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PATIENT FACING SYSTEMS

Combined Transcranial Direct Current Stimulation and Virtual Reality-Based Paradigm for Upper Limb Rehabilitation in Individuals with Restricted Movements. A Feasibility Study with a Chronic Stroke Survivor with Severe Hemiparesis

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Abstract

Impairments of the upper limb function are a major cause of disability and rehabilitation. Most of the available therapeutic options are based on active exercises and on motor and attentional inclusion of the affected arm in task oriented movements. However, active movements may not be possible after severe impairment of the upper limbs. Different techniques, such as mirror therapy, motor imagery, and non-invasive brain stimulation have been shown to elicit cortical activity in absence of movements, which could be used to preserve the available neural circuits and promote motor learning. We present a virtual reality-based paradigm for upper limb rehabilitation that allows for interaction of individuals with restricted movements from active responses triggered when they attempt to perform a movement. The experimental system also provides multisensory stimulation in the visual, auditory, and tactile channels, and transcranial direct current stimulation coherent to the observed movements. A feasibility study with a chronic stroke survivor with severe hemiparesis who seemed to reach a rehabilitation plateau after two years of its inclusion in a physical therapy program showed clinically meaningful improvement of the upper limb function after the experimental intervention and maintenance of gains in both the body function and activity. The experimental intervention also was reported to be usable and motivating. Although very preliminary, these results could highlight the potential of this intervention to promote functional recovery in severe impairments of the upper limb.

Keywords Virtual reality · tDCS · Eye-tracking · Surface electromyography · Upper limb paresis · Monoparesis, stroke

Introduction

Impairments of the upper limb (UL) function, a common sequelae affecting more than 85% of stroke survivors [1] and other neurological conditions, have been reported to have a strong negative impact in the performance of the activities of daily living (ADL's) and the quality of life [2], which makes them one of the major causes for rehabilitation. Although there is no standard intervention for UL rehabilitation [3], recovery of the 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]. According to this, uncertain prognosis is expected when active movements are not present. As a proof, the major predictor of UL recovery after a stroke has been reported to be the baseline condition of the UL function [6]. Traditionally, therapeutic options for severe impairment of the UL function have focused on preserving the mobility and flexibility of the affected extremity [7, 8] and compensating for the deficit by training the opposite limb in daily tasks [4, 9]. However, the non-

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use of the affected limb derived from the latter techniques may lead to a form of "learned paralysis" [10, 11], which could reduce the sensorimotor representation of the arm in the available neural circuits [12] and limit its functional recovery [9].

Techniques based on motor observation and imagination, as mirror therapy [8, 13] or motor imagery [14, 15], have been shown to elicit cortical activity coherent with the observed or imagined movements [15, 16], which is supported by the mirror neuron system theory [17]. Non-invasive brain stimulation, as transcranial magnetic stimulation and transcranial direct current stimulation (tDCS) have been shown to modulate excitability of the brain cortex by facilitating somatosensory evoked potentials [18, 19]. The promotion of brain activity in absence of movement may support the use of these therapies and techniques as therapeutic options in cases of severe UL impairment. Interestingly, their combined use has been shown to synergistically increase their effect. For instance, the combination of tDCS and a motor observation intervention has been reported to have additive effects on motor performance [20]. And, moreover, the addition of tDCS to a motor observation and execution task mediated by virtual reality (VR) has reported to increase short-term corticospinal facilitation [21]. The capacity of VR to provide controlled multi-modal stimulation in one or more sensory channels [22] has motivated its use in motor observation and imagery interventions [23, 24]. Its capacity to enable real-time user interaction with metaphors that do not require real movements is specially interesting to allow for participation of individuals with severe impairments of the UL function, and close the loop of interaction-stimulation [25].

In light of the previous work, we hypothesize that a paradigm combining tDCS and a VR-based motor observation task triggered by conscious active responses would provide a feasible rehabilitation framework for individuals with severely affected UL function. The objective of this paper is twofold: first, to describe the experimental rehabilitation paradigm; and second, to determine its clinical efficacy and acceptance in a chronic stroke survivor with severe hemiparesis.

System description

Instrumentation

A standard laptop, a Dell Inspiron 7520 (Dell Inc., TX, USA) that incorporates an 8-core Intel(R) Core(TM) i7-3632QM CPU@2.20GHz with 8 GB of RAM and runs Windows 10 Pro 64-bit, is used in the experimental setting (Fig. 1). Unity version 5.1 (Unity Technologies, CA, US) is used to generate stimuli and manage communication between devices.

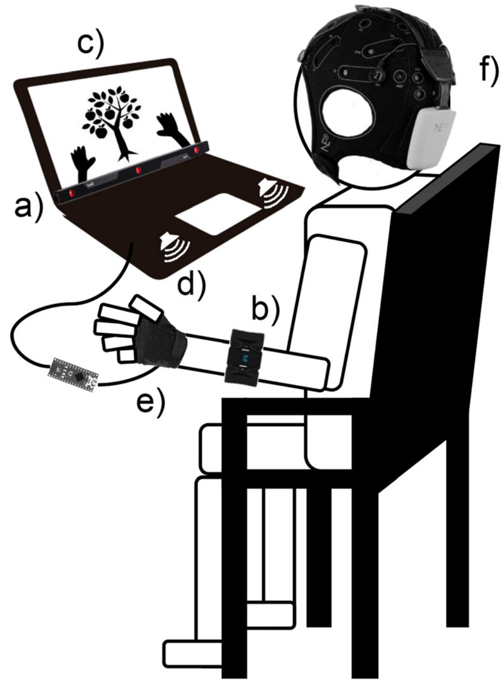

Fig. 1 Interaction and stimulation paradigm. The system enables interaction through **a** gaze and/or **b** muscular activity or movement, and provides **c** visual, **d** auditory, and **e** vibritactile feedback, and **f** transcranial direct current stimulation

Interaction

Interaction is enabled by gaze and/or muscular activity or movements. Users' gaze is estimated using a portable low-cost eye-tracking system, the EyeX (Tobii Technology AB, Danderyd, Sweden) (Fig. 1a). The device can estimate the spot on a screen where users are looking from the reflections of an infrared light in their pupils [26] and provide gaze data with a minimum framerate of 30 Hz in an operating range of 50 to 90 cm.

The users' muscular activity and movements are estimated using a low-cost gesture and motion control armband, the Myo (Thalmic Labs, Kitchener, ON, Canada) (Fig. 1b). The device includes different types of sensors to detect surface electromyographic activity (sEMG) [27], angular velocity, and acceleration. The sEMG data are provided by seven medical-grade stainless steel sensors that surround the users' arm while in use, angular velocity data are provided by a three-axis gyroscope, and acceleration data are provided by a three-axis accelerometer at a framerate of 200, 50, and 50 Hz, respectively. Main potential contributors to the sEMG data are the brachioradialis, palmaris longus, and flexors and extensors of the fingers. The Myo can expand from 19 to 34 cm forearm circumference and has a weight of 93 g and about 1 cm of thickness.

Stimulation

Stimulation involves provision of audiovisual and vibrotactile feedback, and non-invasive brain stimulation. Visual stimulation is provided by the 15.6″ laptop screen (Fig. 1c). Auditory feedback is provided by two speakers, which are embedded in the laptop and located at opposite ends of the keyboard (Fig. 1d).

Vibrotactile feedback is provided using three coin vibrators with 4 mm of radius that are embedded in a hand-made Velcro band (Fig. 1e). The band was designed to wrap the users' hands in such a way that vibrators are located approximately in the palmar side of the metacarpophalangeal joint of the thumb, index, and pinky fingers (Fig. 2). The frequency of the vibration is set to 200 ± 40 Hz and controlled through an Arduino Nano (Interaction Design Institute Ivrea, Ivrea, Italy). The weight of the vibration band is 75 g.

tDCS was provided using a wireless hybrid EEG/tDCS headset, the StarStim 8 (Neuroelectrics, Barcelona, Spain), which includes an 8-channel amplifier and a neoprene headcap with 39 positions based on the 10–10 system, where the electrodes can be inserted (Fig. 1f). The headset enable currents up to 2 mA with a resolution of 1 μA.

Setting

Interaction and stimulation are modular, so the number of responses for interaction and the modes of stimulation, with the only exception of the visual feedback, are configurable (Table 1).

Interaction with the system considering all the responses and stimulation modes requires users to wear the armband and the vibration band in the affected limb, and the tDCS headset. Users are also required to sit in a chair with armrests, with their arms resting on them, their backs leaning against the backrest, and their heads fixed in a comfortable position (Fig. 1). The laptop is placed approximately at 50 cm in front of the users, 20 cm below eye-level. The eye-tracking system is fixed to the laptop and tilted towards their eyes. Brain stimulation can be unilateral or bilateral. In case of unilateral stimulation, the anode is placed over the ipsilesional primary motor cortex (M1) (C3 or C4 for left or right impairment, respectively) and the cathode is placed in the contralesional supraorbital cortex (Fp2 or Fp1 for left or right impairment, respectively). In case of bilateral stimulation, the anode is placed over the ipsilesional primary motor cortex and the cathode is placed in the contralesional primary motor cortex. The brain stimulation can be passive, where stimulation is administered constantly throughout the session, or active, where stimulation is administered only when intention of movement is detected from the muscular activity and movements. In any configuration, the tDCS electrodes are soaked in saline solution before their arrangement, impedances are kept below 10 kΩ, voltage below 26 V, and output intensity is set to 2 mA.

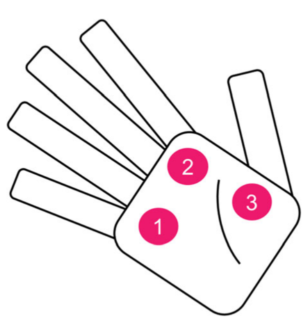

Fig. 2 Location of the vibrators. The vibration band is fixed so that the three coin vibrators are approximately located in the palmar side of the metacarpophalangeal joint of the thumb, index, and pinky fingers

Table 1 Possible configurations of the interaction and stimulation

Parameters	Options
Interaction	
Gaze	Yes/No
Muscular activity	Left/Right/None
Movement	Left/Right/None
Stimulation	
Sound	Yes/No
Vibration	Left/Right/None
Brain stimulation	Active/Passive/None Unilateral/bilateral

Interaction with the system and stimulation are modular. The number of responses for interaction and the modes of stimulation, with the only exception of the visual feedback, are configurable

Calibration

The capacity of interaction of the users using their gaze, muscular contraction, and arm movements are registered in a customized calibration process.

Calibration of eye-tracking systems usually involves staring at a target that appears and disappears or randomly moves around the screen at a certain speed, while having the head as still as possible. To maximize participation of users with cognitive impairment, who might have difficulties to perform this task, we designed a customized eye-tracking calibration that consists on following a white cross that slowly traces a cross-path on a black background, which has been shown to be effective even in severely affected individuals [28]. The calibration process also allows for using personalized targets, such as images with positive valence or familiar faces, which have demonstrated to modulate visual search [29]. From the position of the target on the screen coordinates and the users' pupils on the coordinates of the eye-tracking system, the calibration process estimates the gaze of the users on the screen coordinates.

Analogously, calibration of the Myo requires performing different movements as pincer grips, adduction and abduction of the fingers, or making a fist, which restricts its use to healthy individuals. To facilitate participation of individuals with restricted arm or hand movements, we developed a customized calibration process that requires users to attempt a reaching movement three times. Specifically, an apple is shown on the screen and users are required to rest their arms on the armrests of the chair initially (resting condition) and try to pick it up using their affected arm for three times. The sEMG activity, the angular velocity, and the acceleration provided by the armband are registered in the resting condition and during the movement. The sEMG is considered a meaningful variable of interaction if the average amplitude during the movement is five or more times the activity during the resting condition in one sensor at least. Similarly, the angular velocity and acceleration are considered meaningful variables of interaction if their average values during the movement are at least twice the average velocity and acceleration registered during the resting condition. The calibration process provided the maximum values of the sEMG activity in the seven sensors and/or the maximum angular velocity and acceleration that users who successfully passed the test were able to generate.

Exercise

The virtual environment presents both left and right virtual arms from a first-person perspective in front of an apple tree (Fig. 3a). A serial of apples appear on the branches and disappear a few seconds after. Apples can appear at four different heights in the left or right part of the environment, corresponding to the ideally reachable space of the real left and right arm, respectively. Environmental sounds, such as birds signing and the sound of the wind are provided. Extrinsic feedback is also provided, including the time left, number of repetitions, and record number of repetitions.

The objective of the task is to pick up the apples before they disappear. To achieve that goal, users have to attempt the reaching movement while looking at the apple. An attempt is considered successful if users stare at the apple for a required number of seconds and if the intended movement generates a peak of muscular activity, angular velocity, or acceleration greater than the 80% of the maximum values registered in the calibration process. In this case, a winning sound effect is provided and the virtual environment shows an animation of the virtual arm extending towards the apple (Fig. 3b), which is also indicated with the consecutive vibration of the three vibrotactile actuators (Fig. 2), grasping it (Fig. 3c), bringing it towards the users' virtual mouth (Fig. 3d), and biting it (Fig. 3e). The virtual environment then simulates that the apple is bitten several times, which is also indicated with synchronous biting sound effects and vibrations, and the arm

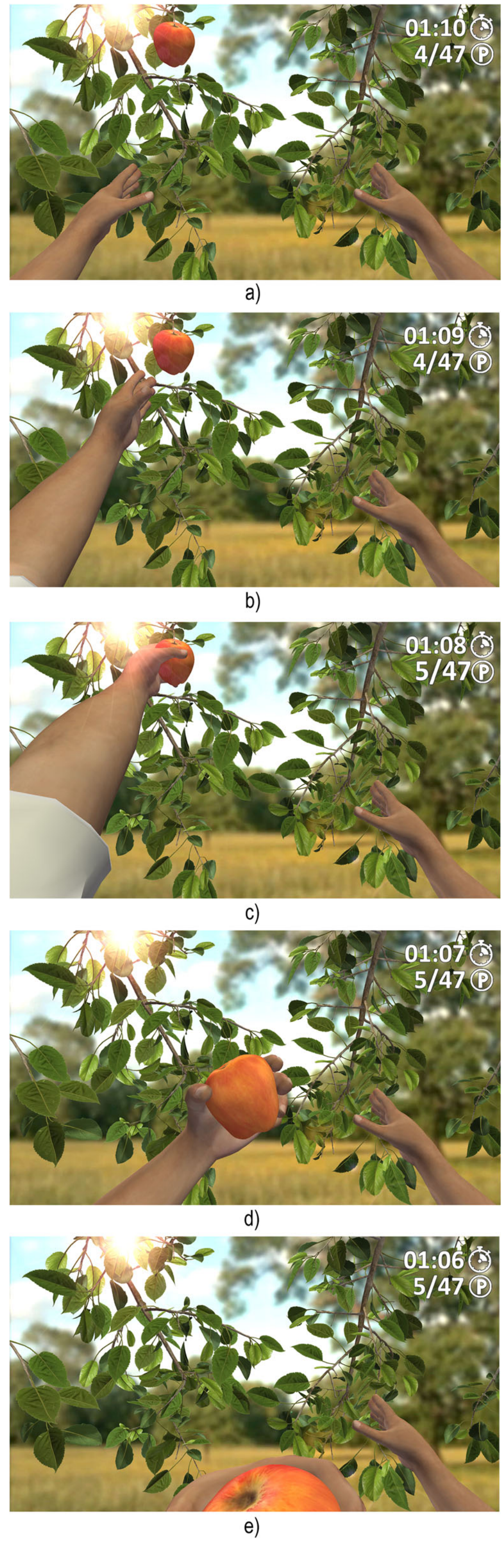

Fig. 3 Virtual environment. The virtual environment shows **a** the users' arms in front of an apple tree. The objective of the exercise is to pick the apples that appeared on a branch with the closer arm to the apple. If the intended movement to pick the apple is sufficient, the virtual environment displays an animation of **b** the virtual hand moving towards the apple, **c** grasping the apple, **d** bringing it to the mouth, and **e** biting the apple

is finally moved to the initial resting position. An attempt is considered unsuccessful if the generated activity does not exceed the specified threshold, which is represented by a losing sound effect and showing no movement of the virtual arms, or if the activity is sufficient but users do not stare at the apple for the required number of seconds, which is represented by the same sound effect and by a reaching movement of the virtual arm towards a wrong direction. Brain stimulation is provided according to the configuration of the session.

Feasibility study

Participant

R.V. is a 38-year-old male with a severe left hemiparesis secondary to a right intraparenchymal temporoparietal hemorrhage with reactive ischemic gliosis confirmed by magnetic resonance examination four years prior to this intervention. R.V. had an intraparenchymal and auricular rebleeding with acute hydrocephalus one year after the first lesion, and underwent a craniotomy and exeresis of an arteriovenous malformation the following year. When he was admitted to our long-term neurorehabilitation program six months after the craniotomy, presented a left sensory-motor deficit with left spastic hemiparesis and hypesthesia, which affected the UL function, and to a lesser extent, the balance ability and gait (Table 2). R.V. showed independence in the performance of ADL's but not on instrumental activities. Neuropsychological examination evidenced a mild cognitive impairment with important attentional deficits, specially in alternating and sustained attention, with slow reaction time, and difficulties to organize and plan tasks of medium complexity. For two years before the experimental intervention with the system, R.V. attended a holistic neurorehabilitation program that included physical therapy. Motor intervention on the ULs focused on maximizing functionality of the paretic UL while preserving mobility and flexibility of the articular joints. Specifically, it included passive mobilization of those segments where no active movement was detected, assisted active movements in case of residual active movement capability, functional electrotherapy, mirror therapy, Perfetti-based therapy, robot-assisted reaching movements with the Armeo (Hocoma AG, Volketswil, Switzerland), and botulinum toxin treatment administered on biceps bracii, palmaris longus, flexor digitorum profundus, and superficialis. The motor condition of R.V. progressed for the first year and a half, but the assessment two years after admission seemed to evidence a motor plateau (Table 3). Basing on his progress and prognosis he was prescribed to an intervention with the experimental system, three years and four months after the first onset. R.V. provided informed written consent before the intervention.

Procedure

Intervention consisted of 75 sessions, divided in three phases of a reversal A-B-A design. Each phase included 25 one-hour sessions administered three times a week. In phase A, R.V. underwent a rehabilitation program combining the rehabilitation approaches mentioned above. In phase B, R.V. combined 40 min of this program with 20 min with the experimental system. Interaction with the system included gaze, muscular activity, and arm movements. Stimulation included audiovisual and vibrotactile feedback, and passive unilateral brain stimulation. The exercise included four interaction areas in the left side. Interaction, activity, and inactivity time were set to 10 s, 10 s, and 4 s, respectively. A fixation time of 2 s was required. All the sessions were supervised by a physical therapist in a dedicated area of the physical therapy unit. Before each session, the physical therapist equipped R.V. with the instrumentation and conducted the calibration. During the session, the physical therapist provided him with instructions and prevented him from making extreme compensatory movements.

Assessment was administered by a blind physical therapist at baseline and at the end of each phase, and evaluated the body functions with the UL subscale of the Fugl-Meyer Assessment Scale (FMA-UE) [30], and the body activities with the time and functional ability scores of the Wolf Motor

Table 2 Configurable parameters of the exercise

Parameter	Explanation
Interaction side (left/right)	Side of the environment where apples will appear (left or right)
Areas of interaction (2/4)	Number of areas where apples can appear in both sides (2 or 4)
Time of interaction (s)	Time between the appearance of an apple and its disappearance
Activity time (s)	Time of the whole animation in case of successful attempt (time of brain stimulation in each repetition during active condition)
Inactivity time (s)	Time between the end of the animation and the appearance of the next apple
Fixation time (s)	Required time to stare at the apples

Interaction and intensity of the exercise can be configured according to the clinical demands

Table 3 Clinical progress of the participant before the intervention

Scale	Admission	6 months	12 months	18 months	24 months
NIH Stroke Scale [0–42]	8	6	4	4	4
Motor Index. Left upper limb [0–99]	34	34	39	44	44
Shoulder abduction [0–33]	14	14	14	19	19
Elbow flexion [0–33]	19	19	25	25	25
Pinch grip [0–33]	0	0	0	0	0
Tinetti Performance-Oriented Mobility Assessment					
Balance [0–16]	14	15	15	15	15
Gait [0–12]	6	8	8	10	10

The motor condition of RV improved for the first year and a half but seemed to reach a rehabilitation plateau two years after admission

Function Test (WMFT) [31]. At the end of the intervention, R.V. was also asked to provide feedback about the usability of the system using the System Usability Scale (SUS) [32] and about his motivation with four subscales of the Intrinsic Motivation Inventory (IMI) [33].

Results

After the first physical therapy program, no changes were detected in the FMA-UE and limited improvements were detected in both the time and ability subscales of the WMFT, which represented a relative amelioration of less than 1.8% and 4.2%, respectively (Table 4). After the experimental intervention with the system, the participant showed an improvement of 13 points in the FMA-UE, which represented a relative increase of 86.7%, an improvement of 120 s in the performance time of the WMFT, which represented a 10.9%, and increased their score in the functional ability subscale of the WMFT in 3 points, which represented a relative improvement of 12%. Importantly, improvement exceeded the minimally clinically important difference of both scales [31, 34]. Results of the final assessment showed relative maintenance of gains after the second physical therapy program, with a slight decrease in the FMA-UE and in the timed subscale of the WMFT. With regard to the subjective acceptance of the experimental intervention, the system was perceived as being usable (80 from a total score of 100), enjoyable (7 of 7), and useful (7 of 7) and R.V. felt himself competent (7 of 7) but not pressured (1 of 7).

Discussion

This paper presents a combined tDCS and VR-based intervention for the rehabilitation of severely affected upper limb function and evaluates its clinical use in a chronic post-stroke participant.

Our results confirmed the limited effects provided by a physical therapy program where the participant was included and evidenced a dramatic improvement of the upper limb function after the experimental intervention in both the body functions and activity, which was retained after coming back to the physical therapy intervention.

The improvement experimented by R.V. should be highlighted. First, he entered the experimental intervention with a chronicity of more than two years, a remarkable time after the 6-month period that traditionally has been considered to encompass endogenous recovery mechanisms [35]. Second, he presented a severe hemiparesis of the upper limb

Table 4 Clinical progress of the participant during the intervention

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)
Clinical data				
Fugl-Meyer Assessment Scale – Upper extremity [0–66]	15	15	28	27
Wolf Motor Function Test				
Performance time (s)	1120	1100	980	990
Functional ability [0–75]	24	25	28	28

Results showed limited improvement during the first phase A and a dramatic improvement after phase B, which was maintained in the follow-up assessment, after the second phase A that seemed to stall despite his participation in a physical therapy program. As previously stated, the motor condition of the upper limb is the most relevant prognostic factor for recovery function [6]. Finally, the improvements detected in both the body function and activity after the experimental intervention were clinically meaningful, which evidence promising clinical relevance of this intervention. Besides improved scores in the clinical scales, R.V. experimented changes that had noticeable effects on his daily life.

The improvement detected in this feasibility study are supported by previous research with post-stroke individuals. Existing literature not only shows efficacy of both techniques, VR [24, 36, 37] and tDCS [38–40], when applied in isolation, but also additional improvements when they are applied simultaneously [41], which has been argued to facilitate corticospinal excitability [21]. Comparable clinical improvement has been reported after similar interventions in both the body [41, 42] and activity functions [42], and in both the subacute [41] and chronic phase after stroke [42]. Improvement experienced by R.V., however, should be highlighted, as the motor function of his UL was severely impaired, and this is the major predictor of poor UL recovery [6]. The provision of multisensory feedback in absence of movement but in response to voluntary actions triggered by each attempt to make a movement could have promoted the motor learning process [43], and facilitate the maintenance of gains after coming back to the previous program, which is also supported by previous VR interventions on UL function [24].

Although the clinical effectiveness of the intervention must be confirmed in further studies, the progress detected in R.V. questions the existence of a rehabilitation plateau, and opens the possibility of new therapeutic options when the observed improvement is limited. Confirmation of these results, together with the good acceptance of the intervention, could support the potential of the experimental system as a therapeutic alternative in severe impairment of the UL function, where available options are scant and many have poor acceptance [44], limited effects [8], and high cognitive demands [14]. Future studies should also determine whether these changes were promoted by the intervention itself or by a change of intervention.

Conclusion

This paper describes a combined tDCS and VR-based paradigm for UL rehabilitation in individuals with restricted movements and a feasibility study with a chronic stroke survivor with severe hemiparesis. Preliminary results showed that the system was effective at improving the UL function, usable, and motivating.

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Compliance with Ethical standards

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

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

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