

ORIGINAL REPORT

ROBOT-BASED REHABILITATION OF THE UPPER LIMBS IN MULTIPLE SCLEROSIS: FEASIBILITY AND PRELIMINARY RESULTS

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Objective: To make a preliminary evaluation of the feasibility of a robot-based rehabilitation protocol for the improvement of upper limb motor co-ordination in a group of patients with multiple sclerosis.

Patients and methods: Seven patients with multiple sclerosis underwent a training protocol of 8 sessions. During each session patients performed reaching movements toward virtual targets presented on a screen, by moving the handle of a robot, which generated resistive and disturbing forces. Each subject was evaluated before and after the treatment by means of clinical and instrumental tests.

Results: After the 8-session treatment, all patients significantly improved the velocity, linearity and smoothness of their reaching movements. Moreover, this amelioration was also present in other kinds of movement, not executed during the sessions. Results on the Nine-Hole Peg Test showed a clinically relevant improvement in the treated arm of 4 out of 7 patients, suggesting also a transfer of the therapy effect to tasks more related to activities of daily living.

Conclusion: The preliminary results of this pilot study suggest that robot therapy can be applied to patients with multiple sclerosis in a clinical setting and may be beneficial for reduction of the upper limb motor co-ordination deficit.

Key words: multiple sclerosis, upper extremity, rehabilitation, robotics.

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INTRODUCTION

Multiple sclerosis (MS) is a neurodegenerative, demyelinating disease that affects mostly young and middle-aged people (1). Two of the most disabling symptoms of MS are ataxia (2) and tremor (3). Motor rehabilitation has been proved to be effective in reducing the disability of subjects with MS (4), but no data regarding specific effects on the upper limbs are available. It is known that when the alteration in upper limb motor co-ordination occurs during the disease progress, it greatly affects the performance of many activities of daily living (5). Clinical and magnetic resonance imaging studies have

demonstrated that defective motor co-ordination typical of MS is correlated with lesions in the brainstem and the cerebellum (3, 6) and that this anomaly depends on the alteration of the anticipatory (feed-forward) control, in which the motor commands required for a desired movement are pre-programmed (7). A study by Patton & Mussa-Ivaldi (8) has demonstrated that healthy subjects exposed to a force that perturbs their arm movements are able to adapt to this dynamic field and recover their original movements by cancelling the perturbation using a pre-programmed pattern of forces. Moreover, this motor learning mechanism based on the feed-forward control component, has been demonstrated to be completely lost in subjects with cerebellar degeneration (9, 10), but to be still present, although impaired (11), in subjects with MS, both in the early stages (12) and in more advanced phases of the disease (13). On the basis of these considerations, a rehabilitative exercise that trains this anticipatory component of motor control through motor learning and force field adaptation, would seem appropriate for the improvement of upper limb co-ordination and the reduction of disability in subjects with MS.

Robot devices, which are increasingly used in the rehabilitation treatment of subjects after stroke (14), therefore may also be good candidates for neuromotor rehabilitation of subjects with MS, as they allow the design of personalized training protocols based on the application of force fields otherwise not achievable, and simultaneously permit quantitative measurement of the motor performances during training.

In the present study we designed an experimental protocol of robot therapy, which combines both quantitative evaluation of motor performance and a training exercise for the neuromotor rehabilitation of the upper limbs in subjects with MS. The aim of this pilot study was to make a preliminary evaluation of the feasibility of robot therapy in MS.

METHODS

Subjects

Seven subjects with MS [4 women and 3 men, mean age 46.0 years (standard deviation (SD) 11.8), Expanded Disability Status Scale (EDSS) (15): 4.5–6.5] and 9 healthy control subjects (mean age 41.0 years (SD 13)) participated in the study. All subjects signed an informed consent to the protocol. Inclusion criteria were: clinically or laboratory definite relapsing-remitting, primary or secondary progressive MS on the basis of McDonald criteria (16); Nine-Hole Peg Test (9HPT) (17) score between 30 and 180 sec; EDSS \leq 7.5; Mini-Mental

State Examination (18) >24; Ashworth scale (19) <2. Subjects were excluded if they had reduced and not amendable visual acuity or ocular motility, which interfered with the execution of the reaching task with the robot. Table I shows the demographic and clinical data of the participating subjects with MS.

Experimental equipment

The apparatus consisted of a planar robotic manipulandum with 2 degrees of freedom (Braccio di Ferro). The device, designed by Casadio et al. (20) is capable of delivering different kinds of forces (up to 25 N continuous) on the end-effector, which are then perceived by the subject’s hand grasping the handle. The robot can be programmed in order to design either resistive, assistive and/or perturbing force fields, which, in turn, can help or disturb the subject during the execution of movements of the upper limb.

Task description

The subjects sat on a chair, with their trunk restrained by means of suitable holders, and grasped the robot handle with the hand of the most affected side. Each subject performed centre-out reaching movements, starting from the same central position towards targets presented in 2 directions (45° and 135° with respect to the horizontal axis, respectively). The amplitude of the nominal trajectory from the centre to the target was 26 cm. Both target and cursor were displayed on a 19” liquid crystal display (LCD) screen placed at a distance of approximately 1 m from the subjects. The position of the robot’s end-effector in the workspace was shown continuously on the monitor as a yellow circle with a radius of 1 cm, while targets, represented by green circles with a radius of 1 cm, were displayed on the screen in a random order. Subjects were allowed to look at the screen.

Rehabilitation protocol design

The rehabilitation protocol was composed of 3 main phases: (i) pre-treatment evaluation; (ii) robot-based treatment (8 sessions); and (iii) post-treatment evaluation.

In the pre- and post-treatment phases, subjects with MS underwent clinical evaluations; in particular 9HPT score and Tremor Severity Scale (21) score were used as outcome measures. The subjects with MS were then required to perform a test by means of the manipulandum, which consisted in tracking of a figure-of-8 shape (length ~1 m) displayed on the screen, in both the clockwise and anticlockwise directions. This test, used as a “transfer test”, was administered in order to evaluate whether the possible improvement related to the reaching movements executed during the training sessions (see below) could also be transferred to another kind of movement. Pre- and post-treatment evaluations were administered respectively the day before the first session and the day after the last session of the treatment.

The treatment phase was composed of 8 sessions, once per day, 5 days per week. Each treatment session consisted of 200 reaching movements, organized as suggested by Casadio et al. (12):

- *Baseline (20 movements)*: no forces were applied on the end-effector, as a daily familiarization for the subject with the task.
- *Baseline RF-Resistive Force (20 movements)*: the manipulandum generated a position-dependent resistive force F_r proportional ($K = 50 \text{ N/m}$) to the distance between the actual position of the end-effector and the central position and directed along the line that connected the target and the central position.

Baseline phases had the purpose of establishing a background level of performance.

- *Training (120 movements)*: the manipulandum generated both the resistive force F_r and a perturbing, velocity-dependent force F_v perpendicular to the instantaneous movement direction of the handle and proportional ($B = 30 \text{ Ns/m}$) to the hand speed.
- *Washout RF (20 movements)*: the manipulandum generated only the resistive force F_r .
- *Washout (20 movements)*: no forces were applied.

Washout phases had the purpose of detecting the short-term daily effect of the training phases on the reaching performance.

Data elaboration

Handle co-ordinates (x, y) were sampled at 100 Hz and low-pass filtered using a sixth-order Savitzky-Golay filter (12) with a 200 msec window and a cut-off frequency of approximately 9 Hz. The same filter was used to estimate the first and the third time derivatives to obtain the movement velocity and the linear jerk.

Data related to the reaching exercises were subdivided into single trajectories, corresponding to each reaching movement from the centre to a target. Then, for each trajectory, the following 3 parameters were extracted: (i) trajectory duration (sec): time needed to complete the reaching of one target; (ii) jerk metric ($1/\text{sec}^2$): jerk magnitude averaged over the single trajectory and normalized with respect to the peak speed. Jerk metric was used as an indicator of the smoothness of the trajectory: the smaller the jerk metric the smoother the movement; (iii) lateral deviation: largest distance of the actual trajectory from the nominal trajectory (straight line connecting the centre and a target), normalized with respect to the nominal trajectory. This parameter represented the hand-path deviation from linearity.

From data related to the tracking of the figure-of-8 shape, instead, the following parameters were computed: (i) tracking duration (sec): time needed to track the figure-of-8 shape; (ii) tracking error (cm): mean distance of the actual tracking trajectory with respect to the nominal trajectory; (iii) jerk metric ($1/\text{sec}^2$): mean jerk magnitude normalized with respect to the mean tracking velocity.

Statistics

Data related to reaching tasks were averaged for each subject and for each session. Taking into account the small sample tested, data were analysed using non-parametric tests. In particular, differences among the 8 sessions were analysed by means of Friedman test (Ft) for multiple dependent samples, while comparison between pre- and

Table I. Demographic and clinical data of participating patients with multiple sclerosis (MS)

Patient	Age, years/ sex	MS type	Disease duration, years	Most evident symptom (upper limb)	EDSS	Dominant hand	Treated hand
P1	63/F	Sec prog	23	Clumsiness	6	R	R
P2	37/F	Relap rem	14	Tremor	6	R	R
P3	60/F	Sec prog	29	Clumsiness	6	R	L
P4	32/F	Relap rem	1	Clumsiness	5	R	R
P5	37/M	Sec prog	17	Weakness	6	R	R
P6	45/M	Prim prog	16	Clumsiness	4.5	R	R
P7	48/M	Sec prog	13	Weakness	6.5	R	R

EDSS: Expanded Disability Status Scale; F: female; L: left; M: male; Prim prog: primary progressive; R: right; Relap rem: relapsing-remitting; Sec prog: secondary progressive.

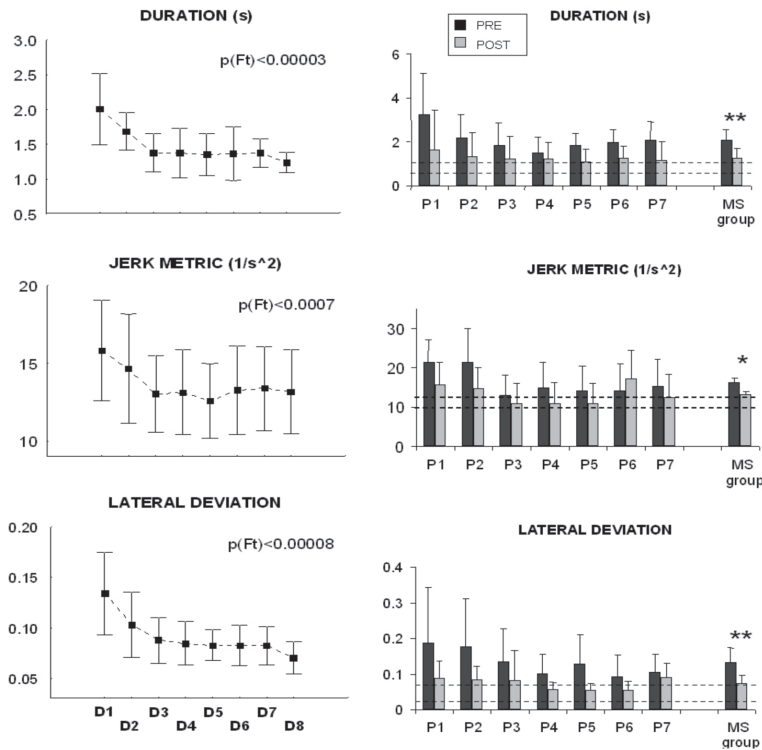


Fig. 1. Left column: movement duration, jerk metric and lateral deviation (overall mean and standard deviation (SD)) for the baseline phase of the 8 days (D1–D8) of treatment. Level of statistical difference among sessions (Friedman test – Ft) is indicated. Right column: movement duration, jerk metric and lateral deviation (mean and SD) for each patient (P1–P7) with multiple sclerosis (MS) and for the whole MS group during the pre- and post-treatment evaluations. Dashed lines represent the control range. * $p < 0.05$; ** $p < 0.01$ (PRE vs POST, Wilcoxon matched pairs test).

post-treatment results was evaluated using Wilcoxon matched pairs test (Wt). Differences between control and subjects with MS were tested by means of Mann-Whitney U test (MWt).

RESULTS

Comparison between control subjects and MS patients at the beginning of the training programme revealed significant differences between the 2 groups. In particular, the duration of the reaching movements was significantly higher (MS subjects: 2.01 sec (SD 0.51); Control: 1.07 sec (SD 0.21); p (MWt) < 0.01) and the trajectories were more jerky (MS: 15.81 1/sec² (SD

3.23); Control: 10.97 1/sec² (SD 1.00); p (MWt) < 0.001) and more deviated from linearity (MS: 0.12 (SD 0.03); Control: 0.08 (SD 0.02); p (MWt) < 0.001) with respect to healthy controls.

During the 8 sessions of the treatment, the quality of the reaching movements improved, as indicated in Fig. 1 (left column) which showed how MS group improved all the indicators over the 8 sessions of therapy, with greater amelioration during the first 3 days. A specific analysis of data related to the pre- and post-treatment evaluations of each single subject (see Fig. 1 right column) revealed that all participating subjects with MS improved their indicators after therapy, except for the jerk metric parameter, which was not improved in one subject (P6).

Table II. Scores of clinical tests of both treated and not treated arms of the subjects with multiple sclerosis (MS) before (Pre) and after treatment (Post)

	9HPT				Tremor severity scale (Kinetic tremor)				Tremor severity scale (Intention tremor)			
	Treated		Non-treated		Treated		Non-treated		Treated		Non-treated	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
P1	138.7	107.1	38.9	34.4	3	1	1	2	4	3	2	2
P2	45.8	44.8	62.9	60.5	2	1	2	1	5	2	4	2
P3	52.5	42.3	na	na	na	na	na	na	na	na	na	na
P4	31	23.5	31.3	30.4	1	2	0	0	3	1	2	1
P5	37	32.3	38.5	39.9	2	1	3	3	3	1	4	2
P6	41.5	40.7	28	35.4	1	1	1	2	1	1	1	2
P7	62	35.9	46	20.2	3	5	3	3	2	4	2	3
Mean	58.4	46.7*	40.9	36.8	2	1.8	1.7	1.8	3	2	2.5	2
SD	36.9	27.6	12.5	13.4	0.9	1.6	1.8	1.2	1.4	1.3	1.2	0.6

* $p < 0.05$ (PRE vs POST, Wilcoxon matched pairs test)

The mean score of the Nine-Hole Peg Test (9HPT) showed a significant improvement for the treated limb after the rehabilitation sessions, but not for the non-treated arm. Results related to kinetic and intention tremor scores failed to reveal statistically significant differences between pre- and post-treatment in both upper limbs.

na: not available.

Results related to the “transfer test” revealed that after the 8 sessions of treatment MS subjects significantly reduced the duration of the tracking movement (Duration Pre: 32.7 sec (SD 11.8); Duration Post: 18.1 sec (SD 7.3); $p(\text{Wt}) < 0.05$) and improved the smoothness of the trajectory (Jerk metric Pre: 40.2 1/sec² (SD 5.8); Jerk metric Post: 32.0 1/sec² (SD 4.6); $p(\text{Wt}) < 0.05$), even though the tracking accuracy was not significantly different between pre- and post-treatment (Tracking error Pre: 0.8 cm (SD 0.3); Tracking error Post: 0.7 cm (SD 0.2); $p(\text{Wt})$ not significant).

The results of the clinical tests performed by the subjects with MS pre- and post-treatment are shown in Table II.

DISCUSSION

The aim of this pilot study was to make a preliminary evaluation of the feasibility of robot therapy in subjects with MS. The results obtained from the treatment of a few subjects suggest that robot therapy can be applied to MS patients in a clinical setting. Subjects were motivated to participate to the training sessions and the improvement observed through instrumental analysis was correlated with improvement of one clinical variable (i.e. 9HPT).

As expected, the upper arm trajectories of subjects with MS during reaching movements before the treatment were slower, less smooth and more deviated from linearity compared with healthy subjects. Previous studies (12, 13, 22) reported similar findings. The lack of smoothness may be caused not only by motor impairment, but also by sensory disorders and integration deficits of sensory inputs, as discussed by Quintern et al. (22). Impairment of the cerebellar system may also have played a role (3, 6), as found by Erasmus et al. (2) who assessed 342 consecutive subjects with MS using a graphic tablet. They asked the patients to draw figure-of-8 shape similar to that used in our study. Their results revealed that patients with cerebellar upper limb ataxia tended to have larger mean errors than patients with other predominant symptoms. In agreement with these results, we found that the patient whose dominant symptom was upper limb ataxia (P2) had the worst performance in the tracking test.

At the end of the treatment subjects showed, during the reaching task, a reduction in jerk metric and lateral deviation, whose values reached the healthy control range. It is interesting to note that the improvement in these variables was associated with a significant reduction in task duration. According to Fitt's law (23), the accuracy of the movement tends to be reduced as the velocity increases; moreover, the increase in speed attained by the patients throughout the 8 sessions of the treatment resulted in an increase in the perturbing forces generated by the robot during the training. Despite these 2 factors, at the end of the treatment subjects were able to improve not only the velocity, but also the smoothness and linearity, of their movements, suggesting that they learned to compensate for the perturbation by modifying their internal model to produce appropriate motor commands.

A general issue related to rehabilitative exercises is the transferability of the results to motor tasks different to those

repeatedly executed during the training sessions (24). Subjects were therefore required to track a figure-of-8 shape only pre- and post-treatment. The results were encouraging, as subjects showed a reduction in the tracking duration and an increase in the trajectory smoothness after the training.

To assess the impact of robot therapy on activities of daily living, clinical tests were carried out. At pre-treatment evaluation, subjects showed mild to moderate impairments: all subjects were able to perform 9HPT. According to Hermens et al. (25), we set a decrement of 6 sec between pre- and post-treatment scores as clinically significant. Four out of 7 MS subjects showed a clinically relevant improvement in performance, suggesting that there was also a transfer of the therapy effect to tasks more related to activities of daily living. Moreover, the improvements appeared to be therapy-specific, since they were obtained only in the treated upper limb. This result suggests that the observed amelioration seems not to be due to a general improvement in the clinical conditions. Mild improvements were also observed in the level of intentional tremor in 4 subjects; however, similar results were also observed in the non-treated arm. As expected, less effect was observed on kinetic tremor, which is a less specific variable considering the task required during the training.

In conclusion, these preliminary results suggest that robot therapy could be beneficial for patients with MS, although this pilot study has some limitations. Firstly, half of the recruited sample consisted in subjects with low levels of impairment. This may have reduced the amount of improvement, as the scores in clinical and instrumental tests approached the level of healthy subjects at post-treatment tests, reaching a plateau of performance after only 3 training sessions. It is possible that, with the inclusion of patients in a more severe stage of the disease, the number of treatment sessions would be insufficient to promote more pronounced clinical improvements. Secondly, only the 9HPT was used, so it was impossible to assess the impact of therapy on different movements and activities. Other functional tests should be included in future studies. Thirdly, a follow-up evaluation is required in order to analyse the duration of the rehabilitation effects.

According to the concept that the treatment of the patient's skills should follow a task-oriented approach (26), future studies will be conducted on the implementation of a functional-based robotic training, which will also allow the use of the hand and the manipulation of real objects to improve skill transfer from the experimental setting to activities of daily living. In a previous paper, Krebs et al. (27) compared, in subjects with chronic stroke, traditional training with MIT-Manus (i.e. reaching of virtual targets) with a functional training with the same robot (i.e. reaching and manipulation of real objects). Although the results did not demonstrate a significant difference between the 2 approaches, the group that received functionally-based robot rehabilitation showed an improvement in hand/wrist function twice as large that of the group treated with the traditional training protocol. Following this approach, we intend to design a wrist splint to be connected to the robot handle in order to implement reaching exercises including manual activities such as grasp, key grip and pinch.

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