

The combined action of a passive exoskeleton and an EMG-controlled neuroprosthesis for upper limb stroke rehabilitation: first results of the RETRAINER project*

E. Ambrosini, S. Ferrante, J. Zajc, M. Bulgheroni, W. Baccinelli, E. d'Amico, T. Schauer, C. Wiesener, M. Russold, M. Gfoehler, M. Puchinger, M. Weber, S. Becker, K. Krakow, M. Rossini, D. Proserpio, G. Gasperini, F. Molteni, G. Ferrigno, and A. Pedrocchi

Abstract— The combined use of Functional Electrical Stimulation (FES) and robotic technologies is advocated to improve rehabilitation outcomes after stroke. This work describes an arm rehabilitation system developed within the European project RETRAINER. The system consists of a passive 4-degrees-of-freedom exoskeleton equipped with springs to provide gravity compensation and electromagnetic brakes to hold target positions. FES is integrated in the system to provide additional support to the most impaired muscles. FES is triggered based on the volitional EMG signal of the same stimulated muscle; in order to encourage the active involvement of the patient the volitional EMG is also monitored throughout the task execution and based on it a happy or sad emoji is visualized at the end of each task. The control interface control of the system provides a GUI and multiple software tools to organize rehabilitation exercises and monitor rehabilitation progress. The functionality and the usability of the system was evaluated on four stroke patients. All patients were able to use the system and judged positively its wearability and the provided support. They were able to trigger the stimulation based on their residual muscle activity and provided different levels of active involvement in the exercise, in agreement with their level of impairment. A randomized controlled trial aimed at evaluating the effectiveness of the RETRAINER system to improve arm function after stroke is currently ongoing.

I. INTRODUCTION

Stroke is the third most common cause of death and the main cause of acquired adult disability in high-income countries [1]. Motor impairment, typically affecting movement of the upper and lower limb of one side of the body, affects about 80% of stroke survivors [2]. The most common deficit after stroke is motor impairment of the

contralateral arm, with more than 80% of stroke survivors experiencing this condition in the acute phase, and only half regaining some useful upper limb function after six months [3]. A reduced arm mobility impacts the patients' independence in performing activities of daily living (ADL) [4], their capability to perform social and occupational activities, and is associated with anxiety, depression, and poorer perception of quality of life [5], [6]. Therefore, the recovery of arm movements is one of the most important goals of stroke rehabilitation.

Due to its crucial role, several interventions have been proposed to improve arm functions after stroke, such as biofeedback and virtual reality, the Bobath approach, mirror therapy, constrained-induced movement therapy, functional electrical stimulation (FES), manual therapy, repetitive task training, task-specific training, mental practice, strength training, stretching and positioning, and robotics [7], [8].

Overall, there is a common agreement that functional recovery after stroke is positively influenced by goal-specific sensorimotor input through training or everyday use of the arm and hand [9]. A recent Cochrane review found there is a low quality evidence that repetitive task training improves arm and hand functions after stroke [10]. Within this framework, FES can be used as a motor relearning tool by enabling hemiparetic patients to participate in goal-oriented repetitive movement therapy [8], [11]. Recently, a systematic review observed that FES has a positive effect on upper limb activity compared with both no intervention and training alone [12]. However, which is the most effective FES modality is still under debate. A recent randomized controlled trial (RCT) [13], involving 122 post-acute stroke patients, compared the effects of three different FES modalities: cyclic, EMG-triggered, and sensory FES. The Authors found that all intervention groups exhibited significant functional improvement but there was no difference based on the type of stimulation. To maximize the effect of FES on the central nervous system so as to promote motor relearning, several neurophysiological studies advocated the use of FES synchronized with the residual voluntary effort of the patient [14]-[16]. However, EMG-triggered FES may be not enough to guarantee a close association between motor intention and stimulated motor response, because the subject could use the residual activation only to trigger the FES assistance and not to contribute to the overall task execution. Thus, there is the need of FES controllers able to promote the subject's active involvement during the whole exercise execution [17].

*Research supported by European Union's Horizon 2020 research and innovation program under grant agreement No 644721.

E.A., S.F., G.F., and A.P. are with NEARLAB, Department of Electronics, Information and Bioengineering, Politecnico di Milano, Italy (E.A. is the corresponding author; phone: +39-02-23999509; e-mail: emilia.ambrosini@polimi.it).

M.B., W.B., and E.d'A. are with Ab.Acus, Milan, Italy.

T.S. and C.W. are with the Control Systems Group, Technische Universität Berlin, Germany.

J.Z. and M.R. are with Ottobock Health Products GmbH, Wien, Austria.

M.G. and M.P. are with Technische Universität Wien, Austria.

M.W. and S.B. are with Hasomed GmbH, Magdeburg, Germany.

K.K. is with Asklepios Neurologische Klinik Falkenstein, Königstein, Germany.

M.R., D.P., G.G., and F.M. are with Villa Beretta Rehabilitation Center, Valduce Hospital, Costamasnaga, Lecco, Italy.

In the last thirty years, several electromechanical and robot-assisted arm training devices have been developed to improve arm function and ADL after stroke. Some examples are the MIT-MANUS®, developed by Massachusetts Institute of Technology [18], or the Arm robot, ARMin [19]. Most devices provide passive movement of the patient’s arm, some provide a partial assistance in order to maximize the active participation of the subject. Robots allow a therapy paradigm which is intensive, frequent and repetitive, in agreement with the motor learning principles. This hypothesis is confirmed by the results of a recent Cochrane review, which observed patients involved in robot-assisted arm training after stroke are more likely to improve their ADLs [20].

In the recent years, the combined use of FES and robotic technologies, referred as Hybrid Robotic Rehabilitation Systems, has been proposed as a solution to overcome the limitations of each single approach and improve the rehabilitation outcomes [21]. A study observed on 5 chronic stroke patients the positive effects of a platform combining a commercial passive exoskeleton (ArmeoSring, Hocoma), FES mediated by iterative learning control and applied to the triceps and anterior deltoid muscles, and voluntary effort [22]. Positive results were also found on 11 chronic stroke patients using an EMG-driven NMES-robotic system which support elbow, wrist and fingers movement [23].

The present work proposes a hybrid system for arm rehabilitation developed within the European project RETRAINER [24], which is composed by a custom-built passive arm exoskeleton for weight relief, EMG-triggered FES of arm muscles, and a visual feedback to maximize the patient’s involvement. The main novelties of the system are the support provided both to shoulder and elbow movements, the close temporal association between motor intention and stimulated motor response, and the use of a non-cumbersome and lightweight exoskeleton, which might be transferred into patients’ homes, increasing the training intensity and reducing the hospitalization time and costs.

II. METHODS

A. Apparatus

The apparatus, shown in Fig. 1, consists of a lightweight passive arm exoskeleton for weight compensation, a current-controlled stimulator with 2 channels of stimulation and 2 channels of EMG recordings (RehaMovePro, Hasomed GmbH) [25], and interactive objects, which are daily life objects equipped with RFID (Radio Frequency Identification) tags used to identify the target positions so as to drive the execution of the rehabilitation exercises. A suitable reader is embedded in the exoskeleton with the antenna on the wrist joint. The control system is shared between an Embedded Control System (ECS), running on a BeagleBoneBlack™, for real-time operation, and a Windows-based table (Microsoft Surface 3 running Windows 8), which provides a control interface (CI) for the therapist and the patient.

The exoskeleton is characterized by four degrees of freedom (DOFs), as shown in Fig. 2: three of them, e.g. shoulder elevation, shoulder rotation in the transversal plane and elbow flex-extension, are equipped with angle sensors (Vert-X 13 E, ConTelec AG) to measure the position and electromagnetic brakes to avoid the fatiguing and

unnecessary use of FES to hold a target position once reached [26]-[28]. The additional DOF is provided by an inclination module, which enables the patient to move the trunk 20° forward without constriction. The inclination module consists of a four-bar linkage, as show in Fig. 2; the shoulder joint head is integrated in the four-bar linkage and remains in a vertical position independent of the inclination angle. Since the inclination angle is not measured, it is not possible to know the 3D Cartesian position of the end-effector. In addition to the 4 DOFs, the humeral rotation, the pronosupination as well as the length of the forearm and the upper arm can be adjusted at the beginning of the training session at subject-specific positions. Table I report the joints range of motion (ROM) of the exoskeleton.

Figure 1. A schematic diagram of the experimental setup. The top left block shows the positioning of FES and EMG electrodes for an exemplary muscle (e.g. biceps brachii).

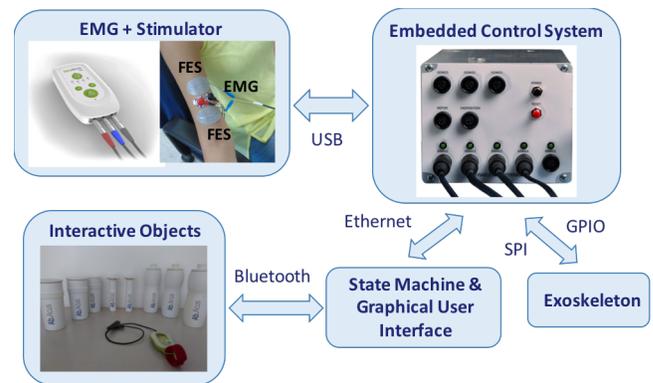
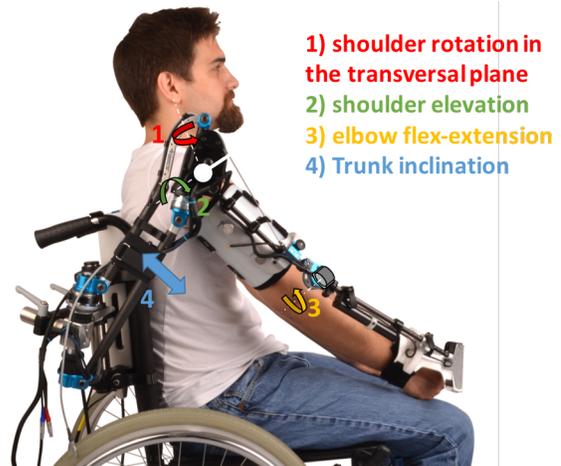


Figure 2. The RETRAINER exoskeleton. The 4 DOFs are shown.



The gravity compensation modules for upper arm and forearm consist of a carbon fiber-tube with springs inside whose pre-tension can be adjusted at the beginning of the training session in order to change the level of compensation. Thanks to the adjustability of the lengths and the level of compensation, the exoskeleton can fit and support patients within 5th and 95th female/male percentile. The exoskeleton can be mounted on the user’s wheelchair or on a normal chair by means of a universal clamping mechanism which assures

easy and stable mounting. The exoskeleton weighs about 4kg plus 2kg for the clamping mechanism.

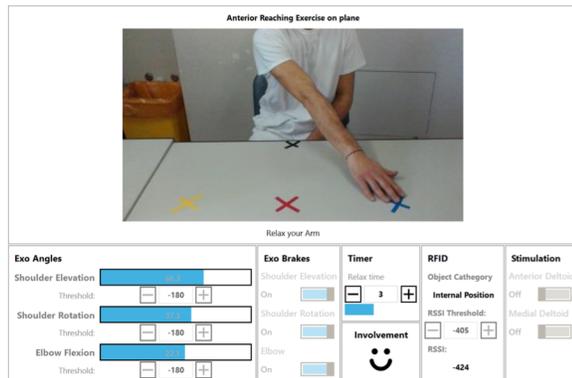
TABLE I. JOINTS ROM OF THE RETRAINER EXOSKELETON.

Elbow flex-extension	0° ... 120°
Shoulder rotation	-10° ... 120°
Shoulder elevation	0° ... 120°
Prono-supination	-50° ... 50° (10° steps)
Humeral rotation	0° ... 90° (10° steps)

B. Control system architecture

The CI of the system, implemented in .Net 4.6, provides a graphical user interface (GUI) including multiple software tools to organize rehabilitation exercises and monitor rehabilitation progress. The heart of the CI is a State Machine, which drives both the parameterization and the execution of the exercises. Each exercise is divided into single tasks: the State Machine drives the exercise execution throughout the tasks, while the execution of each single task is controlled by the ECS. The ECS controls all the modules requiring real time constraints, such as the stimulator, the FES controller and the exoskeleton sensors. To keep the CI and the ESC synchronized, a strict master slave concept using a custom made communication protocol was implemented, meaning that the ECS must not act independently, but only reacts to commands sent by the high level control. Transitions between states of the state machine and thus tasks of the exercise are triggered by angle sensors data, RFID data or a timer (depending on the task). Transitions have to fulfill certain conditions, so called guards. These guards are predefined for each task and have to be parameterized as described in the Section D. The GUI guides the user through the training by providing visual instructions and feedback. Fig. 3 shows an example of the GUI for a single task during the execution of the “Anterior reaching Exercise on a plane”.

Figure 3. The RETRAINER Graphical User Interface. The picture shows the task the subject has to perform; the lower part of the GUI shows, from right to left, the exo angles and their target values, the status of the brakes, the timer and a happy or sad emoji based on the voluntary effort of the subject (the emoji is shown at the end of the task execution), the RFID data and the stimulated muscles.



C. FES controller

An EMG-triggered stimulation controller is included in the ECS. Up to two muscles, selected by the therapist based on the subject-specific needs, can be stimulated simultaneously. The other muscles involved in the movement have to be voluntarily activated by the subject. For each stimulated muscle, the residual volitional EMG signal is

detected and used to trigger the onset of a predetermined stimulation sequence applied to the muscle itself. In case the muscle does not reach the pre-defined threshold, the stimulation sequence is automatically started after a time-out. EMG signals are acquired at 4kHz, the stimulation frequency is set at 25Hz, the pulse width is fixed at 300µs, while the stimulation intensity is set at the beginning of the training session on each muscle individually at a value tolerated by the subject and able to induce a functional movement. Separate EMG and stimulation (Pals® electrodes, Axelgaard Manufacturing Ltd) are placed over the muscle belly, as shown in Fig. 1.

When the stimulation starts, EMG signals are continuously measured in order to provide a visual feedback about the patient’s volitional involvement at the end of the execution of each task. An adaptive linear prediction filter is used to estimate the volitional EMG during hybrid muscle contractions [17]. If the mean value of the volitional EMG estimate during the stimulation phase is over a pre-defined threshold, a happy emoji is shown to the patient through the GUI (Fig. 2); conversely, if it is below the pre-defined threshold a sad emoji is shown in order to promote the active involvement of the subject.

A fast and automatic calibration procedure is required before the beginning of each session. This procedure aims at setting the current amplitude and the EMG threshold values. During the procedure the subject is asked to be relaxed. Specifically, three thresholds are set on each muscle: two of them are used to trigger the stimulation, one in case the muscle is activated as first and one in case the muscle is activated as second one; the third threshold is used to define the subject’s active involvement in the task. The thresholds are defined as twice the mean volitional EMG during a phase of no stimulation (first threshold), during a phase of stimulation of the other muscle (second threshold), and during a phase of simultaneous stimulation of the two muscles (third threshold).

D. Description of a typical training session

The workflow of a typical training session consists of four main phases: the setting, donning and parameterization of the system, and the training following a pre-defined sequence of exercises. The CI supports the therapist and the patient throughout all the phases via the GUI.

The setting starts with the therapist creating a new user, or selecting an existent one, and selecting the exercises. Afterwards, the donning phase starts with the placement of the EMG and stimulation electrodes. Once the electrodes placement is checked through the CI, the therapist should adjust the exoskeleton lengths to fit with the patient and let the patient don the exoskeleton. The following step is the calibration of the FES controller by means of the automatic procedure described in the previous paragraph. The therapist sets the gravity compensation both at the arm and forearm level and saves the final exoskeleton settings. On the following training days, the setting and donning procedure is partly simplified since the therapist can load the settings of the previous day and eventually adjust them.

The parameterization step is designed to set the guards of the State Machine. In this process the GUI guides the patient

and the therapist through each task of the selected exercises without stimulation. The patient-specific parameters for each task, such as the target positions, the desired time for the execution of each task, and the time of the relax phases, are determined. At the end of the parameterization phase, all the parameters are stored and the training session can start.

The training consists of the execution of a series of exercises involving the arm during daily life activities. Typical exercises are anterior reaching on a plane or in the space, moving an object on a plane or in the space, moving the hand to the mouth, with or without an object in the hand, and lateral elevation of the shoulder. The execution of the exercises is controlled by the CI which leads the patient throughout the single tasks by means of both visual and audio messages via the GUI.

E. Participants

A pilot test was conducted in order to validate the functionality of the system and verify its usability in a clinical environment. Four stroke patients (3 post-acute and 1 chronic) were recruited. Table II reports the demographic and clinical details of the participants. They were characterized by different levels of impairment, as highlighted by the Motricity Index score, but all of them had some residual muscle activity in the upper arm muscles of the affected side (MRC scale > 2). Both the right-hand and the left-hand side exoskeletons were tested, since two patients had a right affected side, and the other two a left affected side.

TABLE II. DEMOGRAPHIC AND CLINICAL DETAILS OF THE PATIENTS

Sub	Age	Sex	Time since stroke	Affected side	Type of stroke	MRC scale ^a	MI score ^b
S1	69y	M	2 months	Right	Ischemic	M3 (P) M3 (D)	51
S2	64y	M	1 month	Right	Ischemic	M3 (P) M3 (D)	77
S3	27y	M	7 years	Left	Hemorrhagic	M3 (P) M1 (D)	29
S4	49y	F	2 months	Left	Ischemic	M3 (P) M2 (D)	48

a. Medical Research Council (MRC) scale of the affected arm muscles; range: 0 (no contraction)-5 (normal strength). P/D: proximal/distal muscles.

b. Motricity Index (MI) score of the affected arm; range: 0 (maximal) – 100 (no impairment).

F. Data analysis

Movement performance was evaluated in terms of time to complete one exercise repetition. The completion time was computed by summing the time needed to complete each task, excluding the relax phases. The beginning of each task corresponded with the command sent by the CI, and this means that the total completion time included also the reaction time of the subject for each task composing the exercise. Performance was also evaluated in terms of number of “active” tasks, at the end of which a happy emoji was shown by the GUI, and number of tasks in which the subject was able to trigger the stimulation.

III. RESULTS

Fig. 4 and 5 show two exemplary tasks of the “Moving object on a plane” exercise, performed by S2. In both figures, the upper panel shows the angular joint values of the 3 sensorized DOFs; the middle and lower panel report the current amplitude and the volitional EMG estimated by the adaptive filter [17] for the stimulated muscles. Please note

that the following angular conventions were used: 0° at the elbow indicates a complete extension; 0° at shoulder elevation corresponds to the arm lying along the side; 0° at shoulder rotation indicates the neutral position.

Figure 4. A task of the exercise “Moving object on a plane” performed by S2. The task consists of going back to rest from the internal lateral position. The green area in the lower panel indicates the subject was actively involved in the task. The solid and dashed horizontal line correspond to the thresholds to trigger FES and to determine the patient’s active involvement, respectively. PD: posterior deltoid; AD: anterior deltoid.

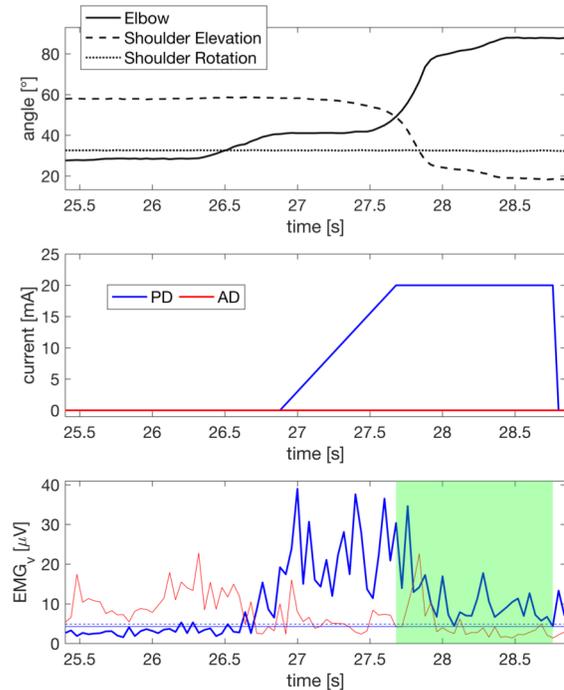


Fig. 4 shows the task which consists from going from the internal lateral position (blue cross in Fig. 3) to the rest position (black cross in Fig. 3). This task mainly requires an elbow flexion and a shoulder extension. The posterior (PD) and the anterior deltoid (AD) were selected for stimulation during the parameterization of the training session, but during this particular task only the stimulation of the PD muscle was allowed since it was the only one among the two selected functional to the movement. The subject was able to trigger FES based on his own residual volitional EMG about 1s after the “start” command of the CI: as soon as the volitional EMG of the PD muscle (blue line in the lower panel) overcame the threshold (solid horizontal line), the current amplitude (blue line in the middle panel) started to increase with a ramp up to reach the maximal value identified during the calibration procedure. Since the subject maintained an active muscle contraction throughout the execution of the task (mean volitional EMG over the dashed horizontal line when FES was equal to the maximal value), a happy emoji was shown by the GUI at the end of the task. We decided to evaluate the “active” involvement of the subject only when FES reached the plateau to reduce the number of false positive due to involuntary reactions when FES was switched on. This of course does not mean that the subject couldn’t have been actively involved also during the ramp phase. Once the target position was automatically recognized by the CI, the brakes

were switched on to maintain the target position and the stimulation was switched off. A relax phase was then allowed before the execution of the next task.

Figure 5. A task of the exercise “Moving object on a plane” performed by S2. The task consists of reaching the internal position from rest. The green area in the lower panel indicates the subject was actively involved in the task. The solid and dashed horizontal line correspond to the thresholds to trigger FES and to determine the patient’s active involvement, respectively. PD: posterior deltoid; AD: anterior deltoid.

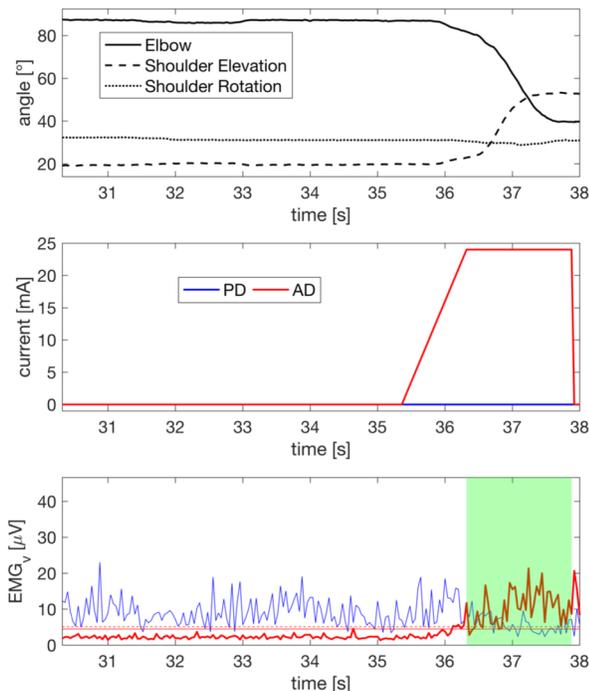


TABLE III. RESULTS OF THE TRAINING SESSIONS

Sub	Exercises	Stimulated muscles ^a	EMG-triggered tasks ^b	Active tasks ^c	Completion time ^d [s]
S1	Anterior Reaching on a plane	AD; PD	40 / 43	6 / 43	22.3 ± 6.2
	Moving object on a plane	AD; PD	10 / 12	0 / 12	19.9 ± 4.7
	Hand to mouth with an object	BC	10 / 18	10 / 18	12.4 ± 4.3
S2	Anterior Reaching on a plane	PD; AD	30 / 30	29 / 30	8.8 ± 2.1
	Moving object on a plane	PD; AD	22 / 23	21 / 23	28.2 ± 4.1
S3	Anterior Reaching on a plane	TC; PD	10 / 21	7 / 21	25.1 ± 7.9
	Anterior Reaching in the space	TC; PD	3 / 19	1 / 19	52.0 ± 1.8
	Hand to mouth	TC	5 / 6	5 / 6	5.3 ± 3.3
S4	Anterior Reaching on a plane	AD; PD	7 / 20	5 / 20	19.8 ± 5.9
	Hand to mouth with an object	BC; TC	34 / 51	31 / 51	5.4 ± 3.6

a. AD: anterior deltoid; PD: posterior deltoid; BC: biceps; TC: triceps.

b. Number of tasks in which FES was EMG-triggered / Total number of tasks which involved the stimulation of at least one muscle.

c. Number of tasks with active involvement (happy emoji) / Total number of tasks which involved the stimulation of at least one muscle.

d. Time to complete one exercise repetition (mean ± standard deviation)

Fig. 5 shows the task which consists of reaching the internal lateral position from the rest position (the following task in the exercise). The direction of the movement was the opposite: elbow extension and shoulder flexion. In this case the subject was not able to activate the stimulation based on his own voluntary activity and FES started after a time-out of 5s. However, when FES was switched on the subject was able to voluntarily participate in the movement, as indicated by the volitional EMG in the lower panel (red line), and a happy emoji was displayed at the end of the task execution.

Table III summarizes the performances of the four subjects during training: it reports the performed exercises, the stimulated muscles, the number of “active” tasks, the number of tasks in which the subject was able to trigger the stimulation based on his/her own voluntary activity, and the exercise completion time.

IV. DISCUSSION

The feasibility of the RETRAINER system for the upper limb rehabilitation after stroke has been shown. All of the patients were able to use the system and through semi-structured interviews judged positively its wearability and the support provided in performing ADLs. During the first training session about 30 minutes were needed to set the exoskeleton lengths, to don it, to place the electrodes and to calibrate the FES controller parameters. Once the exoskeleton was set on the anthropometric lengths of the patient, on the following days the setting, donning, and calibration of the system required no more than 10 minutes, which are compatible with a use in a clinical environment.

To maximize the therapeutic effect of FES, there is a common agreement in the literature about the need to combine FES with the voluntary effort of the subject [14]-[16]. For this purpose, EMG-triggered FES controllers are used. Our results show that to be able to trigger FES based on the residual volitional EMG of the same stimulated muscle does not guarantee a close temporal association between FES and voluntary effort. Indeed, once the stimulation starts, the volitional EMG can decrease and the subject can let FES drive the movement. This is what happened for S1, who was able to trigger the majority of the task with his own activity but then he almost never maintained the voluntary contractions during the stimulation phase (see Table III). Furthermore, the level of the impairment was in agreement with the level of the active involvement; indeed, S2, who was the least impaired subject (MI=72/100, Table II), was the most actively involved in the training. The completion time for one repetition of the different exercises was quite long, but it has to be considered that it included also the reaction time of the subject and that FES support was provided only when the subject was able to produce a voluntarily contraction or after a time-out.

The main concept of the RETRAINER system is to help the subject in performing upper limb movements both in terms of weight relief and FES, but the actual movement has to be performed by the subject. Therefore, the target group of the RETRAINER system consists of stroke patients who preserve at least a visible muscle contraction at the arm and shoulder muscles (MRC \geq 1, [9]).

The system here presented has some limitations. Firstly, the gravity compensation is based on preloaded springs, which represent a cheap and practical solution but cannot assure a uniform compensation in case of changes of the arm configuration. If the gravity compensation is set for motions with fully extended arm, movements with flexed elbow are overcompensated. Otherwise, if compensated with flexed elbow, the extended arm is undercompensated. To partially limit this problem, a special mechanism was included in the shoulder module; this mechanism makes everything slightly undercompensated but on a constant level. Secondly, some tasks are potentially dangerous (e.g. the task consisting of reaching the mouth with or without an object in the hand). Safety is assured by the pre-calibration of the target points and by the presence of an emergency button which can be activated directly by the patient with the unaffected side.

Our results show the functionality and the feasibility of the RETRAINER system in a clinical environment. In order to evaluate its efficacy in the recovery of arm functions after stroke, a multi-center RCT is now ongoing. This study will compare a control group, trained with an advanced rehabilitative program, including physical training, occupational therapy, FES, and virtual reality, to an experimental group, trained with the RETRAINER system in addition to the same program of the control group.

ACKNOWLEDGMENT

We would like to acknowledge Axelgaard Manufacturing Ltd for donating the stimulation electrodes.

REFERENCES

- [1] C. Warlow, J. van Gijn, M. Dennis, J.M. Wardlaw, J.M. Bamford, G.J. Hankey, et al. "Stroke: Practical Management," in *Oxford: Blackwell Publishing*, 3rd ed., 2008.
- [2] P. Langhorne, F. Coupar, A. Pollock, "Motor recovery after stroke: a systematic review," *Lancet Neurology*, vol. 8, pp. 741–54, 2009.
- [3] G. Kwakkel, B.J. Kollen, J. Van der Grond, A.J. Prevo, "Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke," *Stroke*, vol.34, no. 9, pp. 2181–6, 2003.
- [4] U. Sveen, E. Bautz-Holter, K.M. Sodrting, T.G. Wyller, K. Laake, "Association between impairments, self-care ability and social activities 1 year after stroke," *Disabil Rehabil*, vol. 21, pp. 372–7, 1999.
- [5] J.H. Morris, F. van Wijck, S. Joice, M. Donaghy, "Predicting health related quality of life 6 months after stroke: the role of anxiety and upper limb dysfunction," *Disabil Rehabil*, vol. 35, pp. 291–9, 2013.
- [6] M. Franceschini, F. La Porta, M. Agosti, M. Massucci, "Is health-related quality of life of stroke patients influenced by neurological impairments at one year after stroke?," *Eur J Phys Rehabil Med*, vol. 446, pp. 389–99, 2010.
- [7] A. Pollock, S.E. Farmer, M.C. Brady, P. Langhorne, G.E. Mead, J. Mehrholz, F. van Wijck, "Interventions for improving upper limb function after stroke," *Cochrane Database Syst Rev*, vol. 12, no. 11, pp. CD010820, 2014.
- [8] C. J. Winstein, J. Stein, R. Arena, B. Bates, L. R. Cherney, et al, "Guidelines for adult stroke rehabilitation and recovery", *Stroke*, vol. 47, pp. e98-e169, 2016.
- [9] S. M. Hatem, G. Saussez, M. Della Faille, V. Prist, X. Zhang, D. Dispa, Y. Bleyenheuft, "Rehabilitation of Motor Function after Stroke: A Multiple Systematic Review Focused on Techniques to Stimulate Upper Extremity Recovery," *Front Hum Neurosci*, vol. 13, no. 10, art. 442, 2016.
- [10] B. French, L.H. Thomas, M.J. Leathley, C.J. Sutton, J. McAdam, A. Forster, P. Langhorne, C.I. Price, A. Walker, C.I. Watkins CL. "Repetitive task training for improving functional ability after stroke," *Cochrane Database Syst Rev*, vol. 17, no. 4, CD006073, 2007.
- [11] J.S. Knutson, M.J. Fu, L.R. Sheffler, J. Chae J, "Neuromuscular Electrical Stimulation for Motor Restoration in Hemiplegia," *Phys Med Rehabil Clin N Am*, vol. 26, no. 4, pp. 729-45, 2015.
- [12] O.A. Howlett, N.A. Lannin, L. Ada, C. McKinstry, "Functional electrical stimulation improves activity after stroke: a systematic review with meta-analysis," *Arch Phys Med Rehabil*, vol. 96, pp. 934-43, 2015.
- [13] R.D. Wilson, S.J. Page, M. Delahanty, J.S. Knutson, D.D. Gunzler, L.R. Sheffler, J. Chae J4, "Upper-Limb Recovery After Stroke: A Randomized Controlled Trial Comparing EMG-Triggered, Cyclic, and Sensory Electrical Stimulation," *Neurorehabil Neural Repair*, vol. 30, no.10, pp. 978-987, 2016.
- [14] G.I. Barsi, D.B. Popovic, I.M. Tarkka, T. Sinkjaer, M.J. Grey, "Cortical excitability changes following grasping exercise augmented with electrical stimulation," *Exp Brain Res*, vol. 191, pp. 57–66, 2008.
- [15] M. Gandolla, S. Ferrante, F. Molteni, E. Guanziroli, T. Frattini, A. Martegani, G. Ferrigno, K. Friston, A. Pedrocchi, N. S. Ward, "Re-thinking the role of motor cortex: Context- sensitive motor outputs?," *Neuroimage*, vol. 91, no. 100, pp. 366–374, 2014.
- [16] M. Gandolla, N.S. Ward, F. Molteni, E. Guanziroli, G. Ferrigno, A. Pedrocchi, "The Neural Correlates of Long-Term Carryover following Functional Electrical Stimulation for Stroke", *Neural Plast*, no. 2016:4192718, 2016.
- [17] E. Ambrosini, S. Ferrante, T. Schauer, C. Klauer, M. Gaffuri, G. Ferrigno, A. Pedrocchi, "A myocontrolled neuroprosthesis integrated with a passive exoskeleton to support upper limb activities," *J Electromyogr Kinesiol*, vol. 24, no. 2, pp. 307–17 2014.
- [18] H.I. Krebs, N. Hogan, M.L. Aisen, B.T. Volpe, "Robot-aided neurorehabilitation," *IEEE Trans Rehabil Eng*, vol. 6, pp. 75–87, 1998.
- [19] R. Riener, T. Nef, G. Colomb, "Robot-aided neurorehabilitation of the upper extremities," *Med Biol Eng Comput*, vol. 43, no. 1, pp. 2-10, 2005.
- [20] J. Mehrholz, M. Pohl, T. Platz, J. Kugler, B. Elsner, "Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke," *Cochrane Database Syst Rev*, vol. 11, CD006876, 2015.
- [21] F. Resquín, A. Cuesta Gómez, J. Gonzalez-Vargas, F. Brunetti, et al., "Hybrid robotic systems for upper limb rehabilitation after stroke: A review," *Med Eng Phys*, vol. 38, no. 11, pp. 1279-1288, 2016.
- [22] K.L. Meadmore, A.M. Hughes, C.T. Freeman, Z. Cai, D. Tong, J.H. Burridge, E. Rogers, "Functional electrical stimulation mediated by iterative learning control and 3D robotics reduces motor impairment in chronic stroke," *J Neuroeng Rehabil*, vol. 9, art. 32, 2012.
- [23] W. Rong, W. Li, M. Pang, J. Hu, X. Wei, B. Yang, H. Wai, X. Zheng, X. Hu, "A Neuromuscular Electrical Stimulation (NMES) and robot hybrid system for multi-joint coordinated upper limb rehabilitation after stroke", *J Neuroeng Rehabil*, vol. 14, vol. 1, art. 34, 2017.
- [24] M. Bulgheroni, E. d'Amico, I. De Vita, E. Ambrosini, S. Ferrante, T. Schauer, M. Gfoehler, J. Zajc, M. Russold, M. Weber, S. Micera, K. Krakow, M. Rossini, G. Gasperini, A. Pedrocchi, "Reaching and grasping training based on robotic hybrid assistance for neurological patients" in *Proc 1st IASTED International Conference on Intelligent Systems and Robotics*, pp. 1-8, 2016.
- [25] M. Valtin, K. Kociemba, C. Behling, B. Kuberski, S. Becker, T. Schauer, "RehaMovePro: A versatile mobile stimulation system for transcatheter FES applications," *Eur J Transl Myol*, vol. 26, no. 3, art. 6076, 2016.
- [26] A. Pedrocchi, S. Ferrante, E. Ambrosini, M. Gandolla, C. Casellato, et al., "MUNDUS project: MULTImodal neuroprosthesis for daily upper limb support," *J Neuroeng Rehabil*, vol. 10, art. 66, 2013.
- [27] E. Ambrosini, S. Ferrante, M. Rossini, F. Molteni, M. Gföhler, W. Reichenfelfer, A. Duschau-Wicke, et al, "Functional and usability assessment of a robotic exoskeleton arm to support activities of daily life," *Robotica*, vol. 32, no. 8, pp. 1213–1224, 2014.
- [28] C. Klauer, T. Schauer, W. Reichenfelfer, J. Karner, et al, "Feedback control of arm movements using Neuro-Muscular Electrical Stimulation (NMES) combined with a lockable, passive exoskeleton for gravity compensation," *Front Neurosci*, vol. 2, no. 262, 2014.