NeuroRehabilitation 33 (2013) 621–629
DOI:10.3233/NRE-131002
IOS Press

Robot-aided neurorehabilitation in sub-acute and chronic stroke: Does spontaneous recovery have a limited impact on outcome?

R. Colombo[a,b,*], I. Sterpi[a], A. Mazzone[b], C. Delconte[c] and F. Pisano[c]
[a] *"Salvatore Maugeri" Foundation, IRCCS, Service of Bioengineering, Pavia, Italy*
[b] *"Salvatore Maugeri" Foundation, IRCCS, Service of Bioengineering, Veruno (NO), Italy*
[c] *"Salvatore Maugeri" Foundation, IRCCS, Division of Neurologic Rehabilitation, Veruno (NO), Italy*

Abstract.
BACKGROUND: Robotic neurorehabilitation, thanks to high dosage/intensity training protocols, has the potential for a greater impact on impairment.
OBJECTIVE: We aimed to analyze how time since the acute event may influence the motor recovery process during robot-assisted rehabilitation of the upper limb.
METHODS: A total of 41 patients after stroke were enrolled: 20 in subacute phase, i.e. ≤ 6 months elapsed since their unilateral cerebrovascular accident (CVA), and 21 at chronic stage, i.e. > 6 months since CVA. All subjects underwent 30 minutes of robot-aided rehabilitation twice a day, 5 days a week for at least three weeks of training. Patients were evaluated at the start and end of treatment using the Fugl-Meyer and Modified Ashworth clinical scales and by a set of robot measured kinematic parameters. The time interval from stroke was considered as a grouping factor to analyze its impact on time course of recovery.
RESULTS: After training both groups significantly improved their impairment ($F = 44.25$, $p < 0.001$) but sub-acute patients showed a greater improvement on the Fugl-Meyer scale than chronic patients. The time course of recovery of the kinematic variables showed higher time constants of motor improvement in the sub-acute than chronic group, but they were one order lower than spontaneous recovery time constants.
CONCLUSIONS: Spontaneous recovery seems to have a limited impact on the improvement of sub-acute patients, most of their changes being likely due to re-learning during rehabilitation. In addition, a longer recovery time was required to maximize outcome in sub-acute than in chronic patients.

Keywords: Robotic therapy, motor recovery, stroke, spontaneous recovery, neurorehabilitation

1. Introduction

Despite the significant advances in prevention and acute treatment protocols, stroke remains the most important cause of adult disability worldwide (Langhorne, Sandercock, & Prasad, 2009). Motor impairment, restricting function in arm and leg movements and mobility, is the most widely recognised impairment caused by stroke. About half of stroke survivors have impaired hand-arm, and often remain disabled for the remainder of their life (Broeks, Lankhorst, Rumping, & Prevo, 1999; Timmermans, Spooren, Kingma, & Seelen, 2010). Strong evidence shows that repeated task-oriented practice can assist the natural pattern of functional recovery (Levin, Kleim, & Wolf, 2009). Robotic neurorehabilitation, thanks to

---

[*] Address for correspondence: Ing. R. Colombo, Fondazione Salvatore Maugeri, Via Salvatore Maugeri 10, 27100 Pavia, Italy. Tel.: +39 0382 592207; Fax: +39 0382 592081; E-mail: roberto.colombo@fsm.it.

its capacity to deliver high dosage and high intensity training protocols, has the potential for a greater impact on impairment as demonstrated by the recent literature (Aisen, Krebs, Hogan, McDowell, & Volpe, 1997; Kwakkel, Kollen, & Krebs, 2008; Mehrholz, Hädrich, Platz, Kugler, & Pohl, 2012; Prange, Jannink, Groothuis-Oudshoorn, Hermens, & Ijzerman, 2006).

Recovery from a stroke event is a complex process that likely occurs through a combination of spontaneous and learning mediated processes (Cramer, 2008a, 2008b; Murphy & Corbett, 2009). The high number of patients involved every year in stroke rehabilitation interventions calls for urgent understanding of the neural mechanisms underlying both spontaneous and rehabilitation-induced recovery.

The improvement with rehabilitation increases with the training intensity and is related mainly to the tasks practiced during therapy. Recovery related to spontaneous biological processes seems to improve performance across a range of tasks whereas recovery mediated by training like sensorimotor learning is more task specific (Krakauer, 2006). Knowledge of the pattern of recovery after stroke is helpful in determining when to expect recovery and for customizing appropriate treatment and timing of rehabilitation (Verheyden et al., 2008). Some models have broken down post-stroke brain recovery into three epochs partly overlapping. The first epoch is related to the acute event and takes place in the initial hours after stroke, when numerous profound changes evolve in blood flow, edema, metabolism, inflammatory state, etc. (Cramer, 2008a; Tan, Lip, & Blann, 2003). A second epoch, usually called sub-acute, is related to repair; most recovery and functional performance is obtained by patients in the first weeks/months after stroke, as reported in previous studies (Gresham, 1986; Kwakkel, Kollen, & Lindeman, 2004; Kwakkel, Kollen, & Twisk, 2006). This is the moment when most spontaneous behavioural recovery is seen. In particular it has been shown that at least 16% of recovery in body functions and activities observed can be explained by time alone. The recovery after stroke displays a non linear logarithmic pattern in which the largest improvements are observed early after stroke onset and subsequently gradually level off (Kwakkel et al., 2006). A third epoch begins weeks to months after stroke when spontaneous behavioural gains have generally reached a plateau, and represents a stable but still modifiable chronic phase. Therefore, the time window for defining a restorative therapy may be any time after the acute phase. The second epoch might be defined as the optimal time window given the prominence of spontaneous repair-related biological targets during this phase (Cramer, 2008a). Knowledge about the extent and duration of spontaneous recovery allows clinicians to predict outcome early after stroke, enabling the setting of feasible and attainable treatment goals. It has been hypothesized that the observed time-dependent changes reflect progress over time depending on several factors, such as training intensity and duration, environment, type of therapy etc., rather than on intrinsic recovery alone (Kwakkel et al., 2006). In patients after stroke it is assumed that there is a large inter-individual variability in the capacity to recover. In addition, patients with chronic stroke who seek further treatment can be subdivided into two categories: those with severe initial impairment who will recover to moderate levels of impairment and those who will remain severely impaired (Prabhakaran et al., 2008).

At present, knowledge about how different patients improve their motor impairment is still incomplete. In particular, to what extent patients can benefit from robot-assisted training and how long robotic treatment should be continued remain open questions. Most of the literature about robot-assisted rehabilitation deals with recovery in chronic stroke patients; few studies report on training in sub-acute patients (Aisen et al., 1997; Hesse et al., 2005; Lum et al., 2006; Masiero, Armani, & Rosati, 2011; B T Volpe et al., 2000).

The present study aimed to analyze how different patient characteristics may influence the motor recovery processes during robot-assisted rehabilitation of the upper limb. In particular, we analyzed the impact of time since the acute event (i.e. sub-acute vs. chronic stroke) on the pattern of motor recovery in order to investigate the implications for customization of treatment protocols.

2. Methods

2.1. Subjects

The study was conducted in a group of 41 patients after stroke (19 females and 22 males; age 54 ± 12 years) at the Salvatore Maugeri Foundation, IRCCS Rehabilitation Institute of Veruno (Veruno, NO, Italy). Patients were divided into two groups according to time since the acute event. The first group (Sub-Acute, $n = 20$) were in a recent phase of recovery that we term sub-acute; their unilateral cerebrovascular accident (CVA) having occurred $\leq$ 6 months prior to enrolment (2.3 ± 1.4 months from CVA). Patients of

Table 1
Patient characteristics according to stroke phase (sub-acute vs. chronic)

Patient characteristics	Sub-acute ($n = 20$)	Chronic ($n = 21$)
Age (years)	58.4 ± 12.9	50.7 ± 11.3
Sex	12F/8 M	7F/14 M
Time since acute event (months)	2.3 ± 1.4	29.2 ± 40.7
Fugl-Meyer (0–66 range)	24.6 ± 11.2	20.0 ± 8.2
Impaired arm (Left/ Right)	12/8	10/11
Type of stroke (hemorrhagic/ischemic)	5/15	4/17

the second group (Chronic, $n = 21$) were at a chronic stage, their CVA having occurred > 6 months prior to enrolment (29.2 ± 40.7 months from CVA). Inclusion criteria were the presence of a first single focal unilateral lesion with diagnosis verified by brain imaging, and the presence of at least 10° of motion in the treated joints (shoulder and elbow). Table 1 summarizes the main characteristics of patients at baseline (before treatment). Exclusion criteria were the presence of severe elbow contractures, severe visual deficits, neglect syndrome, apraxia and pain. The study was carried out in conformity with the Declaration of Helsinki of the World Medical Association; all patients gave their informed consent to participate in the study, which had been approved by the local scientific and ethics committees.

2.2. *Training devices and experimental protocol*

The two DoF elbow-shoulder manipulators MEMOS (Colombo et al., 2005) and "Braccio di Ferro" (Casadio, Sanguineti, Morasso, & Arrichiello, 2006) were used for the treatment of patients. The end-effector of the robot apparatus consisted of a sensorized handle which is grasped by the patient and moved through the workspace of the device (i.e. in the horizontal plane). The robot controller enabled subjects to execute both completely voluntary movements and 'shared' controlled movements in which the device assisted the subject to complete the part of the task he/she was not able to do autonomously. Patients were seated with the trunk fastened to the back of the chair by a special jacket and were instructed to limit compensation phenomena. Patients were requested to complete a motor task consisting of a sequence of point to point reaching movements in the shape of a geometrical figure. A practice session preceded the treatment, during which detailed instructions were given to fully explain the task and shorten the exercise learning phase. Details of the administered tasks and procedures have been extensively reported before (Colombo et al., 2008; 2005).

Patients underwent training twice a day, 5 days a week for at least three weeks. Each training session consisted of 4 cycles of exercise lasting 5 min. each followed by a 3 min. resting period. On the same days as robot treatment, all patients underwent physical therapy performed by professional therapists according to the Italian Stroke Prevention and Educational Awareness Diffusion (SPREAD) guidelines for 45 min a day.

2.3. *Evaluation tools*

The Fugl-Meyer (FM) scale was used to assess patients' level of impairment. The evaluation was limited to the upper limb section (FM range = 0–66). The Modified Ashworth scale (MAS) was used to evaluate muscle tone at the elbow and shoulder. Both scales were administered at the start and end of treatment by an evaluation team blinded to the study.

During training the robot devices recorded the position of the end-effector at 100 Hz sampling rate and computed the following performance parameters (Colombo et al., 2008):

1) Active Movement Index (AMI): The patient's ability to execute the assigned motor task without robot assistance. This index represents the percentage of trajectory travelled by means of the patient's voluntary activity.
2) Mean Velocity (MV): The mean value of the velocity of the end-effector.
3) Normalized Path Length (nPL): Obtained by computing the path length of the trajectory travelled by the patient to reach the target and normalized to the theoretical path. This parameter is a measure of the error of movement efficiency; therefore decreasing values during training reflect an improvement of efficiency in the motor task execution. It can be considered also an indirect measure of movement effort.
4) Movement Smoothness (SM): Obtained by measuring the number of peaks in the tangential speed profile of a reaching movement. The parameter was expressed as a negative value so that increases in the peak metrics equal increases in smoothness.

The performance parameters were always measured during the voluntary activity phase (unassisted phase) of each reaching movement, and averaged so as to obtain for each parameter one mean value for each training session.

2.4. Statistical analysis

In order to assess how time since the acute event influences the time course of recovery, stroke phase (sub-acute vs. chronic) was considered as a grouping factor.

Pre and post treatment values of the kinematic variables were computed by averaging the values obtained during the first and last three training sessions. The analysis of variance (ANOVA) was conducted to assess the difference of variables between groups at baseline and at the end of treatment. Repeated measures ANOVA with one grouping factor was conducted on each kinematic variable and on the FM scale to assess the effect of time and interaction with the grouping variable. A significance level of 0.05 was adopted for the statistical tests. The Wilcoxon matched-pairs signed rank test was conducted to compare pre vs. post-treatment values of the MAS scale (Sheldon, Fillyaw, & Thompson, 1996).

To better investigate the impact of time on observed improvements in the kinematic variables the values of each parameter collected during each training session were averaged for each group of patients. The time course of recovery was assessed by fitting an exponential improving/decaying model ($y = a \bullet e^{bx} + c$). Six subjects (2 sub-acute and 4 chronic) who did not exhibit a clear exponential decreasing effort (nPL) pattern from the outset of training were excluded from the analysis, leaving a total of 35 subjects for the analysis of time course of recovery. Details about this specific pattern of recovery can be found elsewhere (Colombo et al., 2012).

Student's t-test was applied for the comparison between model's parameters of different patient groups (Motulsky & Christopoulos, 2004). Statistical analysis was performed using the StatView statistical package (SAS Inst., NC-USA) and the Matlab® software development environment (The MathWorks Inc., Natick, MA, USA).

3. Results

The changes observed after training in the 41 stroke patients showed a significant improvement of both their clinical impairment and movement kinematics, thus demonstrating the effectiveness of the rehabilitation intervention. No significant changes were observed after treatment in the MAS scale evaluating muscle tone both at shoulder and elbow joints.

Figure 1 shows the motor improvement in the sub-acute and chronic stroke patients, as indicated by changes in the FM scale, compared to the spontaneous recovery curves (minor, moderate, and major impairment) reported by Duncan (Duncan, Lai, & Keighley, 2000). It displays pre-, post-treatment values and the changes due to rehabilitation intervention of each subject. The time constant of the estimated exponential model of improvement fitted on the spontaneous recovery curves of the sub-acute patients was respectively 2.39 weeks for patients with minor impairment, 3.62 weeks for moderate impairment and 11.11 weeks for major impairment.

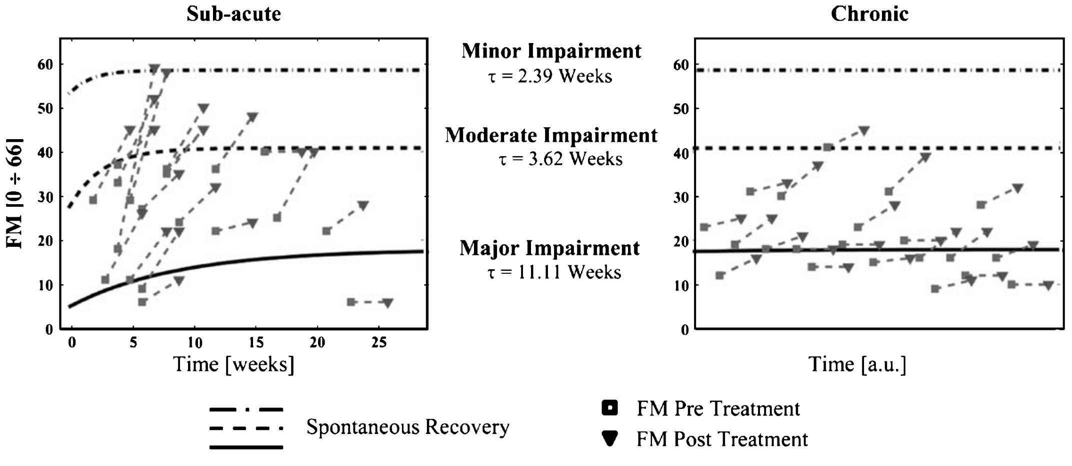

Fig. 1. Motor improvement of stroke patients. Motor improvement of the sub-acute and chronic stroke patients superimposed on the spontaneous recovery curves for minor, moderate, and major impairment. The squares represent pre-treatment values, triangles the post-treatment values and connecting dashed lines the change due to the rehabilitation intervention. The time scale of the chronic patients panel is arbitrary: it was devised to represent the three weeks of treatment with the same scale used for the sub-acute group, but in this case patients were artificially distributed in proportion to their time since the acute event.

Table 2 reports the pre-, post-treatment and the changes as mean values and standard deviations of the clinical and kinematic variables in sub-acute and chronic patients. Both groups had a similar level of impairment at the start of training; no significant difference was found at baseline (pre-treatment). After training both groups significantly improved their impairment ($F = 44.25$, $p < 0.001$) but the sub-acute patients showed a greater improvement on the Fugl-Meyer scale with respect to the chronic patients. The repeated measures ANOVA showed a significant interaction between time and stroke phase ($F = 15.27$; $p < 0.001$). Figure 2 reports the line interaction plots for the Fugl-Meyer Scale and the shoulder and elbow MAS of the sub-acute and chronic patients.

Figure 3 reports the time course of recovery of the AMI, MV, nPL and SM parameters during 29 training sessions in 18 sub-acute (grey) and 17 chronic (black) patients. Pre-treatment values of the kinematic parameters showed no significant difference between the two groups for all parameters; in other words the two groups had the same quality of movement at baseline. The AMI, MV and SM increased and reached a plateau that was higher in the sub-acute than in the chronic patients. Similarly, in the sub-acute group the nPL decreased and reached a plateau that was lower than that obtained in chronic patients. At the end of treatment only the nPL differed significantly between the two groups. In the chronic group, the plateau was reached after about 10 training sessions (one week of training) for AMI, nPL and SM and after about 20 training sessions (two weeks of training) for MV. Figure 3 reports also the time constants and the R^2 values of the exponential models fitted on the data of the four kinematic parameters. The AMI ($p < 0.02$) and MV ($p < 0.001$) time constants of the sub-acute group were significantly higher (unpaired t test) than those of the chronic group. The fitted models had a very high correlation with the mean data; R^2 ranged from 0.83 to 0.99.

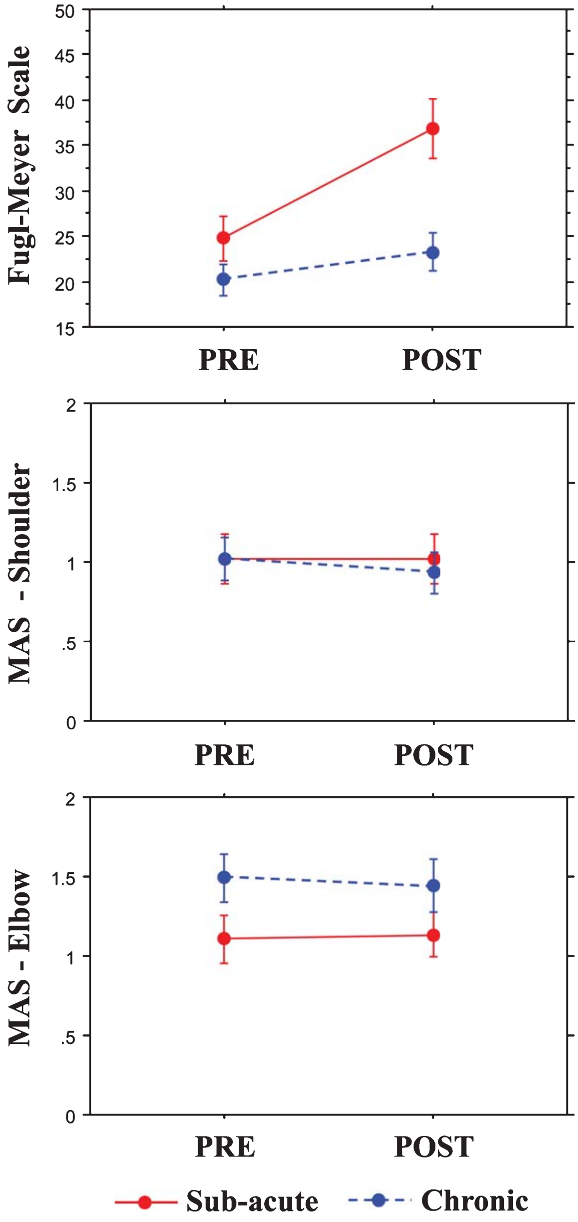

Fig. 2. Impairment and muscle tone changes. Line interaction plots for the Fugl-Meyer and MAS clinical scales of the sub-acute and chronic patients. Circles represent mean values at the start (PRE) and end (POST) of training and vertical bars the standard errors.

4. Discussion

This study reports the findings in a group of stroke patients who underwent robot assisted neurorehabilitation of the upper limb. All patients after training significantly improved both their clinical impairment and movement quality as indicated by the changes observed in the Fugl-Meyer scale and a set of kinematic variables, thus suggesting effectiveness of the rehabilitation intervention. No significant changes of spasticity in the treated joints were observed after training. Our findings are in agreement with those of other studies showing a nonlinear exponential pattern of improvement (Kwakkel et al., 2006; Verheyden et al., 2008). The patients treated in recent post-stroke phase showed a larger improvement than those in whom more than 6

Table 2
Mean values and standard deviations of the clinical and kinematic variables in the sub-acute and chronic stroke patients

	Sub-acute			Chronic		
	Pre	Post	Change	Pre	Post	Change
FM	24.6 ± 11.16	36.65 ± 14.87*	12.05 ± 9.61	20.05 ± 8.16	23.05 ± 9.58*§	3.00 ± 2.61
$\text{MAS}_{\text{shoulder}}$	1.01 ± 0.71	1.01 ± 0.71	0.0 ± 0.35	1.01 ± 0.61	0.92 ± 0.58	−0.09 ± 0.29
$\text{MAS}_{\text{elbow}}$	1.10 ± 0.67	1.13 ± 0.62	0.03 ± 0.43	1.49 ± 0.68	1.44 ± 0.75	−0.05 ± 0.35
AMI (%)	89.00 ± 9.08	97.16 ± 4.26*	8.16 ± 7.52	86.98 ± 10.10	95.60 ± 7.18*	8.62 ± 10.40
MV (mm/s)	38.72 ± 18.09	70.96 ± 20.15*	32.24 ± 13.48	40.50 ± 16.47	69.90 ± 16*	29.40 ± 17.92
nPL (a.u.)	1.73 ± 0.41	1.21 ± 0.24*	−0.52 ± 0.48	2.03 ± 1.01	1.67 ± 0.86*§	−0.36 ± 0.80
SM (a.u)	−15.61 ± 8.50	−3.75 ± 2.08*	11.86 ± 7.71	−15.98 ± 8.08	−6.82 ± 6.49*	9.16 ± 6.86

a.u. = arbitrary units; $^{*}p < 0.001$ Pre vs. Post; $^{§}p < 0.05$ Post-Subacute vs. Post-Chronic.

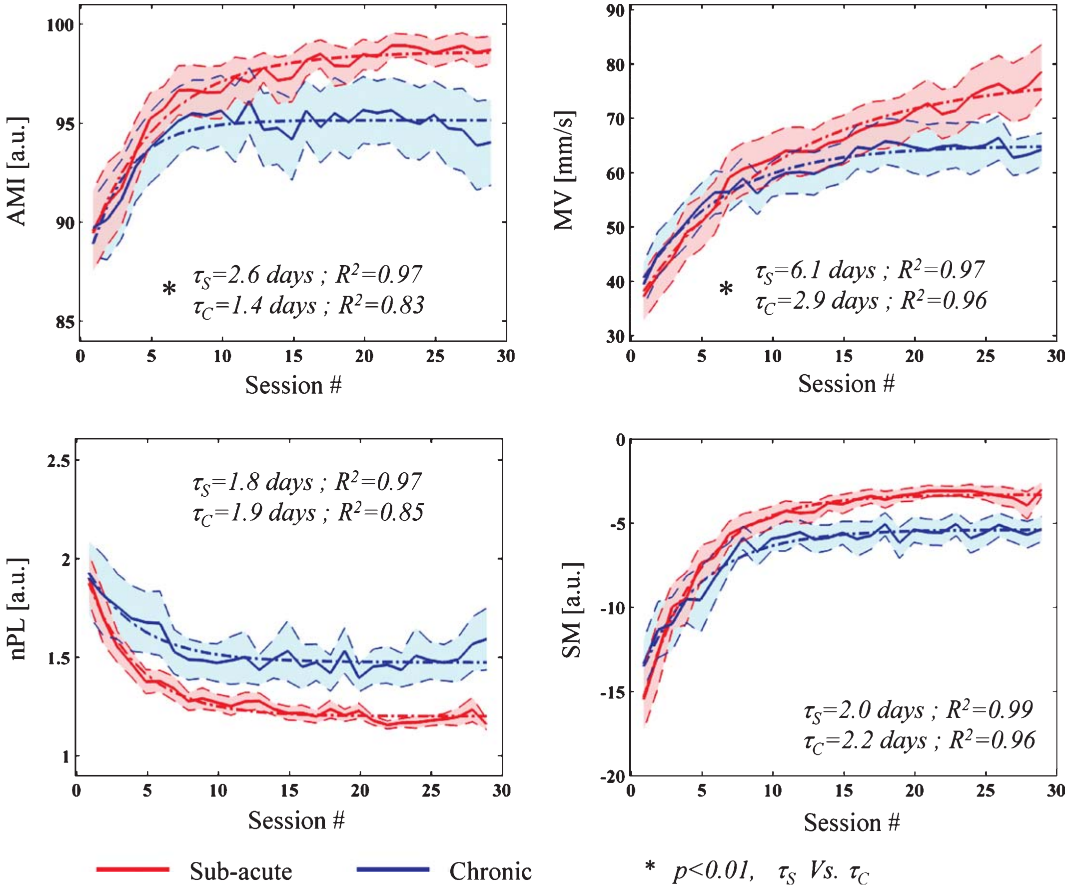

Fig. 3. Time course of recovery of kinematic parameters. Time course of recovery of the AMI, MV, nPL and SM parameters during 29 exercise sessions in 18 sub-acute (grey) and 17 chronic (black) patients. Solid lines connect the average value obtained by each group during each training session. The coloured area represents the standard error. Dot-dashed lines represent the exponential increasing/decaying model fitted on the data. τ_S and τ_C are the time constants of the exponential model of each kinematic parameter, respectively, for the sub-acute and chronic patients. The R^2represent the goodness of fit value of each model.

months had elapsed since the acute event. In addition, in line with other studies, our data demonstrate that persistent impairments in patients with chronic stroke may not reflect exhausted capacity for improvement (Dipietro et al., 2012; Lo et al., 2010; Bruce T Volpe et al., 2008).

4.1. The limited impact of spontaneous recovery

Spontaneous behavioural recovery, at least some degree, is usually observed in the weeks to months after a stroke. At present, it is recognized that most spontaneous recovery tends to occur within the first 3 months after stroke onset even if different patterns of recovery, depending on severity and other factors, may extend this period (Cramer, 2008a).

Kwakkel et al. reported that time alone may explain approximately 25% of the Fugl-Meyer scale changes (Kwakkel et al., 2006), but often the observed time-dependent changes in stroke patients reflect progress over time whose variability is generally due to intervention modality, intensity and duration rather than purely to intrinsic spontaneous recovery.

In our sub-acute patients the motor improvement was characterized by a time constant that was greater than that found in the chronic patients. In actual fact, both groups had a similar rate of improvement at the start of training but the former required an extra improvement time because the plateau to be reached was higher than that for chronic patients. This result implies that patients in the sub-acute phase require longer training programs to maximize outcome. Furthermore, it is usually supposed that the recovery in sub-acute patients is the result of a mixed effect of spontaneous and intervention related recovery, but if we compare the improvement of our patients to the spontaneous recovery curves reported by Duncan (Duncan et al., 2000) we see that the model of spontaneous recovery obtained in sub-acute patients (Fig. 1) has a time constant that is one order higher than the robot training models (Fig. 3), i.e. weeks for spontaneous recovery vs. days for intervention-related recovery. This is also in agreement with the recovery model reported by Verheyden et al. which, for the upper limb, exhibited a time constant of 3.5 weeks (Verheyden et al., 2008). To our knowledge, this difference in the time constants should demonstrate for the first time that in sub-acute patients spontaneous recovery has a limited impact on their improvement, and most of their changes are due to learning during the rehabilitation intervention.

In this perspective, we suggest that robotic as well other types of intervention in the sub-acute patients may represent a way to quickly shift patients from a slow to a faster curve of recovery, thus quickly improving their level of impairment. Conversely, the improvement obtained in chronic patients should be regarded as a jump in the level of their motor ability, in that no further spontaneous recovery should be expected.

Limitations of the study include the lack of a control group to assess the time course of recovery, which means that we were not able to distinguish during training whether the observed kinematic improvements were due to robot or to physical therapy or, more likely, to a combination of them. Lo et al. demonstrated that in chronic stroke patients robot-assisted therapy did not significantly improve motor function as compared with intensive therapy (Lo et al., 2010). Actually, it was not the aim of our study to verify the effectiveness of robot training but simply to analyze how time since the acute event may influence the way patients recover during rehabilitation. In addition, it would have been difficult to submit patients of the control group to a strict monitoring procedure of their motor performance (2 sessions a day) without this influencing their course of recovery. In fact, the evaluation sessions would have required the execution for a limited time of the same tasks executed by the treated subjects, but without robot assistance.

Furthermore, Duncan et al. divided their study population into three groups (minor, moderate and major stroke) based on the Orpington Prognostic Scale and not according to the level of impairment (FM score) as we did. The use of cut-off values within ordinal scales is controversial and in many cases considered inappropriate (Grimby, Tennant, & Tesio, 2012). However, this should not nullify our considerations on intervention and spontaneous recovery time constants.

Finally, patients in both groups had a mean age of about 60 years; therefore caution is needed in extending our results to older subjects.

5. Conclusions

We have demonstrated that sub-acute and chronic patients after stroke exposed to robot assisted rehabilitation of the upper limb show a significant motor improvement and reduction of their level of impairment. Spontaneous recovery seems to have a limited impact on the improvement of sub-acute patients, and most of the changes are likely due to relearning during rehabilitation. In addition, a longer recovery time was required to maximize outcome in the sub-acute patients than in the chronic patients. These findings may have important clinical implications for future training approaches, timing of intervention, and protocols for upper extremity rehabilitation.

Acknowledgments

This research was partly funded by the EU-Research project "HUman behavioral Modeling for enhancing learning by Optimizing hUman-Robot interaction." (HUMOUR). EU grant FP7-ICT-231724, and by the "5 per mille"-2009 project funded by the Italian Ministry of Health.

Disclosures

None.

References

Aisen, M. L., Krebs, H. I., Hogan, N., McDowell, F., & Volpe, B. T. (1997). The effect of robot-assisted therapy and rehabilitative training on motor recovery following stroke. *Archives of Neurology*, *54*, 443-446.

Broeks, J. G., Lankhorst, G. J., Rumping, K., & Prevo, A. J. (1999). The long-term outcome of arm function after stroke: Results of a follow-up study. *Disability and Rehabilitation*, *21*, 357-364.

Casadio, M., Sanguineti, V., Morasso, P. G., & Arrichiello, V. (2006). Braccio di Ferro: A new haptic workstation for neuromotor rehabilitation. *Technology and Health Care*, *14*, 123-142.

Colombo, R., Pisano, F., Micera, S., Mazzone, A., Delconte, C., Carrozza, M. C., & Minuco, G. (2008). Assessing mechanisms of recovery during robot-aided neurorehabilitation of the upper limb. *Neurorehabilitation and Neural Repair*, *22*, 50-63.

Colombo, R., Pisano, F., Micera, S., Mazzone, A., Delconte, C., Carrozza, M. C., & Minuco, G. (2005). Robotic techniques for upper limb evaluation and rehabilitation of stroke patients. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *13*, 311-324.

Colombo, R., Sterpi, I., Mazzone, A., Delconte, C., & Pisano, F. (2012). Taking a lesson from patients' recovery strategies to optimize training during robot-aided rehabilitation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *20*, 276-285.

Cramer, S. C. (2008a). Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Annals of Neurology*, *63*, 272-287.

Cramer, S. C. (2008b). Repairing the human brain after stroke. II. Restorative therapies. *Annals of Neurology*, *63*, 549-560.

Dipietro, L., Krebs, H. I., Volpe, B. T., Stein, J., Bever, C., Mernoff, S. T., & Hogan, N. (2012). Learning, not adaptation, characterizes stroke motor recovery: Evidence from kinematic changes induced by robot-assisted therapy in trained and untrained task in the same workspace. *IEEE transactions on neural systems and rehabilitation engineering*, *20*, 48-57.

Duncan, P. W., Lai, S. M., & Keighley, J. (2000). Defining post-stroke recovery: Implications for design and interpretation of drug trials. *Neuropharmacology*, *39*, 835-841.

Gresham, G. E. (1986). Stroke outcome research. *Stroke*, *17*, 358-360.

Grimby, G., Tennant, A., & Tesio, L. (2012). The use of raw scores from ordinal scales: Time to end malpractice? *Journal of rehabilitation medicine*, *44*, 97-98.

Hesse, S., Werner, C., Pohl, M., Rueckriem, S., Mehrholz, J., & Lingnau, M. L. (2005). Computerized arm training improves the motor control of the severely affected arm after stroke: A single-blinded randomized trial in two centers. *Stroke*, *36*, 1960-1966.

Krakauer, J. W. (2006). Motor learning: Its relevance to stroke recovery and neurorehabilitation. *Current Opinion in Neurology*, *19*, 84-90.

Kwakkel, G., Kollen, B. J., & Krebs, H. I. (2008). Effects of robot-assisted therapy on upper limb recovery after stroke: A systematic review. *Neurorehabilitation and Neural Repair*, *22*, 111-121.

Kwakkel, G., Kollen, B., & Lindeman, E. (2004). Understanding the pattern of functional recovery after stroke: Facts and theories. *Restorative Neurology and Neuroscience*, *22*, 281-299.

Kwakkel, G., Kollen, B., & Twisk, J. (2006). Impact of time on improvement of outcome after stroke. *Stroke*, *37*, 2348-2353.

Langhorne, P., Sandercock, P., & Prasad, K. (2009). Evidence-based practice for stroke. *Lancet Neurology*, *8*, 308-309.

Levin, M. F., Kleim, J. A., & Wolf, S. L. (2009). What do motor "recovery" and "compensation" mean in patients following stroke? *Neurorehabilitation and Neural Repair*, *23*, 313-319.

Lo, A. C., Guarino, P. D., Richards, L. G., Haselkorn, J. K., Wittenberg, G. F., Federman, D. G., & Peduzzi, P. (2010). Robot-assisted therapy for long-term upper-limb impairment after stroke. *The New England journal of medicine*, *362*, 1772-1783.

Lum, P. S., Burgar, C. G., Van der Loos, M., Shor, P. C., Majmundar, M., & Yap, R. (2006). MIME robotic device for upper-limb neurorehabilitation in subacute stroke subjects: A follow-up study. *Journal of Rehabilitation Research and Development*, *43*, 631-642.

Masiero, S., Armani, M., & Rosati, G. (2011). Upper-limb robot-assisted therapy in rehabilitation of acute stroke patients: Focused review and results of new randomized controlled trial. *Journal of Rehabilitation Research and Development*, *48*, 355-366.

Mehrholz, J., Hädrich, A., Platz, T., Kugler, J., & Pohl, M. (2012). Electromechanical and robot-assisted arm training for improving generic activities of daily living, arm function, and arm muscle strength after stroke. *Cochrane database of systematic reviews (Online)*, *6*, CD006876.

Motulsky, H., & Christopoulos, A. (2004). *Fitting models to biological data using linear and nonlinear regression: A practical guide to curve fitting*. Oxford University Press.

Murphy, T. H., & Corbett, D. (2009). Plasticity during stroke recovery: From synapse to behaviour. Nature reviews. *Neuroscience*, *10*, 861-872.

Prabhakaran, S., Zarahn, E., Riley, C., Speizer, A., Chong, J. Y., Lazar, R. M., & Krakauer, J. W. (2008). Inter-individual variability in the capacity for motor recovery after ischemic stroke. *Neurorehabilitation and Neural Repair*, *22*, 64-71.

Prange, G. B., Jannink, M. J. A., Groothuis-Oudshoorn, C. G. M., Hermens, H. J., & Ijzerman, M. J. (2006). Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. *Journal of Rehabilitation Research and Development*, *43*, 171-184.

Sheldon, M. R., Fillyaw, M. J., & Thompson, W. D. (1996). The use and interpretation of the Friedman test in the analysis of ordinal-scale data in repeated measures designs. *Physiotherapy research international*, *1*, 221-228.

Tan, K. T., Lip, G. Y. H., & Blann, A. D. (2003). Post-stroke inflammatory response: Effects of stroke evolution and outcome. *Current Atherosclerosis Reports*, *5*, 245-251.

Timmermans, A. A. A., Spooren, A. I. F., Kingma, H., & Seelen, H. A. M. (2010). Influence of task-oriented training content on skilled arm-hand performance in stroke: A systematic review. *Neurorehabilitation and Neural Repair*, *24*, 858-870.

Verheyden, G., Nieuwboer, A., De Wit, L., Thijs, V., Dobbelaere, J., Devos, H., & De Weerdt, W. (2008). Time course of trunk, arm, leg, and functional recovery after ischemic stroke. *Neurorehabilitation and Neural Repair*, *22*, 173-179.

Volpe, B. T., Krebs, H. I., Hogan, N., Edelstein, O. T. R., Diels, L., & Aisen, C., M. (2000). A novel approach to stroke rehabilitation: Robot-aided sensorimotor stimulation. *Neurology*, *54*, 1938-1944.

Volpe, Bruce, T., Lynch, D., Rykman-Berland, A., Ferraro, M., Galgano, M., Hogan, N., & Krebs, H. I. (2008). Intensive sensorimotor arm training mediated by therapist or robot improves hemiparesis in patients with chronic stroke. *Neurorehabilitation and neural repair*, *22*, 305-310.