

Effects of Robot-assisted Upper Extremity Rehabilitation on Change in Functioning and Disability in Patients With Neurologic Impairment: A Pilot Study

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Abstract

Introduction: The aim is to evaluate the effect of robot-assisted training on the most important aspects of functioning and disability in patients with upper extremity neurologic impairment.

Materials and Methods: A prospective six-week pilot study included robot-assisted training of the upper extremity and conventional neurorehabilitation in 12 participants after a stroke or traumatic brain injury. Outcome measurements were range of motion (ROM), the International Classification of Functioning, Disability and Health (ICF) Core Set for Hand and the Visual Analog Scale (VAS) for pain sensation. A Wilcoxon test was used for the analysis of pre- and post-test differences and Spearman's correlation was used for connecting the data collected.

Results: A statistically significant difference was found for ROM (shoulder abduction/adduction, shoulder flexion/extension, shoulder internal/external rotation and forearm pronation/supination) and a number of ICF categories (Body Function: b280, b710, b715, b730, b760; Activities and Participation: d230, d430, d440, d445, d5). A significant positive correlation of medium intensity ($r=0.589$) was found between the duration of movement coordination training and the ICF category b760. We did not find a statistically significant difference in pain sensation (VAS) with regard to the direct use of the device. For all analyses, $p<0.05$ and CI was 95%.

Conclusion: Robot-assisted training and conventional neurorehabilitation improved motor and functional recovery. There was a correlation between training a specific goal on the device and one of the ICF Body Function categories.

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Introduction

Advances in medicine are impossible without the combined effort of advances in different technologies. Today, the use of novel technology in medicine is expected. Since 2011, an upper extremity exoskeleton has been commercially accessible for rehabilitation (1). But how can we recognise and subsequently combine the clinical needs of patients with the corresponding devices (2)? Robot-assisted devices for the upper extremity have been created for training and assisting or can combine these two functions (3). According to the World Health Organization, stroke, traumatic brain injury (TBI) and spinal cord injury (SCI) are defined as chronic diseases (4). While various neurological conditions affect different populations and have different pathophysiology, they all damage neural networks and motor system networks in particular. As such, clinical impairment and functional problems of persons with different neurological conditions can often overlap (5) and analysing them together may be of interest (6). Around 70% of patients with stroke (7) and 30% of patients with TBI exhibit upper extremity paresis at rehabilitation admission (8,9). For restoration of upper extremity function in patients with a neurologic deficit, the main therapy strategies target the impaired motor cortex (activation of ipsilateral or inhibition of contralateral) or affect afferent sensory pathways (10). It is well-recognised that an intense training program during rehabilitation for patients in the subacute period (i.e. in the first 6 months) will significantly improve functional outcomes for the upper extremity (10,11). Meta-analyses have demonstrated significant effects on motor control and muscle strength using shoulder/elbow robotics, as well as on motor control using elbow/wrist robotics (12). For persons with neurological deficits in a chronic phase, robot-assisted rehabilitation is more effective than other types of therapies for recovery of upper extremity motor function (13). Together, these results indicate that the use of an exoskeleton device with various possibilities (virtual reality, augmented reality and gamification) lead to general improvement of motoric function in neurorehabilitation (14). But

can it lead to an improvement in overall functional status? In the present study, we decided to use the International Classification of Functioning and Disability (ICF) as a measurement tool in light of the notion that limitations of function and disability are not only related to aetiology, but can also be considered as general manifestations in overall health conditions (15). The ICF also has other advantages in its use of a common language (i.e. it is internationally comparable) (16) and has the essential and most relevant categories for personal functioning when using the ICF Core Set information (17). The first aim of this investigation is to assess the efficacy of robot-assisted training on the motoric function of the upper extremity. Secondly, this study aims to examine change in functioning and disability among persons with upper extremity impairment caused by different neurologic aetiology at a clinical level during inpatient rehabilitation. The first expected effect of robot-assisted training is an increase in the range of motion (ROM) of joints in the trained upper extremity and changes in activity and participation among the participants. The second expected effect is a connection between the time spent in training specific goals on the robot-assisted device and selected body domains of the ICF Core Set. Pain sensation in the trained extremity will also be evaluated.

Materials and Methods

This prospective pilot study was conducted at the Special Hospital for Medical Rehabilitation Krapinske Toplice in Croatia.

Prior to the commencement of the study, informed consent was obtained from all participants and the study was conducted according to the Helsinki Declaration. Consent for publication of the study results was obtained from the Ethical Committee of the Special Hospital for Medical Rehabilitation Krapinske Toplice. Twelve participants (3 women and 9 men) aged between 20 and 61 years who underwent acute neurorehabilitation following a traumatic brain injury or stroke met the inclusion

criteria. Inclusion criteria were: aged 18 years and older, paresis of the upper extremity following a traumatic brain injury or stroke, ability to sit (i.e., exhibits trunk control in a sitting position) and a Rancho level of function of 5 or more. Exclusion criteria were: non-acute rehabilitation phase, paresis of the upper extremity of other aetiology, plegia of the upper extremity, inability to sit (i.e., exhibits inadequate trunk control in sitting position), fixed contractures of shoulder, elbow or wrist joints, a Rancho level of function less than 5, apraxia, hemineglect and receptive aphasia. The study was designed as a six-week program. Participants received robot-assisted training during their regular occupational therapy sessions for 30 minutes, 5 days a week. All participants were assessed at the beginning and at the end of the study. Our primary outcome measurements were ROM (for shoulder and elbow joints) and categories of the ICF Core Set - Hand Conditions Brief (for the trained upper extremity). The evaluation of pain sensation in the trained upper extremity was a secondary outcome measurement. For the assessment of ROM, kinematic parameters of the shoulder and elbow joints (i.e. minimal and maximal shoulder abduction/adduction, minimal and maximal shoulder flexion/extension, minimal and maximal inner/outer shoulder rotation, minimal and maximal elbow flexion/extension and minimal and maximal forearm pronation/supination) recorded during training on the robot-assisted device were collected and analysed. Assessment of the selected ICF Core Set was conducted by one investigator following additional education. The ICF Core Set is made up of 23 categories (9 in Body Function, 3 in Body Structures, 8 in Activities and Participation and 3 in Environmental Factors). Every category was assessed using the ICF qualifiers on an ordinal scale ranging from 0 (no impairment) to 4 (complete impairment), with additional possible values of 8 (not specified) and 9 (not applicable). For most categories, assessment was carried out during clinical examination of the participants, while for some categories, information from a patient-report questionnaire was sufficient. Some categories also have additional qualifiers: Body Structures 2 (for

nature and location of change), Activities and Participation 2 (for capacity and performance) and Environmental Factors (an). The evaluation of pain sensation was also carried out by one investigator. To assess pain directly related to the use of the device, the Visual Analog Scale (VAS) was conducted immediately before and after the first and last training session on the robot-assisted device. Prior to the beginning of the study, three occupational therapists were trained to use the robot-assisted device. An exoskeleton device, the Armeo®Spring Hocoma, Inc., composed of an upper and lower module for the upper arm and the forearm and a pressure sensitive handgrip for the hand was used (18). Both modules were length-adjustable, which allowed adequate positioning of the exoskeleton device and the arm joints of the participants. In addition, the weight compensation feature of exoskeleton (18) was utilised and individually adjusted for all participants. Using this exoskeleton device, our participants were enabled to train the shoulder and elbow joints, flexo-extension of the wrist and manual grip (19). The repetition of movements of the paretic upper extremity during virtual gaming was conducted within a three-dimensional workspace (18). The goals of robot-assisted therapy were to increase ROM (1D and 2D/3D), to improve movement coordination and to improve grasp function and cognitive training. All participants also underwent conventional neurorehabilitation (i.e. they received therapies individually indicated according to their overall clinical status, which included a multidisciplinary approach if needed)..

Statistical analysis

Statistical evaluation was performed using SPSS, version 26.0 (SPSS Inc., Chicago IL, SAD). In the first analysis, a Wilcoxon signed-rank test was used to evaluate pre- and post-test differences for all data collected (kinematic parameters, ICF categories and VAS). Statistical significance was set at $p < 0.05$ and CI was 95%. All quoted p-values are two-tailed. In the second

analysis, we used the Spearman's correlation coefficient to test relationships in the data (duration of training a specific therapy goal on the robot-assisted device and selected ICF categories). A correlation greater than $r > 0.80$ was considered as strongly positive, $0.5 < r < 0.8$ was considered as medium to strongly positive and $0 < r < 0.5$ was considered as weakly positive. A correlation coefficient greater than 0.5, $r > 0.5$ was considered significant.

Results

All 12 participants (3 women and 9 men) successfully completed the pilot study. Seven participants (58.3%) exhibited neurologic impairment following TBI and 5 participants (41.7%) following stroke. The average age of participants was 39.42 years (standard deviation (SD) 16.94) and ranged between 20 and 61 years. The right arm was treated in half of the participants and all participants exhibited right-hand dominance. The average number of therapy sessions with the robot-assisted device was 25.50 (SD 5.98), where the number of sessions ranged between 14 and 33. The average therapy time using the robot-assisted device per treatment was 13.75 minutes (SD 2.67), ranging from 8.74 to 16.84 minutes. From the total number of therapies using the exoskeleton device, the average time spent performing each exercise was: 5.05 minutes (SD 1.21) for increasing ROM 1D, with a minimal value of 3.16 and a maximal value of 7.43; 6.48 minutes (SD 1.86) for increasing ROM 2D/3D, with a minimal value of 4.26 and a maximal value 10.86; 9.41 minutes (SD 2.86) for movement coordination, with a minimal value of 5.30 and a maximal value of 15.58; 2.88 minutes (SD 1.75) for grasp function, with a minimal value of 0.09 and a maximal value of 6.76; and 2.25 minutes (SD 1.09) for cognitive training (11 participants), with a

minimal value of 0.09 and a maximal value of 3.50.

Primary outcomes

Kinematics parameters

A Wilcoxon test showed statistically significant differences between the initial and final measurements for the following kinematics parameters observed: minimal shoulder abduction/adduction, shoulder abduction/adduction range of motion, minimal shoulder flexion/extension, shoulder flexion/extension range of motion, minimal shoulder internal/external rotation, maximal shoulder internal/external rotation, shoulder internal/external rotation range of motion, maximal elbow flexion/extension, minimal forearm pronation/supination and forearm pronation/supination range of motion. CI was 95% (Table 1).

ICF Core Set -Hand Conditions Brief

A Wilcoxon test demonstrated a statistically significant difference between the initial and final assessment using the ICF Core Set for the following categories in Body Function: b280 (sensation of pain), b710 (mobility of joint functions), b715 (stability of joint functions), b730 (muscle power function), b760 (control of voluntary movement function). Similarly, statistically significant differences were found for the following categories in Activities and Participation: d230 (carrying out daily routine), d430 (lifting and carrying objects), d440 (fine hand use), d445 (hand and arm use) and for d5 (self-care). CI was 95% (Table 2).

Table 1. Data of the kinematics parameters (ranges of motion in degrees) for the upper extremity joints presented as test statistics^a

Variable name	Value before (degrees), $\bar{x}\pm SD$	Value after (degrees), $\bar{x}\pm SD$	P-value
Shoulder abd./ ad. min.	-71.14±18.82	-88.12±3.24	0.009
Shoulder abd./ad. max.	16.09±13.50	22.61±14.29	0.117
Shoulder abd./ad. range	86.41±26.44	110.73±16.09	0.028
Shoulder flex./ext. min.	52.90±3.87	50.22±2.05	0.019
Shoulder flex./ext. max.	107.34±17.98	112.34±21.59	0.060
Shoulder flex./ext. range	54.44±18.76	62.12±21.90	0.023
Shoulder int./ext. rotation min.	32.98±18.88	18.16±17.79	0.019
Shoulder int./ext. rotation max.	75.36±20.84	106.14±20.14	0.012
Shoulder int./ext. rotation range	42.38±18.43	87.98±24.45	0.003
Elbow flex./ext. min.	22.72±15.32	18.62±15.81	0.241
Elbow flex./ext. max.	94.77±11.86	102.22±6.17	0.025
Elbow flex./ext. range	72.05±21.98	83.60±19.12	0.062
Forearm sup./pron. min.	-23.52±40.66	-48.74±27.39	0.004
Forearm sup./pron. max.	55.45±13.19	58.49±9.29	0.285
Forearm sup./pron. range	78.97±37.7	107.24±23.53	0.012

a. Wilcoxon signed-rank test $p < 0.05$ was considered significant. Abd./ab.= abduction/adduction; flex./ext.=flexion/extension; int.=internal, ext.=external, min.=minimal; max.=maximal

Table 2: Data of the assessed ICF Core Set presented as test statisticsa, p<0.05 was considered significant.

Variable name	Value before $\bar{x}\pm SD$	Value after $\bar{x}\pm SD$	P-value
b152 (emotional functions)	1.50±0.52	1.42±0.52	0.317
b265(touch function)	0.83±0.94	0.75±0.87	0.317
b270 (sensory functions of sensing surfaces and their texture or quality)	0.17±0.39	0.08±0.29	0.317
b280 (sensation of pain)	1.0±0.95	0.58±0.79	0.025
b710 (mobility of joint functions)	1.92±1.24	1.17±1.12	0.014
b715 (stability of joint functions)	1.25±1.48	0.75±1.22	0.034
b730 (muscle power functions)	2.42±0.80	1.75±0.75	0.005
b760 (control of voluntary movement functions)	2.25±0.97	1.50±0.67	0.014
b810 (protective functions of the skin)	0.08±0.29	0.00±0	0.317
d230 (carrying out daily routine)	2.67±1.07	1.92±0.90	0.003
d430 (lifting and carrying objects)	2.75±1.14	2.17±0.84	0.008
d440 (fine hand use)	2.58±0.90	1.92±1.00	0.011
d445 (hand and arm use)	2.33±0.65	1.50±0.52	0.002
d5 (self –care)	2.42±1.09	1.83±1.12	0.020
d7 p (interpersonal interactions and relationships)	1.58±0.90	1.67±0.89	0.317
d7 c (interpersonal interactions and relationships)	1.08±0.79	1.08±0.79	1.000
e1 (products and technology)	2.25±0.75	2.58±1.08	0.194
e3 (support and relationships)	2.75±1.14	2.58±1.96	0.785
e5 (services, system and policies)	1.83±1.12	1.00±1.35	0.655

a. Wilcoxon signed-rank test

Secondary outcomes

Data connectivity

Spearman's correlation coefficient demonstrated a significant positive correlation of medium intensity, between the duration of the movement coordination therapy session using the robot-assisted device and the ICF category b760, indicating a positive relationship between these variables $r=0.589$ (p-value of 0.044) (Figure 1). No significant correlation between the duration of the therapy session for increasing ROM (1D and 2D/3D) and the ICF category b710 was found (Table 3).

Pain assessment

A Wilcoxon test did not indicate any statistically significant difference in pain sensation for the

trained upper extremity, as measured with VAS. CI was 95% (Table 4).

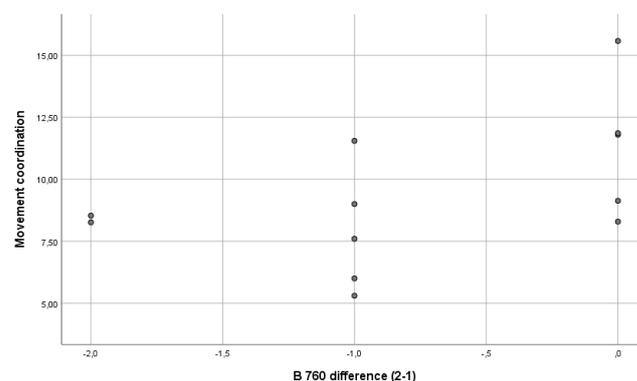


Figure 1: Connection between therapy time for movement coordination and the ICF domain b760) (difference in value of control of voluntary movement functions) as measured by Spearman's correlation coefficient

*Correlation is significant at the 0.05 level (two-tailed).

Table 3. Connection between therapy time, ROM 1D, ROM 2/3D and the ICF domain b710 (mobility of joint functions), as measured by Spearman's correlation coefficient.

Variable name		Therapy time	ROM 1D	ROM 2/3D	b710 (difference)
Therapy time	r	1.0	0.21	0.33	-0.21
ROM 1D	r	0.21	1.0	0.13	-0.35
ROM 2/3D	r	0.33	0.13	1.0	-0.5
B710 (difference)	r	-0.21	-0.35	-0.5	1.0

*Correlation is significant at the 0.05 level (two-tailed). ROM 1D=range of motion, one dimension; ROM2/3D=range of motion, two and three dimension ICF=International Classification of Functioning, Disability and Health.

Table 4. : Test statisticsa for pain sensation data, $p<0.05$ was considered significant

Variable name	Value before	Value after	P-value
VAS I	13.83±24.53	10.42±13.89	0.385
VAS II	9.17±13.95	15.33±18.36	0.327

a. Wilcoxon signed-rank test

VAS I= sensation of pain immediately before therapy session using the device.

VAS II= sensation of pain immediately after therapy session using the device.

Discussion

This pilot study confirmed the hypothesis that the use of a robot-assisted device in the rehabilitation of patients with paresis of the upper extremity leads to increased ROM in joints of the trained upper extremity. Other studies have also demonstrated motor improvement (ROM, strength or motor control) following robot-assisted training in persons with neurologic impairment (20-23). The added advantage of the robot-assisted device as an assessment tool (24) was used for in this study for measuring ROM in order to attain objective, quantitative data while avoiding the subjectivity of the investigator (25-27). In addition, another feature of the device – the ability to conduct a large number of repetitions – was used for improving ROM. In a study by Lo and colleagues, over 1,000 repetitions per session were achieved during a single hour of robot-assisted therapy (28). Because motor recovery in neurologic impairment is considered to depend not only on CNS damage, but also on the intensity (29) and duration of therapy, the ability to achieve a large number of repetitions in treatment is particularly important. In other words, more intense therapy is positively related to clinical improvements (30). The results of our study demonstrating a significant correlation between the duration of movement coordination therapy using the device and the ICF body category that describes control of voluntary movement are consistent with this evidence. But what happens when participants exercise ROM? The results of a neuroradiology study demonstrated that, when the sensation of movement is induced, the somatosensory, primary and supplementary motor areas of the cortex are activated and different proprioceptive inputs are associated with differently located activation patterns in these cortical areas (31). However, another important question is whether the patient will transfer this acquired motoric knowledge to everyday life? Some investigators have developed and tested new strategies that aim to facilitate the transfer of new motor skills to everyday activities following robot-assisted training (32). In this study, we used the ICF Core Set to understand and measure limitations in

functioning and disability among our participants (33, 34) and to examine change following robot-assisted upper extremity training. The results demonstrated significant changes in various categories of Body Function and Activity and Participation. Specifically, participants exhibited significant improvement in motoric function (as measured by the robot-assisted device and the specific ICF Core Set category) and had fewer limitations in functioning during inpatient rehabilitation (as measured by the ICF Core Set categories). A study by Goljar and colleagues demonstrated that the ICF categories have the potential to reveal time-related changes in a patient's functioning (35). The ICF is also considered a useful framework for recognising the possibilities offered by devices in clinical or research settings (15). Our findings are consistent with those of others who have investigated the effects of robot-assisted training on functional recovery. In a study by Colomer and colleagues, significant improvement was found on both function and activity scales for the upper extremities, as measured by the Motricity Index, the Fugl-Meyer Assessment Scale, the Motor Assessment Scale, the Manual Function Test and the Wolf Motor Function Test (36). In another study using the FIM as a measurement tool, Daunoraviciene and colleagues found significant upper extremity improvement among participants who trained with a robotic device, as compared with a control group (37). The update of the Cochrane review by Mehrlotz and colleagues not only demonstrated improved muscle strength and function of the arm, but also improved scores for daily activities following the use of robot-assisted and electromechanical training in rehabilitation for persons after stroke (38). In regard to pain sensation, we did not find a significant difference related to the direct use of the exoskeleton device. In a study by Busching and colleagues, semi-autonomous training was used for patients with severe paresis and no side effects were found with regard to training using the same type of the device (39). It is possible that our participants did not experience changes in pain sensation immediately after the use of the exoskeleton because the degree to which the

upper extremity was unweighted was individually adjusted for all participants with the intention of adequately supporting the paretic extremity and therefore facilitating the number of repetitions (40). However, when pain sensation is considered independently of the direct use of the exoskeleton device, the results of the ICF Core Set demonstrated a significant change in the domain b280 (i.e., pain sensation decreased for participants during the six-week study period). Findings from a double-blind randomised control study conducted by Taveggia and colleagues also demonstrated a decrease in pain sensation over a six-week study period for both a robot-assisted group and a control group (41). In our study, the degree of spasticity was not considered and participants with upper extremity contractures (including those related to spasticity) were not included in the study in accordance with the exclusion criteria. The main limitation of this pilot study is the lack of a control group due to a small number of participants who met the inclusion criteria. As such, the question remains as to the degree of spontaneous recovery that occurred, which is difficult to distinguish from therapy-induced recovery without a control group for comparison. We also did not take into consideration new sensorimotor interactions between the exoskeleton device and the participants (42). Muscle activity and muscle coordination is different in healthy persons (43, 44) when compared to persons with CNS damage (pathological muscle synergies and altered joint coordination) and, because the exoskeleton device has its own mechanical characteristics and there is kinematic incompatibility during the human-exoskeleton interaction (45), currently the intention is to have as little interference as possible between the exoskeleton and the human body. In order to be as ergonomic as possible, new devices aim to be made on principles very similar to functional anatomy (46).

Conclusion

Robot-assisted training and conventional neurorehabilitation improved the motor and functional recovery of patients with upper extremity paresis of various aetiology. We consider the positive connection between the time spent training a specific goal using the robot-assisted device and one of the ICF Body Function categories to be particularly important evidence. Furthermore, improvement in motoric function achieved by affecting afferent sensory pathways might be responsible for improvement in the Activity and Participation category. In order to develop adequate recommendations for the use of robot-assisted devices in accordance with person-specific rehabilitation goals, future research might further investigate the relationship between robot-assisted training and expected clinical improvement. New robot-assisted devices, body-powered robots and their possible advantages (47) or wearable exoskeleton devices that support or replace muscle movement initiation (48) are developed according to new neurophysiological knowledge (49). However, while neurological impairment affects a large number of the population, overall functional recovery of patients with such impairment is limited. As such, further investigation of these available devices, the assessment of their potential for neurologic improvement and any adverse effects is required.

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References

1. Riener R, Guidali M, Keller U, Duschau-Wicke A, Klamroth V, Nef T. Transferring ARMin to the Clinics and Industry. *Topics in Spinal Cord Injury Rehabilitation*. 2011;17(1):54-59. doi: 10.1310/sci1701-54.
2. Hatem SM, Saussez G, Della Faille M, Prist V, Zhang X, Dispa D, Bleyenheuff Y. Rehabilitation of Motor Function after Stroke: A Multiple Systematic Review Focused on Techniques to Stimulate Upper Extremity Recovery. *Front Hum Neurosci*. 2016 Sep 13;10:442. doi: 10.3389/fnhum.2016.00442.
3. Meng Q, Xie Q. Pilot Study of a Powered Exoskeleton for Upper Limb Rehabilitation Based on the Wheelchair. 2019;2019:9627438. doi: 10.1155/2019/9627438.
4. Masel BE, DeWitt DS. Traumatic brain injury: a disease process, not an event. *J Neurotrauma*. 2010 Aug;27(8):1529-40. doi: 10.1089/neu.2010.1358. P
5. Dobkin BH. Motor rehabilitation after stroke, traumatic brain, and spinal cord injury: common denominators within recent clinical trials. *Curr Opin Neur*. 2009 Dec;22(6):563-9. doi: 10.1097/WCO.0b013e3283314b11.
6. Rahurkar S, McFarlane TD, Wang J, Hoover S, Hammond F, Kean J, Dixon BE. Leveraging Health Information Exchange to Construct a Registry for Traumatic Brain Injury, Spinal Cord Injury and Stroke in Indiana. *AMIA Annu Symp Proc*. 2018 Apr 16;2017:1440-1449.
7. Nakayama H, Jorgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. *Arch Phys Med Rehabil*. 1994;75(4):394-8 doi: 10.1016/0003-9993(94)90161-9.
8. Katz DI, Alexander MP, Klein RB. Recovery of arm function in patients with paresis after traumatic brain injury. *Arch Phys Med Rehabil* 1998; 79(5):488-93. doi: 10.1016/s0003-9993(98)90060-0.
9. Walker WC, Pickett TC. Motor impairment after severe traumatic brain injury: A longitudinal multicenter study. *J Rehabil Res Dev*. 2007;44(7):975-82. doi: 10.1682/jrrd.2006.12.0158.
10. Oujamaa L, Relave I, Froger J, Mottet D, Pelissier J-Y. Rehabilitation of arm function after stroke. Literature review. *Ann Phys Rehabil Med*. 2009;52(3):269-93. doi: 10.1016/j.rehab.2008.10.003.
11. Bains AS, Schweighofer N. Time-sensitive reorganization of the somatosensory cortex poststroke depends on interaction between Hebbian and homeoplasticity: a simulation study. *J Neurophysiol*. 2014 Dec 15;112(12):3240-50. doi: 10.1152/jn.00433.2013. P
12. Veerbeek JM, Langbroek-Amersfoort AC, van Wegen EE, Meskers CGM, Kwakkel G. Effects of Robot-Assisted Therapy for the Upper Limb After Stroke. *Neurorehabil Neural Repair*. 2017; 31(2):107-121. doi: 10.1177/1545968316666957.
13. Bertani R, Melegari C, De Cola MC, Bramanti A, Bramanti P, Calabrò RS. Effects of robot-assisted upper limb rehabilitation in stroke patients: a systematic review with meta-analysis. *Neurol Sci*. 2017; 38(9):1561-1569. doi: 10.1007/s10072-017-2995-5.
14. Mubin O, Alnajjar F. Exoskeletons With Virtual Reality, Augmented Reality, and Gamification for Stroke Patients' Rehabilitation: Systematic Review. 2019; 6(2):e12010. doi: 10.2196/12010.
15. Maggioni S, Melendez-Calderon A, van Asseldonk E, Klamroth-Marganska V, Lünenburger L, Riener R, van der Kooij H. Robot-aided assessment of lower extremity functions: a review. *J Neuroeng Rehabil*. doi: 10.1186/s12984-016-0180-3.
16. Kostanjsek N. Use of The International Classification of Functioning, Disability and Health (ICF) as a conceptual framework and common language for disability statistics and health information systems. *BMC Public health*. 2011; 11 Suppl 4:S3. doi: 10.1186/1471-2458-11-s4-s3.
17. Selb M, Escorpizo R, Kostanjsek N, Stucki G, Üstün B, Cieza A. A guide on how to develop an International Classification of Functioning, Disability and Health Core Set. *Eur J Phys Rehabil Med* 2015; 51(1):105-17.
18. Perry BE, Evans EK, Stokic DS. Weight compensation characteristics of Armeo(R)Spring exoskeleton: implications for clinical practice

and research. *J Neuroeng Rehabil.* 2017; 14(1):14 doi: 10.1186/s12984-017-0227-0.

19. Oña ED, Cano-de la Cuerda R, Sánchez-Herrera P, Balaguer C, Jardón A. A Review of Robotics in Neurorehabilitation: Towards an Automated Process for Upper Limb. *J Healthc Eng.* 2018 Apr 1;2018:9758939. doi: 10.1155/2018/9758939.

20. Lambercy O, Dovat L, Yun H, Wee SK, Kuah CWK, Chua KSG, Gassert R, Milner TE, Teo CL, Burdet E. Effects of a robot-assisted training of grasp and pronation/supination in chronic stroke: a pilot study. *J NeuroEngineering Rehabil.* 2011; 8: 63. doi: 10.1186/1743-0003-8-63.

21. QIAN Q, Nam C, Guo Z, Huang Y, Hu X, Ng SC, Zheng Y, Poon W. Distal versus proximal - an investigation on different supportive strategies by robots for upper limb rehabilitation after stroke: a randomized controlled trial [journal article]. *J Neuroeng Rehabil.* 2019;16(1):64. doi: 10.1186/s12984-019-0537-5.

22. Housman SJ, Scott KM, Reinkensmeyer DJ. A randomized controlled trial of gravity-supported, computer-enhanced arm exercise for individuals with severe hemiparesis. *Neurorehabilitation and neural repair.* 2009 Jun;23(5):505-14. doi: 10.1177/1545968308331148.

23. Mayr A, Kofler M, Saltuari L. ARMOR: an electromechanical robot for upper limb training following stroke. A prospective randomised controlled pilot study]. *Handchirurgie, Mikrochirurgie, plastische Chirurgie: Organ der Deutschsprachigen Arbeitsgemeinschaft für Handchirurgie: Organ der Deutschsprachigen Arbeitsgemeinschaft für Mikrochirurgie der Peripheren Nerven und Gefäße* 2008; 40(1):66-73. doi: 10.1055/s-2007-989425.

24. Merlo A, Longhi M, Giannotti E, Prati P, Giacobbi M, Ruscelli E, Mancini A, Ottaviani M, Montanari L, Mazzoli D. Upper limb evaluation with robotic exoskeleton. Normative values for indices of accuracy, speed and smoothness. *NeuroRehabilitation.* 2013;33(4):523-30. doi: 10.3233/nre-130998.

25. Scott SH, Dukelow SP. Potential of robots as next-generation technology for clinical assessment of neurological disorders and upper-limb therapy. *J Rehabil Res Dev.* 2011;48(4): 335-53. doi: 10.1682/jrrd.2010.04.0057.

26. Balasubramanian S, Colombo R, Sterpi I, Sanguineti V, Burdet E. Robotic assessment of upper limb motor function after stroke. *Am J Phys Med Rehabil.* 2012; 91(11 Suppl 3): S255-69. doi: 10.1097/PHM.0b013e31826bcddc1.

27. Longhi M, Merlo A, Prati P, Giacobbi M, Mazzoli D. Instrumental indices for upper limb function assessment in stroke patients: a validation study. *J Neuroeng Rehabil.* 2016; 13(1):52. doi: 10.1186/s12984-016-0163-4.

28. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, Ringer RJ, Wagner TH, Krebs HI, Volpe BT, Bever Jr CT, Bravata DM, Duncan PW, Corn BH, Maffucci AD, Nadeau SE, Conroy SS, Powell JM, Huang GD, Peduzzi P. Robot-assisted therapy for long-term upper-limb impairment after stroke. *N Engl J Med.* 2010; 362(19):1772-83. doi: 10.1056/NEJMoa0911341.

29. Wu X, Guarino P, Lo AC, Peduzzi P, Wininger M. Long-term Effectiveness of Intensive Therapy in Chronic Stroke. *Neurorehabilitation Neural Repair.* 2016; 30(6):583-90. doi: 10.1177/1545968315608448.

30. Lohse KR, Lang CE, Boyd LA. Is more better? Using metadata to explore dose-response relationships in stroke rehabilitation. *Stroke.* 2014; 45(7):2053-8. doi: 10.1161/strokeaha.114.004695.

31. Radovanovic S, Korotkov A, Ljubisavljevic M, Lyskov E, Thunberg J, Kataeva G, Danko S, Roudas M, Pakhomov S, Medvedev S, Johansson H. Comparison of brain activity during different types of proprioceptive inputs: a positron emission tomography study. *Exp Brain Res.* 2002; 143(3):276-85. doi: 10.1007/s00221-001-0994-4.

32. Fasoli SE, Adans-Dester CP. A Paradigm Shift: Rehabilitation Robotics, Cognitive Skills Training, and Function After Stroke. *Frontiers Neurol.* 2019; 10:1088-1088. doi: 10.3389/fneur.2019.01088.

33. Bernabeu M, Laxe S, Lopez R, Stucki G, Ward A, Barnes M, Kostanjsek N, Reed G, Tate T, Whyte J, Zasler N, Cieza A. Developing core sets for persons with traumatic brain injury based on the international classification of functioning, disability, and health. *Neurorehabilitation Neural Repair.*

- Repair. 2009;23(5):464-7. doi: 10.1177/1545968308328725.
34. Grazio S. International Classification of Functioning, Disability and Health (ICF) in the most important diseases and conditions of rheumatology practice. *Reumatizam*. 2011; 58(1):27-43.
35. Goljar N, Burger H, Vidmar G, Leonardi M, Marincek C. Measuring patterns of disability using the International Classification of Functioning, Disability and Health in the post-acute stroke rehabilitation setting. *J Rehabil Med*. 2011; 43(7):590-601. doi: 10.2340/16501977-0832.
36. Colomer C, Baldovi A, Torrome S, Navarro MD, Moliner B, Ferri J, Noé E. Efficacy of Armeo(R) Spring during the chronic phase of stroke. Study in mild to moderate cases of hemiparesis. *Neurologia*. 2013; 28(5):261-7. doi: 10.1016/j.nrl.2012.04.017.
37. Daunoraviciene K, Adomaviciene A, Grigonyte A, Griškevičius J, Juocevicius A. Effects of robot-assisted training on upper limb functional recovery during the rehabilitation of poststroke patients. *Technol Health Care*. 2018; 26(S2):533-542. doi: 10.3233/thc-182500.
38. Mehrholz J, Pohl M, Platz T, Kugler J, Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. *Cochrane Database of Systematic Reviews*. 2018; 9(9):CD006876. doi:10.1002/14651858.CD006876.pub5.
39. Busching I, Sehle A, Sturner J, Liepert J. Using an upper extremity exoskeleton for semi-autonomous exercise during inpatient neurological rehabilitation- a pilot study. *J Neuroeng Rehabil*. 2018; 15(1):72. doi: 10.1186/s12984-018-0415-6.
40. Raghavan P, Bilaloglu S, Ali SZ, Jin X, Aluru V, Buckley MC, Tang A, Yousefi A, Stone J, Agrawal SK, Lu Y. The Role of Robotic Path Assistance and Weight Support in Facilitating 3D Movements in Individuals With Poststroke Hemiparesis. *Neurorehabil Neural Repair*. 2020; 34(2):134-147. doi: 10.1177/1545968319887685.
41. Taveggia G, Borboni A, Salvi L, Mulé C, Fogliaresi S, Villafañe JH, Casale R. Efficacy of robot-assisted rehabilitation for the functional recovery of the upper limb in post-stroke patients: a randomized controlled study. *Eur J Phys Rehabil Med*. 2016; 52(6):767-773.
42. Schweighofer N, Wang C, Mottet D, Laffont I, Bakhti K, Reinkensmeyer DJ, Rémy-Néris O. Dissociating motor learning from recovery in exoskeleton training post-stroke. *J Neuroeng Rehabil*. 2018;15(1):89. doi: 10.1186/s12984-018-0428-1.
43. Pirondini E, Coscia M, Marcheschi S, Roas G, Salsedo F, Frisoli A, Bergamasco M, Micera S. Evaluation of the effects of the Arm Light Exoskeleton on movement execution and muscle activities: a pilot study on healthy subjects. *J Neuroeng Rehabil*. 2016; 13:9. doi: 10.1186/s12984-016-0117-x.
44. Proietti T, Guigon E, Roby-Brami A, Jarrassé N. Modifying upper-limb inter-joint coordination in healthy subjects by training with a robotic exoskeleton. *J Neuroeng Rehabil*. 2017; 14(1):55. doi: 10.1186/s12984-017-0254-x.
45. Jarrasse N, Proietti T, Crocher V, Robertson J, Sahbani A, Morel G, Roby-Brami A. Robotic exoskeletons: a perspective for the rehabilitation of arm coordination in stroke patients. *Front Hum Neurosci*. 2014;8:947. doi: 10.3389/fnhum.2014.00947.
46. Li N, Yang T, Yu P, Chang J, Zhao L, Zhao X, Elhadj IH, Xi N, Liu L. Bio-inspired upper limb soft exoskeleton to reduce stroke-induced complications. *Bioinspir Biomim*. 2018 Aug 24;13(6):066001 doi: 10.1088/1748-3190/aad8d4.
47. Washabaugh EP, Treadway E, Gillespie RB, Remy CD, Krishnan C. Self-powered robots to reduce motor slacking during upper-extremity rehabilitation: a proof of concept study. *Restor Neurol Neurosci*. 2018;36(6):693-708. doi: 10.3233/rnn-180830.
48. Mikołajczyk T, Klodowski A, Mikołajewska E, Walkowiak P, Berjano P, Villafañe JH, Aggogeri F, Borboni A, Fausti D, Petrogalli G. Design and control of system for elbow rehabilitation: Preliminary findings. *Adv Clin Exp Med* 2018; 27(12):1661-1669. doi: 10.17219/acem/74556.
49. Gassert R, Dietz V. Rehabilitation robots for the treatment of sensorimotor deficits: a neurophysiological perspective. *Journal of*

neuroengineering and rehabilitation. 2018 Jun 5;15(1):46. doi: 10.1186/s12984-018-0383-x.

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