are still considered main treatments, but new adjunct therapies to standard rehabilitation that may optimize functional outcomes are being studied.

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that polarizes underlying brain regions through the application of weak direct currents through electrodes on the scalp, modulating cortical excitability. Increased interest in this technique can be attributed to its low cost, ease of use, and effects on human neural plasticity. Recent research has been performed to determine the clinical potential of tDCS in diverse conditions such as depression, Parkinson's disease, and motor rehabilitation after stroke. tDCS helps enhance brain plasticity and seems to be a promising technique in rehabilitation programs.

A number of robotic devices have been developed to assist in the rehabilitation of upper limb function after stroke. The rehabilitation of motor deficits is often a long process requiring multidisciplinary approaches for a patient to achieve maximum independence. These devices do not intend to replace manual rehabilitation therapy; instead, they were designed as an additional tool to rehabilitation programs, allowing immediate perception of results and tracking of improvements, thus helping patients to stay motivated.

Both tDSC and robot-assisted therapy are promising add-ons to stroke rehabilitation and target the modulation of brain plasticity, with several reports describing their use to be associated with conventional therapy and the improvement of therapeutic outcomes. However, more recently, some small clinical trials have been developed that describe the associated use of tDCS and robot-assisted therapy in stroke rehabilitation. In this article, we describe the combined methods used in our institute for improving motor performance after stroke.

Video Link

The video component of this article can be found at https://www.jove.com/video/58495/

Introduction

Neurological disorders such as stroke, cerebral palsy, and traumatic brain injury are leading causes of long-term disability, due to lesions and subsequent neurologic symptoms that can lead to severe incapacity and restriction of daily activities[1]. Movement disorders significantly reduce a patient's quality of life. Motor recovery is fundamentally driven by neuroplasticity, the basic mechanism underlying the reacquisition of motor skills lost due to brain lesions[2,3]. Thus, rehabilitation therapies are strongly based on high-dose intensive training and intense repetition of movements to recover strength and range of motion. These repetitive activities are based on daily life movements, and patients may become less motivated due to the slow motor recovery and repetitive exercises, which can impair the success of neurorehabilitation[4]. Intensive physical and occupational therapy are still considered main treatments, but newer adjunct therapies to standard rehabilitation are being studied to optimize functional outcomes[1].

The advent of robotic-assisted therapies has been shown to have great value in stroke rehabilitation, influencing processes of neuronal synaptic plasticity and reorganization. They have been investigated for the training of patients with damaged neurological functions and assisting people with disabilities[5]. One of the most important advantages of adding robot technology to rehabilitive interventions is its ability to deliver high-intensity and high-dosage training, which otherwise would be a very labor-intensive process[6]. The use of robotic therapies, along with virtual reality computer programs, allows for an immediate perception and evaluation of motor recovery and can change repetitive actions into meaningful, interactive functional tasks such as cleaning a stovetop[7]. This can elevate patients' motivation and adherence to the long rehabilitation process and allows, through the possibility of measuring and quantifying movements, tracking of their progress[5]. Integration of

robotic therapy into current practices may increase the efficacy and effectiveness of rehabilitation and enable the development of novel modes of exercise[8].

Therapeutic rehabilitation robots provide task-specific training and can be divided into end-effector-type devices and exoskeleton-type devices[9]. The difference between these classifications is related to how movement is transferred from the device to the patient. End-effector devices have simpler structures, contacting the patient's limb only at its most distal part, making it more difficult to isolate movement of one joint. Exoskeleton-based devices have more complex designs with a mechanical structure that mirrors the skeletal structure of the limb, so a movement of the device's joint will produce the same movement on the patient's limb[7,9].

The T-WREX is an exoskeleton-based robot that assists whole arm movements (shoulder, elbow, forearm, wrist, and finger movements). The adjustable mechanical arm allows variable levels of gravity support, enabling patients who have some residual upper limb function to achieve a larger active range of motion in a tridimensional spatial therapy[7,9]. The MIT-MANUS is an end-effector-type robot that works in a single plan (x- and y-axis) and allows a two-dimensional gravity compensated therapy, assisting shoulder and elbow movements by moving the patient's hand in the horizontal or vertical plane[9,10]. Both robots have built-in position sensors that can quantify upper extremity motor control and recovery and an interface for computer integration that allows 1) the training of meaningful functional tasks simulated in a virtual learning environment and 2) therapeutic exercise games, which help the practice of motor planning, eye-hand coordination, attention, and visual field defects or neglects[7,9]. They also allow for the compensation of gravity effects on the upper limb and are capable of offering support and assistance to repetitive and stereotyped movements in severely impaired patients. This progressively reduces assistance as the subject improves and applies minimal assistance or resistance to movement for mildly impaired patients[9,11].

Another new technique for neurorehabilitation is transcranial direct current stimulation (tDCS). tDCS is a non-invasive brain stimulation technique that induces cortical excitability changes through the use of low amplitude direct currents applied *via* scalp electrodes[12,13]. Depending on the polarity of the current flow, brain excitability can be increased by anodal stimulation or decreased by cathodal stimulation[2].

Recently, there has been increased interest in tDCS, as it has been shown to have beneficial effects on a wide range of diseases such as stroke, epilepsy, Parkinson's disease, Alzheimer's disease, fibromyalgia, psychiatric disorders such as depression, affective disorders, and schizophrenia[2]. tDCS has some advantages, such as its relatively low cost, ease of use, safety, and rare side effects[14]. tDCS is also a painless method and can be reliably blinded in clinical trials, as it has a sham mode[13]. tDCS is likely not optimal for functional recovery on its own; however, it is showing increased promise as an associated therapy in rehabilitation, as it enhances brain plasticity[15].

In this protocol, we demonstrate combined robot-assisted therapy (with two state-of-the-art robots) and non-invasive neuromodulation with tDCS as a method for improving rehabilitation outcomes, in addition to conventional physical therapy. Most studies involving robotic therapies or tDCS have used them as isolated techniques, and few have combined both, which may enhance the beneficial effects beyond each intervention alone. These smaller trials demonstrated a possible synergistic effect between the two procedures, with improved motor recovery and functional ability[8,15,16,17,18,19]. Therefore, novel multi-modal therapies may enhance movement recovery beyond the current possibilities.

Protocol

This protocol follows the guidelines of our institution's human research ethics committee.

1. tDCS

1. **Contraindications and Special Considerations**
   Note: tDCS is a safe technique that sends constant and low direct current through the electrodes, inducing changes in neuronal excitability of the area being stimulated.
   1. Prior to device setup, confirm that the patient does not have any contraindications to tDCS, such as adverse reactions to previous tDCS treatment, implanted brain medical devices, or the presence of metal implants in the head.
   2. Use the following inclusion criteria: subacute and chronic stroke patients with light to moderate upper-extremity hemiparesis. Other contraindications include skull defects, which could alter intensity and location of current flow, and subjects must be free of unstable medical conditions such as uncontrolled epilepsy.
   3. Inspect the patient's scalp thoroughly for cutaneous lesions, such as acute or chronic skin disorders, cuts, or other inflammatory signs. Avoid placing the electrodes and stimulating areas with such lesions as a safety precaution.

2. **Materials for tDCS**
   1. Check if all the following listed materials are available (**Figure 1**) before starting the procedure: tDCS stimulator device, 9 V battery, 2 conductive electrodes, 2 sponge electrodes, cables, 2 rubber head bands (or Velcro straps, non-conductive straps), sodium chloride (NaCl) solution, measuring tape

3. **Measurements**
   1. Electrode sites are usually defined as 10/20 EEG positions, as described in a previous publication[20]. Make sure the subject is comfortably seated.
   2. First, localize the vertex (Cz).
      1. Measure the distance from the nasion (bridge of the nose or intersection of the frontal bone and two nasal bones) to the inion (external occipital protuberance or most prominent projection of the protuberance), and mark 50% of this length. Mark this preliminary Cz location as a line, using either an oil pencil or nontoxic water-based marker.
      2. Measure the left and right pre-auricular points distance (*i.e.,* the area anterior to the tragus). Divide this distance in half and mark the calculated point with a line.
      3. Connect both lines to create a cross. The intersection of both lines will correspond to the vertex (Cz) (**Figure 2**).
   3. Identify the target site on the head.

NOTE: Anodal stimulation increases the cortical excitability in the stimulated brain tissue, while cathodal stimulation decreases it. Previous studies have used anodal stimulation in the lesioned hemisphere or cathodal stimulation in the contralesional hemisphere in order to decrease cortical excitability in the unaffected motor cortex and increase it in the affected motor cortex. In this protocol, we will describe both bihemispheric stimulation (with both anodal and cathodal stimulation in the same session) and anodal stimulation over the primary motor cortex.

1. To locate the primary motor cortex (M1), use 20% of the distance from Cz to the left or right pre-auricular point (**Figure 3**). This area should correspond to the C3/C4 EEG location.
2. Place the anode over the center of M1 motor cortex of the ipsilesional hemisphere and the cathode over the contralateral supraorbital region (Fp) (**Figure 3**).
3. Alternatively, place the anode over the center of M1 motor cortex of the ipsilesional hemisphere and the cathode over the contralesional M1. The M1 positions for the tDCS electrodes are located at channels C3 and C4 (**Figure 3**).

4. **Skin Preparation**
   1. Inspect the skin and avoid stimulating over lesions or damaged skin.
   2. Move the hair away from the site of stimulation to improve conductance. Clean the surface of the skin, removing any signs of lotion and gel. For subjects with thicker hair, using conductive gel may be necessary.

5. **Electrode positioning and device setup**[20]
   1. After preparing the skin and localizing the stimulation site, place one head strap under the inion, around the head circumference. Provide head straps made of non-conducting and non-absorbent material such as elastic, Velcro, or rubber straps.
   2. Soak the sponges with saline solution. For a 35 cm^2 sponge, approximately 6 mL of solution per side may suffice. Avoid oversoaking the sponge. Avoid producing fluid leaks over the subject. If necessary, use a syringe to add more solution.
   3. Connect the cables to the tDCS device. Make sure the polarity of the cables is correct, since the effects of tDCS are polarity-specific (as standardized: red corresponds to the anode electrode, and black or blue corresponds to the cathode electrode).
   4. Insert the connector cord pin securely into the conductive rubber inset.
   5. Insert the conductive rubber inset into the sponge. Ensure that the entire conductive rubber inset is covered by the sponge and that the connector cord pin is not visible.
   6. Place the first sponge electrode under the head strap and ensure that excessive fluid is not released from the sponge.
   7. Connect both elastic head straps, according to the electrode montage planned.
   8. Place the second sponge electrode on the head over the area being stimulated, under the second elastic head strap.
   9. If the overall electrical resistance of the electrodes and body is high, it may indicate inadequate electrode set-up. Some devices provide resistance measuring, which should be under 5 kΩ, ideally.
   10. Some devices provide a continuous indication of resistance during stimulation, which is a useful way to detect potentially hazardous situations (such as a dry electrode). In such cases, the device may finish or reduce the stimulation intensity if resistance increases beyond a certain threshold.

6. **Stimulation**
   1. Make sure that the patient is awake, relaxed, and seated comfortably during the procedure[21].
   2. Adjust the tDCS stimulator settings (intensity, time, and sham condition, if applicable). In accordance with previous studies, apply direct current for 20 minutes at an intensity of 1 mA.
      NOTE: For sham intervention, the current is usually applied only for the first 30 s to give the subject the sensation of stimulation. This duration has been established in several studies as being effective in blinding them to the assigned intervention, without stimulating cortical excitability[22].
   3. Initiate the tDCS stimulation. Start the current flow by ramping up the current to avoid the most adverse effects. Ramping up is automatically done on some devices, but if it is not, increase the current slowly during the initial 30 s to reach the maximum programmed current (in our protocol, up to 1 mA).
   4. After starting the electrical stimulation, some patients may perceive temporary slight itching sensations, dizziness, or vertigo. This can be avoided by ramping the current up and down at the start and end of each session.
   5. At the end of the procedure, gradually ramp off the current for 30 s.

7. **After the procedure**
   1. To record and evaluate the safety of the stimulation, ask the patient to fill out a questionnaire of common adverse effects and their intensities after the procedure is done. These may include skin irritation, nausea, headaches, burning sensations, dizziness, tingling, or other discomforts.
   2. Explain to the patient that any possible side effects are usually of mild or moderate intensity and usually temporary.
   3. After tDCS, refer the patients to undergo robotic therapy.
      NOTE: In the next sections of this protocol, we will describe the use of the commercial versions of the MIT-Manus and T-WREX.

2. Robotic Therapy with MIT-Manus

1. **Positioning**
   NOTE: This robot is an interactive robot for rehabilitation of the upper limb. The version utilized in our study allows training of wrist movement in the horizontal plane (planar).
   1. Make sure the subject is seated in a comfortable and ergonomic chair, secured by a four-point seatbelt, and facing the video screen.
   2. Make sure that a trained therapist is supervising the robotic training.
   3. Place the hand that will be subject to training into the grip of the robotic handle. Adjust both straps around the subject's arm. Adjust the support on the back of the arm so that it stays stable during training.

4. Place the paretic upper extremity as indicated: shoulder in a 30° flexion, 90° elbow flexion, forearm in mid-prone position, wrist in neutral position.
5. During machine operation, make sure movement of the shoulder joints and elbow range is limited to about 45°. Make sure that the arm is immobilized, and the wrist has freedom of movement. Movement is possible in the horizontal plane (in all possible directions).

2. **Training**
   1. The number of movements in a robotic training session is variable; however, it is common to perform about 320 repetitions in every possible direction of a plane within a same plane.
   2. The video screen shows cues of the tasks that the subject needs to perform and gives constant feedback of the position of the arm.
   3. The robot's software has several therapeutic exercise games for motor training. The visual feedback usually consists of a yellow ball that the patient must move between targets. Other training scenarios are available.
   4. The robot will only assist the patient if necessary; for example, if the subject cannot realize the intended movement within 2 s, the machine will help complete its movement. If the subject does not have enough motor coordination to carry out the intended movement, the robot will guide the subject's arm to perform the appropriate movement.

3. Training with MIT-Manus Arm

Note: This robotic arm allows training of elbow flexion and extension, shoulder protraction and retraction, and shoulder internal and external rotation on a horizontal plane.

1. **Positioning**
   1. For the MIT-MANUS Arm, make sure the subject is seated comfortably. Adjust the seat belts accordingly. Position the patient's right or left arm on the robot and adjust both straps.
   2. Adjust the robot's height as necessary. Adjust the table height as necessary.
   3. If there is any discomfort or pain, press the emergency stop button to turn off the robot immediately.

2. **Training**
   1. Calibrate the machine by asking the subject to move its arm along the lines.
   2. The robot will only assist the patient if necessary. For example, if the subject cannot realize the intended movement within 2 s, the machine will help complete its movement. If the subject does not have enough motor coordination to carry out the intended movement, the robot will guide the subject's arm to perform the appropriate movement.
      NOTE: The robot's software has several therapeutic exercise games for motor training. The visual feedback usually consists of a yellow ball that the patient must move between targets. Other training scenarios are available.

4. Training with T-WREX

1. **Positioning**
   NOTE: The T-WREX consists of an exoskeleton that fits the subject's arm and allows free movement of the shoulder, elbow, and wrist joints in a tridimensional setting.
   1. Ensure that the subject is seated in a comfortable and ergonomic chair facing the video screen, which provides visual and auditory feedback in a virtual reality setting, helping the patient achieve his or her goal.
   2. Place the patient seated in front of the robot's main module. Use the provided remote control to adjust the exoskeleton's height accordingly. Adjust the robot's exoskeleton arm to the corresponding side of the patient's limb that will be trained (either left or right).
   3. Leave about 4 fingers of height above the shoulder.
   4. Adjust the patient's limb into the exoskeleton, adjusting the straps on the arm and forearm.
   5. Adjust the length of the exoskeleton's arm and forearm accordingly, as well as the weight (gravity) compensation necessary for the arm (A to I) and forearm (A to E). It consists of a linear scale of gravity support, where A has no gravity support.
   6. Input these measurements to the computer.
   7. Before starting the training, adjust and calibrate the range of motion limits of the robot, according to the patient's capabilities.
   8. To test the calibrated range of motion, ask the patient to move the cube in all directions of the screen.

2. **Training**
   1. In each session, have the individual perform about 72 repetitions of the movement towards different functional targets (a T-WREX training session usually lasts about 60 min).
   2. Between each movement, allow a 10-second interval to prevent fatigue. The 72 repetitions are divided into 3 blocks of 24 movements each. Allow an interval of 5 min between each block of 24 movements.

Representative Results

Non-invasive brain stimulation with tDCS has recently generated interest due to its potential neuroplastic effects, comparatively inexpensive equipment, ease of use, and few side effects[22]. Studies have shown that neuromodulation by tDCS has the potential to modulate cortical excitability and plasticity, thus promoting improvements in motor performance through synaptic plasticity by stimulating the primary motor cortex[4]. Anodal stimulation increases cortical excitability by facilitating the depolarization of neurons in the primary motor cortex area, whereas cathodal stimulation hyperpolarizes the resting membrane potential and reduces the neuronal firing, which reduces interhemispheric inhibition from the contralesional primary motor cortex. Dual tDCS combines these two montages by facilitating activity in the ipsilesional area and inhibiting the contralesional hemisphere[12,23].

Previous studies have reported electrophysiological effects of tDCS lasting up to 90 min and behavioral effects lasting up to 30 min, after a single 20 min tDCS session (**Figure 4**)[24,32]. The evidence is still controversial, as these positive findings are not consistent. Lindenberg *et al.*[25] found functional motor improvement after bihemispheric stimulation that outlasted the intervention period (**Figure 5**), and a meta-analysis published in 2012 suggested that the use of non-invasive brain stimulation such as TMS and repetitive TMS were associated with improvements in motor recovery, both individually and when compared to placebo stimulation[2]. An experimental trial by Fusco *et al.*[26] found no functional improvement for cathodal tDCS in early phases of stroke; however, Fregni *et al.*[13] found that both isolated cathodal or anodal (but not sham) stimulation improved motor function significantly. These controversial findings are probably due to heterogeneity of patient characteristics (*i.e.,* acute *vs.* chronic stroke patients, mild *vs.* severe motor impairments) and stimulation characteristics (*i.e.,* number of tDCS sessions, session duration, anodal *vs.* cathodal *vs.* dual stimulation).

The evidence for robotic therapy in rehabilitation is more prominent, demonstrating clear incremental reductions of motor impairment[27]. However, due to the large number of manufacturers and several types of robotic devices, each machine has unique properties, qualities, and limitations. The American Heart Association suggests that robot-assisted therapy for upper extremities has achieved Class I level of evidence for stroke patients in outpatient settings and Class IIa in inpatient settings[1]. A review of 19 trials and 666 patients found that subjects who received robot-assisted arm training after stroke were more likely to show improvements in daily living activities and paretic arm function[6]. A single-blind trial found that children with cerebral paralysis improved significantly in measures of manual dexterity compared to the control group[28], while Timmermans *et al.*[29] found that chronic stroke patients showed significant improvements in task-oriented arm training that was maintained for 6 months post-intervention. Additionally, a multi-center randomized controlled trial found that chronic stroke patients with moderate to severe upper-limb impairments showed significant but modest improvements in arm function, movement, and quality of life measures after robotic training over the 36-week study period compared to the standard of care patients but not intensive physical therapy patients (**Figure 6**)[5].

While trials of neurorehabilitation with either tDCS or robotic therapy have been performed, few have been conducted combining these therapies. Hesse *et al.*[16] performed a preliminary pilot study and found that anodal tDCS to the affected hemisphere combined with robot-assisted arm training caused no significant improvements in motor function in sub-acute stroke patients. Another study by Ochi *et al.*[19] showed that both anodal tDCS to the affected hemisphere and cathodal stimulation to the unaffected hemisphere could achieve a limited but similar magnitude motor improvement. Finally, Edwards *et al.*[18] found that improvements in cortical excitability and reduced cortical inhibition in active groups of tDCS plus robot therapy resulted in larger gains on motor function.

Recent research suggests that the stimulation sequence is important to the improvement of function. Giacobbe *et al.*[15] evaluated the dimension of timing in combined robotic therapy with tDCS for wrist rehabilitation in chronic stroke patients and found that wrist movement speed and smoothness (> 15%) were improved when tDCS was delivered prior to a 20 min session of robotic training but not when delivered during or after training (**Figure 7**). These results contrast with other studies that found that simultaneous occupational therapy and tDCS lead to significant motor improvements[31]. Finally, Nair *et al.*[31] found that the use of simultaneous cathodal tDCS and occupational therapy resulted in significantly higher changes of motor recovery compared to therapy with sham stimulation (**Figure 8**).

Figure 1: Materials for tDCS. Please click here to view a larger version of this figure.

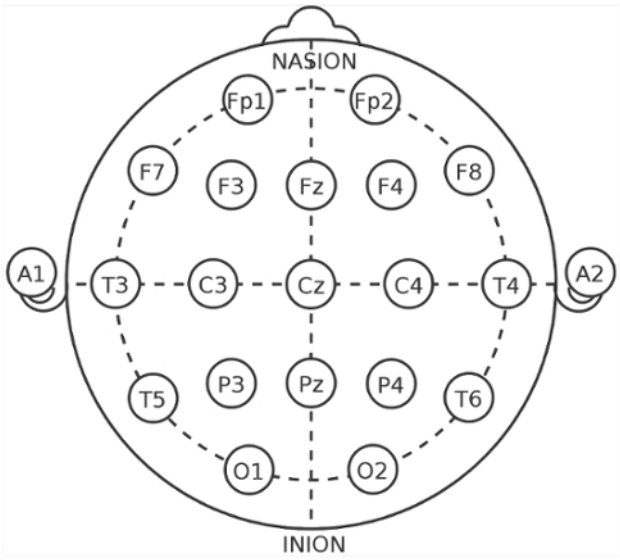

Figure 2: Vertex position. Cortical areas are marked according to the 10/20 system. Please click here to view a larger version of this figure.

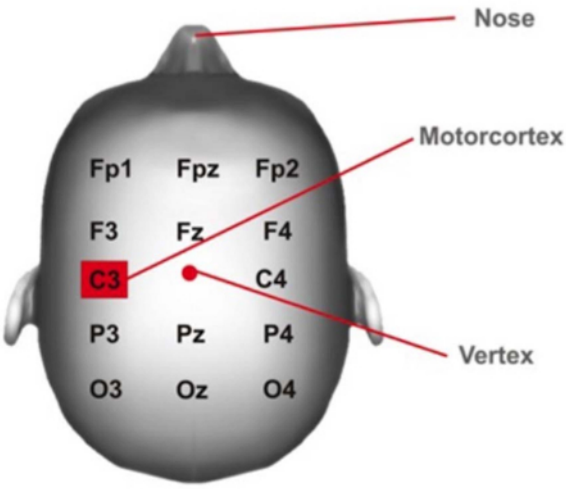

Figure 3: Motor cortex position. Cortical areas are marked according to the 10/20 system. Please click here to view a larger version of this figure.

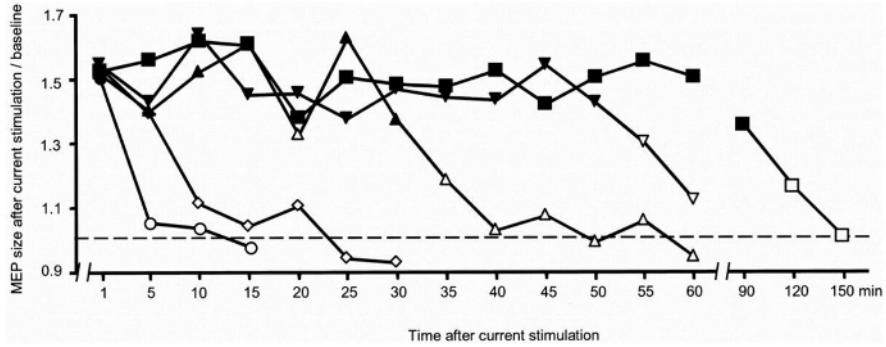

Figure 4: Electrophysiological effects of a single tDCS session. After a single tDCS session of 20 min, electrophysiological effects can last up to 90 min, and behavioral effects up to 30 min after stimulation. Reprinted from Nitsche *et al.*[32], with permission from Springer Nature. Please click here to view a larger version of this figure.

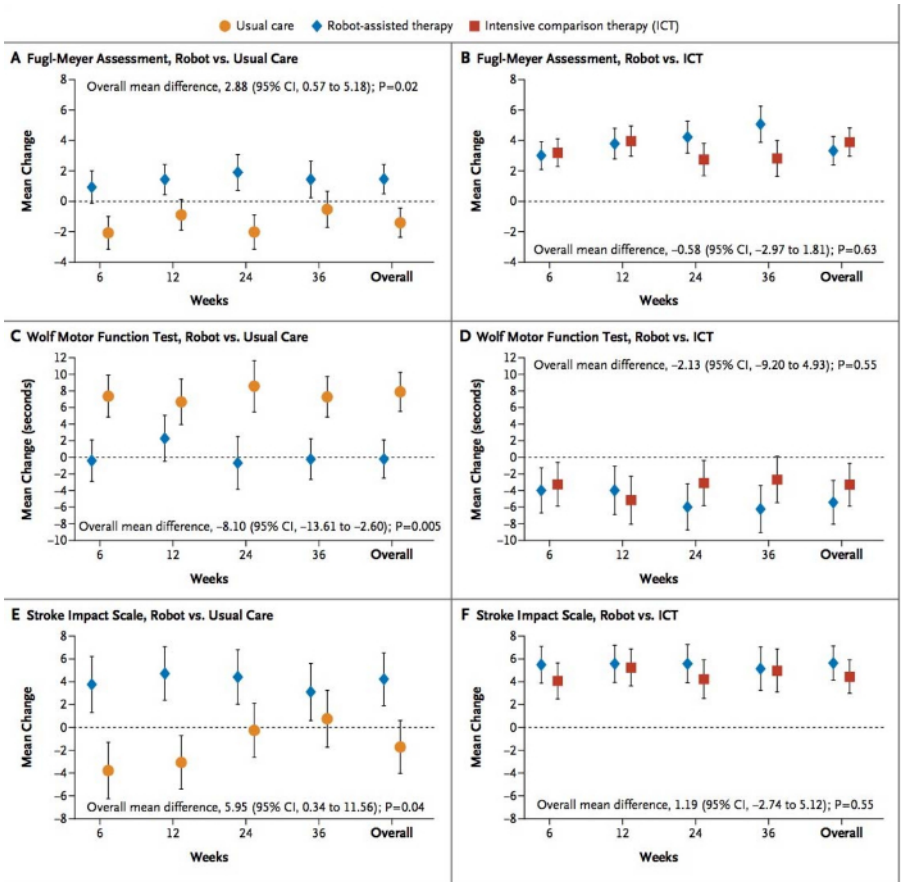

Figure 5: Changes in primary and secondary outcomes during the 36-week study period as compared to baseline. Lo *et al.*[5] found significant but modest improvements in arm function, movement, and quality of life after robot training. This figure is reprinted with permission from Massachusetts Medical Society[5]. Please click here to view a larger version of this figure.

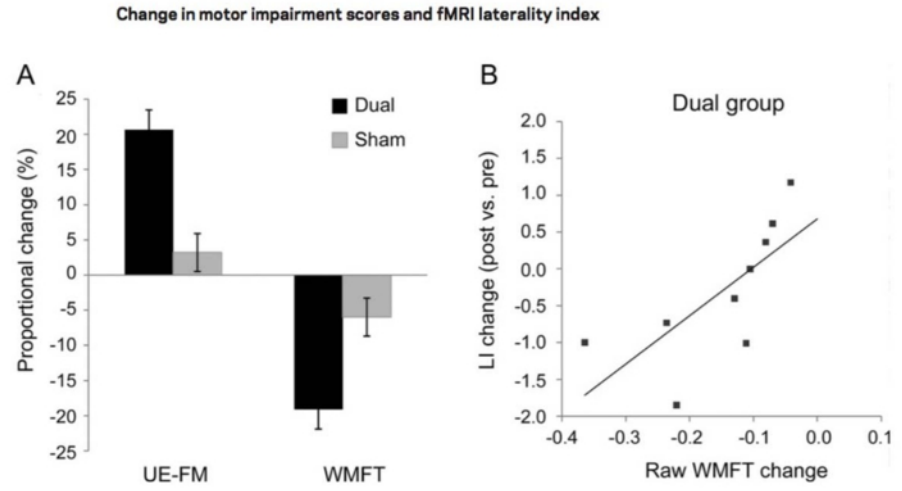

Figure 6: Changes in motor impairment scores and fMRI laterality index. Lindenberg *et al.*[25] found functional changes in motor impairment scores and improved function of the affected limbs after bihemispheric tDCS. Reprinted from Lindenberg *et al*. with permission from Lippincott Williams & Wilkins[25]. Please click here to view a larger version of this figure.

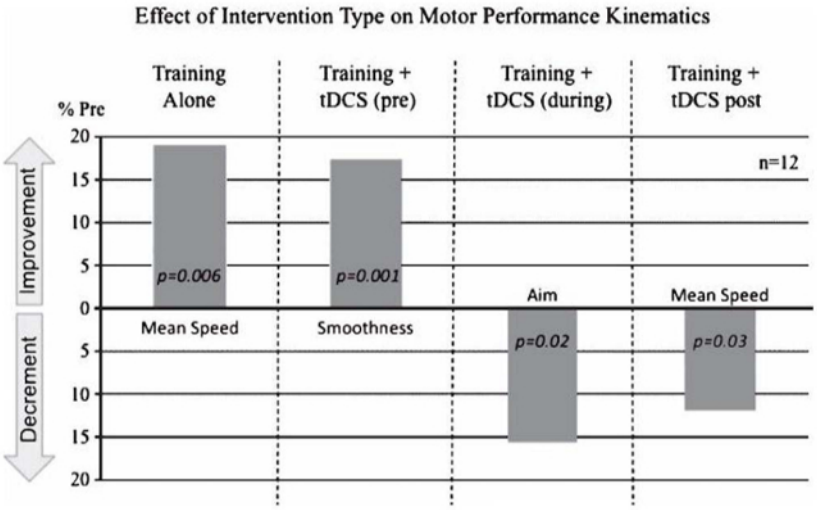

Figure 7: Effect of intervention type on motor performance kinematics. Giacobbe *et al.*[15] found that tDCS delivered prior to robotic therapy improved wrist movements and smoothness. Reprinted from Giacobbe *et al.*[15] with permission from IOS Press. The publication is available at IOS Press through 10.3233/NRE-130927 Please click here to view a larger version of this figure.

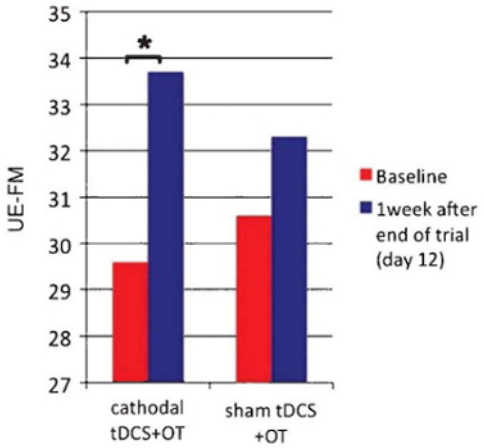

Figure 8: Effect of cathodal tDCS plus occupational therapy[31]. Simultaneous tDCS and occupational therapy resulted in significantly (*) higher changes of motor improvement. Reprinted from*Nair et al.*[31] with permission from IOS Press. The publication is available at IOS Press through 10.3233/RNN-2011-0612 Please click here to view a larger version of this figure.

Discussion

In this protocol, we describe a standard therapy protocol for combined tDCS stimulation associated and robotic therapy, used as a complement to conventional rehabilitation programs in patients with arm impairments. The protocol's goal is to improve motor function and mobility. It is important to observe the ramping-on and ramping-off of the tDCS machine to avoid any risk of adverse effects. tDCS is a safe technique with few side effects described in the literature[2].

The protocol may be modified in minor ways. Previous reports in the literature describe tDCS being applied before, during, or after motor training (either with robots or human assistance). In our protocol, we described a 20 min session of tDCS followed immediately by robotic therapy. Some studies have found better outcomes for simultaneous tDCS and robotic training.

After a stroke, based on the interhemispheric competition model, motor deficits are suggested to be in part due to reduced output from the primary motor cortex (M1) of the damaged hemisphere and to increased inhibitory influence from the contralesional M1 hemisphere. In this protocol, we opted for anodal stimulation of the lesional M1 and described the possibility of bihemispheric stimulation. Anodal tDCS stimulation increases cortical excitability of the damaged M1, while cathodal stimulation decreases cortical excitability in the intact M1; however, dual application of tDCS would target these both areas simultaneously. Other protocols also opt for a bihemispheric stimulation, as some studies have reported larger motor function gains[18,25].

Previous studies have evaluated single-dose or few sessions of tDCS for neurorehabilitation, with short-term after-effects lasting up to 90 min after a 20-30 min stimulation session. Repeated sessions may have a greater duration and magnitude of effects by inducing a more significant manipulation in synaptic efficacy and greater magnitude of effects, as physical rehabilitation for movement disorders is usually a long process. There is a consensus, however, that for lasting motor improvements, tDCS should preferentially be performed in conjunction with training[30].

Robotic therapy associated with non-invasive brain stimulation is still not yet widely accessible, due to the high costs of robotic therapy. Most robots, however, are still cost-prohibitive to many rehabilitation services, resulting in limited use. The cost of robotic technology may decrease in the future as opposed to the cost of human labor, and cost-effectiveness as an advantage of robotic therapy is possible[7]. This protocol is interesting because physical rehabilitation with robotic therapies has shown great promise in being an adjunct to conventional therapy, allowing both inpatients and outpatients to perform more repetitive tasks with higher intensities and for longer periods, resulting in an optimal rehabilitation program. Other advantages include instant feedback and objective measurements of the kinematics and dynamics of movement performance that is possible after each training session, helping to maintain patient motivation for active participation.

The combination of tDCS and physical rehabilitation assisted by robots may enhance the effects of either intervention used alone, resulting in additional motor gains for patients. The combination of robot-training peripheral sensorimotor activities that provide increased sensory feedback to the cortex along with the modulation of cortical excitability due to tDCS may result in a more positive outcome, due to synaptic plasticity. The evidence for this combinatorial approach is promising, though still limited and inconclusive, when compared to the therapies when they are individually applied. More studies are needed to further investigate the synergism and possible additional effects of the combined therapy, such as the optimal number of sessions and timing of each therapy and whether tDCS should be applied before, during, or after rehabilitation activities to effect functional outcomes.

Disclosures

The authors declare that they have no competing financial interests.

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References

1. Miller, E. L., *et al.* Comprehensive overview of nursing and interdisciplinary rehabilitation care of the stroke patient: A scientific statement from the American Heart Association. *Stroke.* **41** (10), 2402-2448 (2010).
2. Adeyemo, B. O., Simis, M., Macea, D.D., Fregni, F. Systematic review of parameters of stimulation, clinical trial design characteristics, and motor outcomes in noninvasive brain stimulation in stroke. *Front Psychiatry.* **3** (8), 1-27 (2012).
3. Johansson, B. B. Current trends in stroke rehabilitation. A review with focus on brain plasticity. *Acta Neurologica Scandinavica.* **123** (3), 147-159 (2011).
4. Hummel, F., Cohen, L. G. Improvement of motor function with noninvasive cortical stimulation in a patient with chronic stroke. *Neurorehabilitation Neural Repair.* **19** (1), 14-19 (2005).
5. Lo, A. C., *et al.* Robot-assisted therapy for long-term upper-limb impairment after stroke. *New England Journal of Medicine.* **362** (19), 1772-1783 (2010).
6. Mehrholz, J., Haedrich, A., Platz, T., Kugler, J. Pohl, M. Electromechanical and robot-assisted arm training for improving generic activities of daily living, arm function, and arm muscle strength after stroke. *Cochrane Database of Systematic Reviews.* (2012).
7. Maciejasz, P., Eschweiler, J., Gerlach-Hahn, K., Jansen-Troy, A., Leonhardt, S. A survey on robotic devices for upper limb rehabilitation. *Journal of NeuroEngineering and Rehabilitation.* **11** (3), 10-1186 (2014).
8. Ang, K. K., *et al.* Facilitating effects of transcranial direct current stimulation on motor imagery brain-computer interface with robotic feedback for stroke rehabilitation. *Archives of Physical Medicine and Rehabilitation.* **96** (3), S79-S87 (2015).
9. Chang, W. H., Kim, Y. H. Robot-assisted therapy in stroke rehabilitation. *Journal of Stroke.* **15** (3), 174-181 (2013).
10. Volpe, B. T., *et al.* A novel approach to stroke rehabilitation: robot-aided sensorimotor stimulation. *Neurology.* **54** (10), 1938-1944 (2000).
11. Volpe, B. T., *et al.* Robotic devices as therapeutic and diagnostic tools for stroke recovery. *Archives of Neurology.* **66** (9), 1086-1090 (2009).
12. Nitsche, M. A., Paulus, W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *TheJournal of Physiology.* **527** (3), 633-639 (2000).
13. Fregni, F., *et al.* Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. *Neuroreport.* **16** (14), 1551-1555 (2005).
14. Kim, D. Y., *et al.* Effect of transcranial direct current stimulation on motor recovery in patients with subacute stroke. *American Journal of Physical Medicine and Rehabilitation.* **89** (11), 879-86 (2010).
15. Giacobbe, V., *et al.* Transcranial direct current stimulation (tDCS) and robot practice in chronic stroke: the dimension of timing. *NeuroRehabilitation.* **33** (1), 49-56 (2013).
16. Hesse, S., *et al.* Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: a pilot study. *Restorative Neurology and Neuroscience.* **25** (1), 9-16 (2007).
17. Hesse, S., *et al.* Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: an exploratory, randomized multicenter trial. *Neurorehabilitation and Neural Repair.* **25** (9), 838-846 (2001).
18. Edwards, D. J., *et al.* Raised corticomotor excitability of M1 forearm area following anodal tDCS is sustained during robotic wrist therapy in chronic stroke. *Restorative Neurology and Neuroscience.* **27** (3), 199-207 (2008).
19. Ochi, M., Saeki, S., Oda, T., Matsushima, Y., Hachisuka, K. Effects of anodal and cathodal transcranial direct current stimulation combined with robotic therapy on severely affected arms in chronic stroke patients. *Journal of Rehabilitation Medicine.* **45** (2), 137-140 (2013).
20. DaSilva, A. F., Volz, M. S., Bikson, M., Fregni, F. Electrode positioning and montage in transcranial direct current stimulation. *Journal of Visualized Experiments.* (51), (2011).
21. Antal, A., Terney, D., Poreisz, C., Paulus, W. Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. *European Journal of Neuroscience.* **26** (9), 2687-2691 (2007).

22. Williams, J. A., Pascual-Leone, A., Fregni, F. Interhemispheric modulation induced by cortical stimulation and motor training. *Physical Therapy.* **90** (3), 398-410 (2010).
23. Zimerman, M., *et al.* Modulation of training by single-session transcranial direct current stimulation to the intact motor cortex enhances motor skill acquisition of the paretic hand. *Stroke.* **43** (8), 2185-2191 (2012).
24. Nitsche, M. A., *et al.* Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *The Journal of Physiology.* **553** (1), 293-301 (2003).
25. Lindenberg, R., Renga, V., Zhu, L. L., Nair, D., Schlaug, G. M. D. P. Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. *Neurology.* **75** (24), 2176-2184 (2010).
26. Fusco, A. *et al.* The ineffective role of cathodal tDCS in enhancing the functional motor outcomes in early phase of stroke rehabilitation: an experimental trial. *BioMed Research International.* (2014).
27. Kwakkel, G., Kollen, B. J., Krebs, H. I. Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. *Neurorehabilitation and Neural Repair.* **22** (2), 111-121 (2008).
28. Gilliaux, M., *et al.* Upper limb robot-assisted therapy in cerebral palsy: a single-blind randomized controlled trial. *Neurorehabilitation and Neural Repair.* **29** (2), 183-192 (2015).
29. Timmermans, A. A., *et al.* Effects of task-oriented robot training on arm function, activity, and quality of life in chronic stroke patients: a randomized controlled trial. *Journal of NeuroEngineering and Rehabilitation.* **11** (1), 45 (2014).
30. Hummel, F. C., *et al.* Controversy: noninvasive and invasive cortical stimulation show efficacy in treating stroke patients. *Brain Stimulation.* **1** (4), 370-382 (2008).
31. Nair, D. G., *et al.* Optimizing recovery potential through simultaneous occupational therapy and non-invasive brain-stimulation using tDCS. *Restorative Neurology and Neuroscience.* **29** (6), 411-420 (2011).
32. Nitsche, M. A., *et al.* Modulation of cortical excitability by transcranial direct current stimulation. *Nervenarzt.* **73** (4), 332-335 (2002).

