A combined transcranial direct current stimulation and virtual reality-based intervention on upper limb function in chronic stroke survivors with severe hemiparesis

A feasibility study

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***Abstract*—Rehabilitation options for stroke survivors who present severe hemiparesis in chronic stages are limited and may end in compensation techniques that involve the use of the less affected arm to achieve some degree of functional independence. Passive mobilization, mirror therapy, or motor imagery are the scant alternatives that try to involve the hemiparetic arm into the rehabilitation process. Transcranial direct current stimulation (tDCS) is a non-invasive technique that has been used after stroke to promote excitability of the surviving neural architecture in order to support functional recovery. Interestingly, cortical excitability has been reported to increase when tDCS is combined with virtual reality. This synergetic effect could explain the promising results achieved by preliminary experimental interventions that combined both approaches on upper limb rehabilitation after stroke. However, the efficacy of these interventions in subjects with severe hemiparesis has not been explored, at least in part, because their restriction of movements may limit their interaction with common virtual reality systems. We present a tDCS enhanced virtual reality-based intervention that enables interaction and multimodal stimulation of subjects with severe hemiparesis after stroke and evaluate its efficacy in seven chronic participants. Results showed clinically important improvement in the body functions and activities after the intervention, and a maintenance of gains weeks after. Although further studies are needed, the efficacy of this intervention is promising.**

Keywords—virtual reality; tDCS; closed-loop; hemiparesis; stroke; rehabilitation.

I. Introduction

Functional impairment of the upper limbs, reported in approximately 85% of the cases [1], is one of the most common sequelae after stroke. Six months after onset, 30-60% of individuals do not regain functional use, and only 5-20% will achieve full recovery of arm function [2]. Given the incidence of upper limb deficits and their implication in the participation in daily living activities and quality of life [3], rehabilitation of the upper limb function is an imperative objective of physical and occupational therapy.

However, rehabilitation of severe arm paresis in chronic stroke survivors is especially challenging because useful reorganization of cortical areas involved in arm function is believed to occur in response to active exercise and to motor and attentional inclusion of the affected arm in task oriented movements [4], [5] but severe paresis impedes active training of the arm. Traditionally, rehabilitation strategies in these subjects have almost exclusively aimed to compensate for the deficit by training the opposite limb in daily tasks [4], [6]. However, as synaptic connectivity is highly use dependent, the absence of stimulation on the chronic paretic arm might result in reduced sensorimotor representation in the available neural circuits over time [7] and, consequently, diminish the possibilities for sensorimotor clinical progress [6]. Accordingly, a reduction in sensorimotor abilities might partly be an effect of non-use of the affected limb [7]. In fact, lack of movement has been considered to be a form of "learned paralysis" [8], [9]. To overcome the deleterious effect of non-use techniques, different rehabilitative approaches have been presented. Most of these alternatives involve passive mobilization (either manual or robotic-guided) [10], [11], mirror therapy [11], [12], or motor imagery-based interventions [13], [14]. The capacity of these interventions to elicit cortical activation in the hemisphere contralateral to the imaginarily moving arm has been evidenced by different neuroimaging techniques [14], [15], and suggests that these interventions may be functionally akin to preparatory and executive motor processes [14].

Transcranial direct current stimulation (tDCS), a type of non-invasive brain stimulation that induces constant low direct currents through electrodes on the scalp to regulate neuronal excitability, has achieved promising results in severe hemiparesis after stroke [16], [17]. Interestingly, this technique has been reported to synergistically promote short-term corticospinal facilitation when combined with virtual reality

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(VR)-based interventions [18], which could explain the promising results reported on upper limb rehabilitation after stroke [19], [20]. The capacity of VR to simulate an environment or activity through the real-time stimulation of one or more sensory channels [21] has recently motivated its use to guide motor imagery interventions in stroke survivors [22]. In addition, the capacity of this technology to allow real-time user interaction could be potentially use to close the loop of interaction-stimulation, which could be specially interesting to facilitate motor learning in subjects with severely affected upper limb function [23], who present limited movement capability.

We hypothesized that a tDCS enhanced VR-based closed-loop intervention could have a cumulative beneficial effect on sensorimotor function of severely affected upper limbs of chronic stroke survivors. The objective of this study was to determine the efficacy of this experimental intervention in chronic stroke survivors with severe hemiparesis.

II. Methods

A. Participants

Participants were recruited from the chronic stroke management program of NISA Valencia al Mar Hospital (Valencia, Spain). The inclusion criteria to participate in the study were: 1) chronicity > six months; 2) severe paresis of the upper limb defined by the Brunnstrom Approach [24] as stages I or II) and by the Upper Extremity subscale of the Fugl-Meyer Assessment [25] as scores below 19; 4) ability to maintain a sitting position for at least 60 minutes; 5) fairly good cognitive condition defined by scores in the Mini-Mental State Examination [26] above 23. Patients were excluded if they had: 1) pacemakers; 2) brain implants or other metallic objects (valves, coils, etc.); 3) impaired comprehension that hinder sufficient understanding of the instructions defined by Mississippi Aphasia Screening Test [27] scores below 45; 4) severe visual impairments; and 5) emotional or behavioral circumstances that impede adequate collaboration.

The study was approved by the Institutional Review Board of the Neurorehabilitation and Brain Injury Service of NISA Hospitals. Written consent was obtained from all of the subjects who satisfied the inclusion criteria and accepted to participate in the study.

B. Instrumentation

The experimental system detected the users' intention of movement from their gaze and residual muscular activity and movement capability, and provided coherent multimodal stimulation including audiovisual and tactile feedback, and tDCS (Fig. 1).

Stimulation: Audiovisual stimulation was provided by the 15.6" screen and integrated speakers of a laptop (Fig. 1.a).

Tactile feedback was provided using three vibrators that were embedded in a hand-made Velcro band (Fig. 1.b). The band was designed to surround the participants' hemiparetic hands in such a way that vibrators were located in the palmar side of the metacarpophalangeal joint of the thumb, index and pinky fingers. Actuators vibrated independently to simulate the contact of those anatomical points with virtual elements.

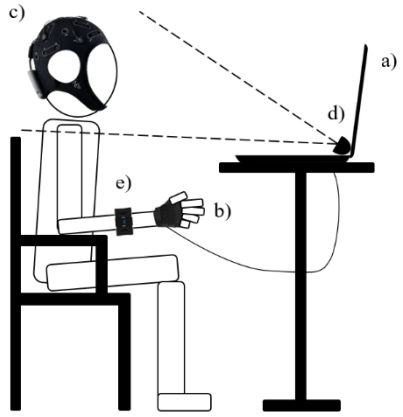

Fig. 1. The experimental system provided a) audiovisual and b) tactile feedback, and c) transcranial direct current stimulation, and allowed interaction through d) eye-tracking and e) muscular activity and movement.

tDCS was provided using a wireless hybrid EEG/tDCS headset, the StarStim (Neuroelectrics, Barcelona, Spain), which includes a neoprene headcap with 39 positions based on the 10-10 system where the electrodes can be inserted (Fig. 1.c). Continuous direct currents were transferred via a pair of saline-soaked surface sponge electrodes (surface of 25 cm^2).

Interaction: The participants' gaze was estimated using a portable eye-tracking bar, the EyeX (Tobii Technology AB, Danderyd, Sweden) (Fig. 1.d). This device provided gaze data with a minimum framerate of 30 Hz.

The residual muscular activity and movements of the participants' hemiparetic arms was registered using a gesture and motion control armband, the Myo (Thalmic Labs, Kitchener, ON, Canada) (Fig. 1.e). This device provided surface electromyographical (sEMG) data from seven medical-grade stainless steel sensors that surrounded the arm, angular velocity provided by a three-axis gyroscope, and acceleration data provided by a three-axis accelerometer at a framerate of 200, 50, and 50 Hz, respectively. The brachioradialis, palmaris longus, and flexors and extensors of the fingers were potential contributors to the sEMG data.

C. Calibration

The coordinates of the participants' gaze and the movement capability of their hemiparetic arms had to be estimated to enable interaction.

Calibration of the eye-tracking required participants to follow a red spot that moved along a cross-shaped path on the screen. This process provided the transform matrix to estimate the X and Y coordinates of the participants' gaze on the screen of the laptop from the movements of their pupils.

Calibration of the movement capability required participants to perform three attempts to move their hemiparetic arm as if they wanted to pick a virtual apple that was shown on the screen. If the sEMG activity during the attempt was at least five times the activity during the resting condition participants were able to

use this variable to interact with the system. Analogously, if the angular velocity or the acceleration during the attempt was at least twice the velocity and acceleration detected during the resting condition, participants were able to interact through these variables. This calibration process provided the maximum sEMG activity in the seven sensors, angular velocity, and acceleration in those participants who passed the process.

D. Exercise

The virtual environment simulated an apple picking task in an apple orchard. The user's view was fixed in front of an apple tree, where a serial of apples appeared and disappeared a few seconds after. The arms of the participants were represented using a first-person perspective (Fig. 2). Extrinsic feedback included the time left, number of repetitions, and record number of repetitions.

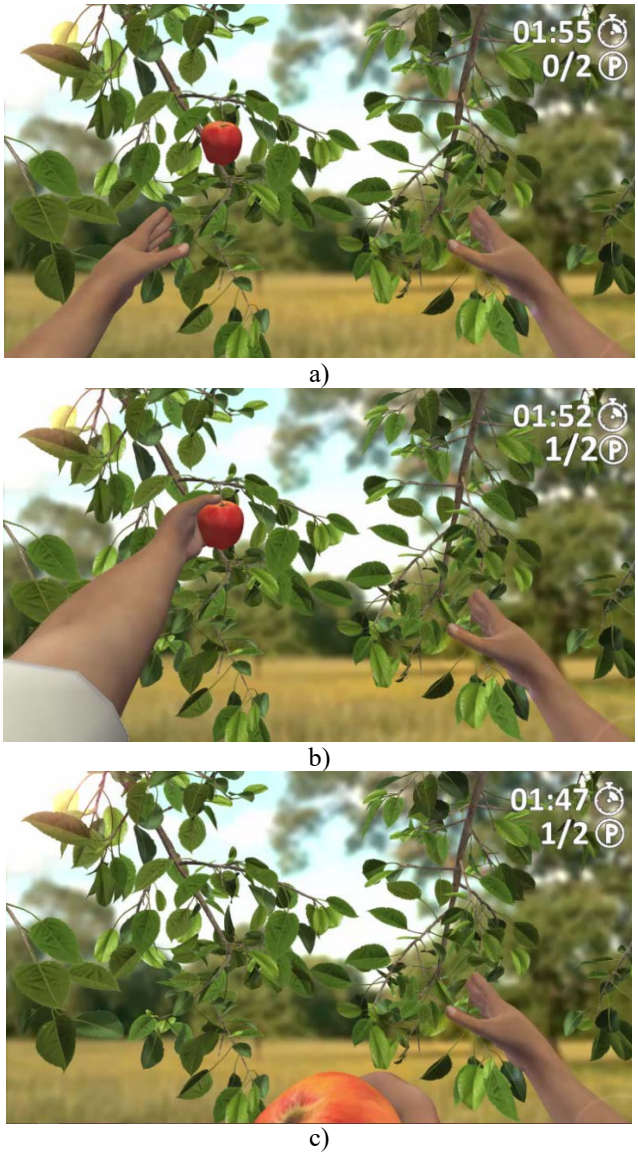

Fig. 2. The virtual environment showed a) an apple tree and the users' arms. The objective of the exercise was to pick the apples that appeared on a branch. In case of succesful interaction, the virtual environment showed how the hand moved towards the apple, b) grasped it, and c) brought it to the mouth.

The objective of the exercise was to pick the apples that sequentially grew in the branches of the tree with the virtual hemiparetic hand (Fig. 2.a). To pick the apples, participants were required to stare at them and to try the movement (it is, to move their affected extremities as if they wanted to pick the virtual apples with their real hands). An attempt was considered successful if participants stared at the apple for 2 s and if they were able to produce a muscular activity, angular velocity, or acceleration greater than 70% of their calibrated values. Participants had 10 s to pick an apple. Time between apples was set to 4 s.

If participants did not performed a successful attempt, audiovisual feedback was provided to them. In the virtual environment, the arm remained still (if not enough muscular activity, angular velocity, or acceleration was detected) or made a grasping movement towards the wrong location that they were staring at (if they were staring at a wrong location on the screen). This was also indicated with a losing sound effect. In the latter case, the visual animation lasted 6 s.

On the contrary, if participants performed a successful attempt, audiovisual and tactile feedback were provided. In the virtual environment, the virtual hand moved towards the apple, grasped it (Fig. 2.b), and brought it towards their mouth (Fig. 2.c). The environment simulated that the participants bit the apple three times and the arm was finally moved to the initial resting position. A biting sound effect was also provided synchronously with the visual animation. The successful attempt was also indicated with a winning sound effect. The visual animation lasted 10 s. Tactile feedback was provided when the hand initially made contact with the apple and during each bite.

tDCS was uninterruptedly provided during the whole session with independence of the success of the attempt.

The workflow of the exercise is shown in Fig. 3.

E. Procedure

Sessions were carried out in a dedicated area of the physical therapy unit free of distractors.

A physical therapist equipped participants with the EMG bracelet, the vibration band, and the tDCS headband. Participants sat in a chair with their backs leaning against the backrest and their arms on the armrests. The laptop was placed approximately 50 cm from the head and 40 cm below eye-level. The eye-tracker was tilted towards the eyes and the tDCS electrodes were soaked in saline solution. The anode was placed over the ipsilesional primary motor cortex (M1) (C3 or C4 for left or right hemiparesis, respectively) and the cathode was placed in the contralesional supraorbital cortex (Fp2 or Fp1 for left or right hemiparesis, respectively). Impedance was kept below 10 kΩ and voltage below 26 V. Maximum output intensity was set to 2 mA. The eye-tracking coordinates and the muscular activity and movement thresholds were calibrated and the session started.

Intervention consisted of a reversal A-B-A design. Both phases included 25 60-minute sessions administered three to

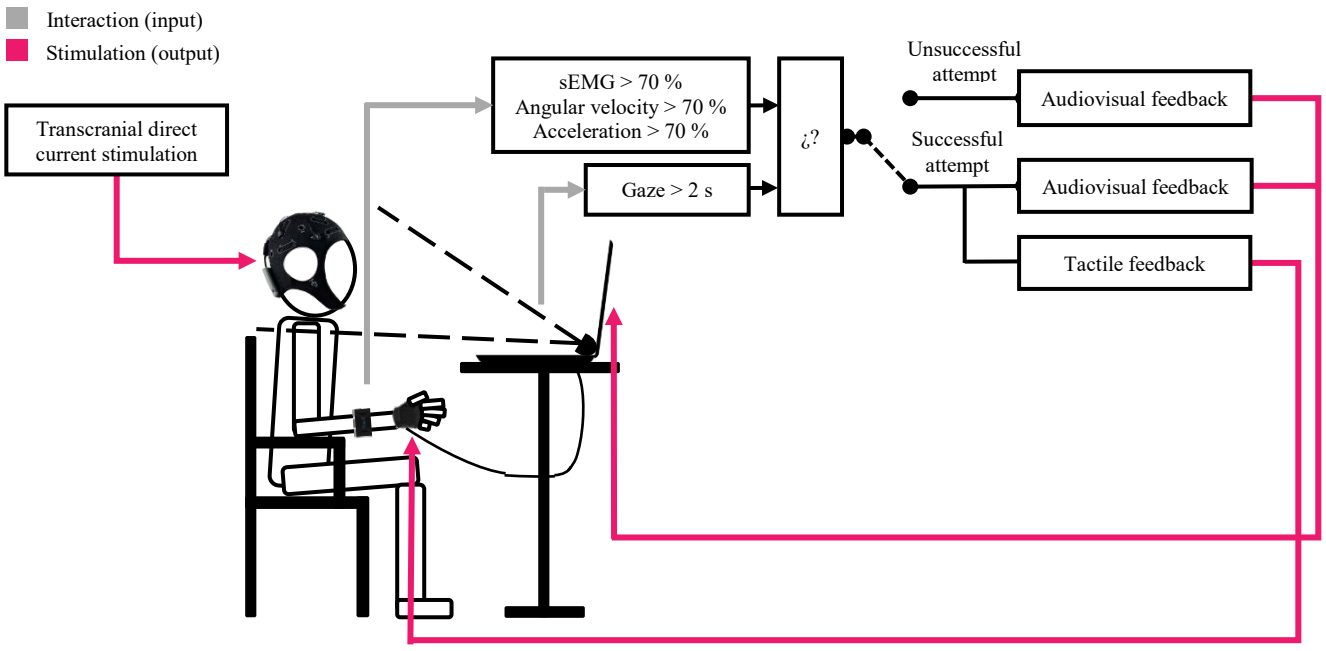

Fig. 3. Worflow of the exercise. At each repetition, gaze, muscular activity, and movements are evaluated to provide adequate audiovisual and tactile feedback. tDCS is provided during the whole session.

five times a week (75 sessions in the whole intervention). In Phase A, participants received conventional physical therapy. Passive range of motion exercises were provided in those segments where no active movement was detected to meticulously reproduce a range of articular movements and muscle and soft tissue elongation. In those segments where residual active movement capability was detected, participants were encouraged to perform the movements with the assistance of the therapists. In phase B, participants combined 20 minutes of the experimental intervention with 40 minutes of described physical therapy program, in that order. A physical therapist supervised all the sessions and prevented extreme compensatory movements.

Participants were assessed by a physical therapist at the beginning of the initial phase A (A_i), at the end of the initial phase A, which was the beginning of phase B (B_i), at the end of phase B, which was the beginning of the second phase A (B_f), and at the end of the second phase A (A_f). The body functions were evaluated with the upper extremity subscale of the Fugl-Meyer Assessment Scale. The body activities were evaluated with the time and functional ability scores of the Wolf Motor Function Test [28].

F. Data analysis

Changes in the outcome measures throughout the intervention were assessed using Wilcoxon match-paired signed-rank tests. The α level was set at 0.05 for all analyses (two-sided). All analyses were computed with SPSS for Windows, version 22 (SPSS Inc., Chicago, USA).

III. Results

A. Participants

From the 77 stroke survivors who were attending the neurorehabilitation program, seven participants satisfied criteria to participate and were included in the study. Two woman and five men, with a mean age of 55.9±8.1 years (ranging from 40 to 63 years), and 365.1±383.9 days post-stroke (ranging from 184 to 1233 days) were included. Five participants presented an ischemic stroke and two participants presented a hemorrhagic stroke. All the participants were right-handed before the lesion. Four of them presented a left hemiparesis, and the other three presented a right hemiparesis.

B. Clinical data

Participants showed a statistically significant improvement in all the outcome measures during the experimental intervention (Phase B), which was not detected during the conventional intervention (Phase A) either before or after it (TABLE I)(Fig 4). Interestingly, improvement was maintained after the second Phase A.

When analyzing the progress of each participant, results showed that two participants, two men with ischemic lesions, did not respond to treatment. One of them improved one point in the Fugl-Meyer, but other measures remained unaltered throughout the intervention.

In contrast, the other five participants experienced a remarkable improvement that even exceeded the minimally clinically important difference in the Fugl-Meyer [29], and in both subscales of the Wolf Motor function test [30].

TABLE I. CLINICAL DATA

Scale/Test	Start of phase A (A_i)	Start of phase B (B_i)	End of phase B (B_f)	End of phase A (A_f)	Significance
Fugl-Meyer Assessment Scale – Upper extremity[a]	12.6±2.4	12.9±2.5	18.0±5.35	17.6±5.1	$B_i>A_i$: p=0.157 $B_f>B_i$: p=0.027 $A_f<B_f$: p=0.083
Wolf Motor Function Test – Time[a] (s)	1580.0±251.1	1581.6±256.5	1429.7±307.5	1421.43±300.5	$B_i>A_i$: p=0.713 $B_f<B_i$: p=0.045 $A_f<B_f$: p=0.171
Wolf Motor Function Test – Functional ability[a]	8.1±9.1	8.3±9.4	11.6±10.0	11.7±10.1	$B_i>A_i$: p=0.317 $B_f>B_i$: p=0.038 $A_f>B_f$: p=1.000

[a] Data are expressed in terms of mean and standard deviation.

Fig. 4. Clinical data of the a) Upper Extremity subscale of the Fugl-Meyer Assessment Scale; and b) Wolf Motor Function Test.

IV. DISCUSSION

There is a growing body of research that supports the efficacy of VR [31]–[33] and tDCS interventions [34]–[36] on upper limb rehabilitation after stroke. Interestingly, the combination of tDCS and VR has been reported to provide greater improvement than each technique alone [20], which could be explained by an increased corticospinal excitability facilitated by the combination of both techniques [18].

Previous interventions combining tDCS and VR-based support the improvement detected in our participants in both the body [19], [20] and activity functions [19]. As in preliminary reports, the changes detected in our study in both domains exceeded the minimally clinically important difference for both scales [19], [20]. Interestingly, this improvement has been reported in the subacute [20] and in the chronic phase after stroke [19], when (in the latter) spontaneous neural recovery is unlikely [37]. The improvement detected in our participants is specially remarkable because they were not only chronic but also presented a severe hemiparesis, and the expected outcome of a rehabilitation program on upper limb mainly has been reported to depend on the baseline condition of the upper extremities. Actually, the baseline motor condition of the upper extremities is the major predictor of upper limb recovery [38].

In addition to the improvement, participants maintained the gains until the end of the study. Although clinical deterioration is expected after discharge of rehabilitation, literature about the maintenance of gains when returning to a physical therapy program after a specific intervention is more limited, especially in virtual reality-based interventions. However, existing studies support our results [31], [39]. The capacity of VR to provide online closed-loop multimodal feedback could have facilitated the effects detected in our sample [23], and visual, auditory, and haptic feedback have been shown to have a considerable impact on the development and on the motor learning process [40].

If these results are confirmed in future controlled studies, the improvement and the maintenance of gains detected after the experimental intervention, could support its use as a feasible alternative to the scant existing therapeutic options available to subjects with severe hemiparesis, which have proved limited effect on motor function [41] and may require high attentional and cognitive demands that can limit its use [13].

Although the limited number of participants did not allow to analyze the responsiveness to the treatment, it is worth mentioning that the two non-responders detected in our study did not present any relevant demographic characteristic. Surprisingly, the greatest improvement was detected in the subject who presented the highest time since injury. In addition to the limited sample, no structural nor functional data was

available to check the integrity of the corticospinal tract of the participants. Lesions of this tract in non-responders could explain the absence of improvement after the intervention. Actually, integrity of the corticospinal tract is the second major predictor of upper limb recovery [38]. Yet, despite the limitations, the combinative use of tDCS and a closed-loop VR intervention showed promising results on upper limb recovery in stroke survivors with severe hemiparesis that would be worthwhile to investigate in future studies.

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