

Advances and challenges of robotic therapy in stroke rehabilitation

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Abstract

Over the last twenty years, study on rehabilitation robotics has developed very quickly and utilization of the therapeutic rehabilitation robots numbers also rising rapidly. Patients with locomotion and movement difficulties induced due to spinal cord disorder or cardiac stroke illness may benefit from robotic rehabilitation treatment because it can offer high-intensity and high-dose training. The exoskeleton and end-effector robotic systems are utilised for motor rehabilitation, and we discuss their clinical applications here. This article provides an overview of existing robotic technologies that are indicative of recent robot-assisted rehabilitation techniques, as well as the data supporting their usefulness, hurdles to general adoption, and innovations under progress. The current data justifies the use of robot-assisted treatment to improve functional ability in patients with stroke as a complementary medical approaches to traditional rehabilitation methods. However, there will be significant technical advancement possibilities in the coming years.

Keywords: stoke, rehabilitation, robot, upper limb, lower limb

Introduction

In the U.S, Europe countries, as well as in China, stroke caused by an ischemic or hemorrhagic cerebral vasculature incident is the primary reason of motion impairment. During 2000-2025, the World Health Organization (WHO) predicts a 30% rise in stroke occurrences in China. Hemiplegia/hemiplegia is the most frequent consequence of a stroke resulting in mobility impairment in the extremities on the opposite side of the brain that is affected by the stroke [1, 2]. The specific muscle weakness, aberrant muscle tone, improper postural modifications, loss of movement, inappropriate motion synergies, impairment of coordination of joints, and failure of responsiveness are the primary clinical features found in hemiplegic individuals. Stroke patients have a significant societal effect due to persistent decreased limb function and impairment in activities of daily living (ADLs): recovery is only partial in stroke patients, with 15%–30% of patients permanently handicapped and 20% needing hospital treatment three months after commencement. The objective of rehabilitation in poststroke patients is to help them regain lost function, gain sovereignty and reintegrate into social and home life as soon as possible. The percentage of people who need rehabilitation poststroke is quickly escalating putting a burden on healthcare expenditures [3, 4]. For example, in 2007, the indirect and direct expenses of stroke in the United States was \$40.9 billion, the direct medical projected expenses of stroke in 2007 was \$25.2 billion, and ischemic stroke the mean lifetime expenditure was \$140,048 [5].

Patients who have had a stroke require ongoing medical treatment as well as intensive rehabilitation, which typically necessitates one-on-one manual engagement with a physiotherapist. Nevertheless, current needs and economic constraints prevent this comprehensive restoration. As a result, innovative technologies that improve the efficiency and efficacy of poststroke therapy are in

high demand. The most successful rehabilitative treatments, according to the current scientific research, are those that provide early, intense, task-specific, and multimodal stimulation. Sensory input, experience, and learning all play a role in the central nervous system's well-known ability to adjust its structural organisation following a brain injury. Nudo et al. were the first to show that a subtotal lesion in adult squirrel monkeys, restricted to a small section of the representation of one hand, results in a subsequent loss of hand territory in the surrounding intact cortex, which could be effectively avoided by retraining the skilled hand [6, 7]. As a result, there is mounting information that the motor system is plastic after a stroke and that motor training may impact it. The term "Neural Plasticity" refers to the processes of healing and operational adaptability that occur as a result of global alterations in neuronal structure. More strong recruitment of motor neuron reservoirs, transmission of function from deteriorated regions to protected adjoining or associated regions, bolstering of parallel or redundant synapses, formation of new synapse, boosted sprouting of dendrites, improved myelination of surviving neurons, and transformation of noncortical and cortical manifestations are all outcomes of neural alteration [8, 9].

Cerebellum has recently been shown to have an important function in regulating motor output from cortical and motor learning. Although cellular growth cannot compensate for brain injury, adaptive processes may provide some compensation, such as changes in neuronal systems via the unmasking of hidden cerebral networks and synapses that, while not typically employed, may arise when the prominent system fails. Based on this, the existing evidence suggests a substantial link between intensive multimodal therapy and stroke recovery. Hence, possibly the best training approaches including strong multisensory stimulation may elicit brain changes and improve paretic upper extremity motor and motor improvement. On these foundations, the employment of automated devices to assist therapists in increasing the intensity of treatments, producing multimodal stimulation, and reducing expenses during their job was recommended [10, 11]. This novel approach began in the early 1990s with the introduction of a new family of robotic devices known as "haptic interfaces," which were engineered to communicate with humans by directing the upper extremity into active and passive-assisted movements, assisting some mobility activities with biofeedback technologies, and assessing alterations in locomotion forces and kinematics. As a result, robotic treatment might be an effective and conventional supplement to multimodal poststroke rehabilitation programmes. The goal of this study is to offer a complete understanding of the main robotic technologies and their potential application in stroke patients' rehabilitation due to the constant and rapid growth of robotic innovation. The following are the most common devices for upper and lower limb rehabilitation accessible today. In this study, areas of agreement among researchers, as well as problematic elements of robotics' application in stroke rehabilitation, are presented and addressed for each type of robot. Finally, the current major research issues and areas of interest for future research are highlighted [12, 13].

Selection of Literature

Using the internet search engines 11 scientific databases were carefully examined; these sources were: PsycINFO (Psychological Information Database), Physiotherapy Evidence Database (PEDro), AMED (Allied and Complementary Medicine Database), DARE (Database of Abstracts of Reviews of Effects), OTseeker (Occupational Therapy Systematic Evaluation of Evidence), REHABDATA (Disability and Rehabilitation Literature Database), Cochrane Database of Systematic Reviews, Cochrane CENTRAL (Central Register of Controlled Trials), MEDLINE (Medical Literature Analysis and Retrieval System Online), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and EMBASE (Excerpta Medica Database). The databases' searching parameters had no commencement date constraint, however date of ending was specified for 1st week of March 2021. The terms used for searching with appropriate MeSH keywords being picked and "exploded" along the way. The strategy for searching was given below: Stroke, CVA, Cerebral Vascular Accident, Cerebrovascular Accident, Robot, Upper extremities, Upper Limb and lower limb. The criteria of inclusion were: Stroke adult patients were as participants; The experimental methodology included the employment of a robot;

RT was targeted at improving the UL's motor recoveries, performance, or management; and significant results evaluating the LL's functional or motor recoveries were employed. The article was accepted for publication in a peer-reviewed journal. The following were the criteria for exclusion: The robotic equipment was not employed as a treatment tool in studies that solely evaluated two distinct RT methods or equipment.

Robots as exercise devices

Exercise-based therapies are most commonly given using somewhat large workstation equipment in the current state of rehabilitation robots. Workstation devices usually consist of a machined system and a monitor screen to involve patients and offer visual information to the user. Exoskeletal workstation and end-effector equipment are the two types of workstation equipment available. The first device of robotic innovations created especially for rehabilitation of stroke is end-effector devices, and their high degree of research demonstrat this. The MIT-Manus is an example of end-effector devices which is commercialized as the G_{Eo} (Reha Technologies, Switzerland), InMotion Shoulder Elbow robot, (Bionik, Inc, Toronto) and the Reo-Go (Motorika, Israel) [14-16]. End-Effector devices direct the whole limb using a single distal point of touch. For the upper extremity an end-effector equipment, for example, may establish connection with the forearm and hand, allowing for easier shoulder and elbow motions. This paradigm, in theory, permits the robot to maintain natural mobility without undue limb restraint and to suit a large number of users with minimum mechanical modifications [17, 18].

In practise, the neurologically damaged limb's movement patterns and anatomical limitations may limit end-effector systems. For example, to create elbow extension, a robot-assisted forward mobility of the forearm might be employed. In a patient with significant rigidity or an elbow contracture, however, the identical action may lead to compensatory trunk flexion rather than elbow extension. The end-effector design's freedom of movement might therefore work to a patient's advantage, allowing for supportive, unfettered mobility, or to their disadvantage, allowing for undesired compensatory mobility patterns. Exoskeletal workstations, on the other hand, allow complete management of each limb part, with independent motors regulating each axis of movement. The Lokomat (Hocoma) and the Armeo Power (Hocoma, Switzerland) are two examples of exoskeletal workstations. This design allows for fine limb control and the limitation of undesirable mobility patterns. However, this level of management is costlier. Exoskeletal workstations are big, cumbersome machines that allow users to manipulate numerous limb parts [19, 20]. The gadget's bulk and inertia could only be partially compensated by the device itself, which has an influence on motion smoothness. Although, the advancement was made throughout this region, these devices still do not have the rapidity or smoothness to precisely replicate natural movements. Exoskeletal workstations are still expensive machines that are mostly used in therapy clinics and centres, and are unlikely to be used in a home location in the near future. Despite advances in performance, due to variations in limb length and size, moving from user to user frequently necessitates changes to different parameters. This, along with the intricacy of these devices, which need close supervision by a physician during usage, limits their influence on efficiency and, as a result, their broad adoption in hospital Locations [21, 22].

Robots for upper extremities exercise

MIT-MANUS

The robotic system of MIT-MANUS, which is saleswise marketed as the In Movement line of equipment (InMotion/Bionik), is among the most researched robots of end-effector for the upper extremity. This modular device is made up of proximal and distal parts that may be used separately or combination for upper extremity training. A module for vertical shoulder and hand grip, horizontal elbow and shoulder movement, and wrist movement in all axes are among the combinations available. The gadget usually works on an assist-as-needed basis, constantly monitoring limb mobility and

beginning or finishing motions to perform a pre-programmed simulated job [23, 24]. The device's most investigated mode, or "therapeutic exercise game," generates about 1000 movements in a single session using a simple focused reaching action similar to reaching around the face of a clock. The MITMANUS has shown efficacy in the sub-acute early stages of recoveries for decreasing motor disability increasing function, and inducing long-term change. The Department of Veterans Affairs evaluated the MIT-MANUS effectiveness for severe stroke in biggest randomised controlled studies of robotics rehabilitation yet. For a duration of 12 weeks, 127 people with moderate to severe upper extremity disability were randomly allocated to robotassisted rehabilitation, intense human-delivered therapy emulating robotic motions, or normal care. At the end, of intervention researchers observed no statistically substantial variation among the robotic and human-delivered treatment centers, indicating that robotic intervention delivers a similar, but not greater, advantage for motor function to human-delivered therapies [25, 26].

Armeo Power

The Armeo Power, a commercialized variant of Hocoma, Inc.'s ARMin gadget, is the most advanced robotic exoskeletal workplace equipment for the upper extremity currently available. The system consists of a big exoskeleton workplace that wraps around the patients's arm and could be modified for limb length and height of shoulder. The equipment offers support to arm weight that compensates for the weight of device as well as a percentage of a weight of limb of patient. Custom software powers the Armeo Power, allowing it to be utilised in a variety of ways. It now includes a functional training, 3D and 2D games, and mobility mode in the form of simulated everyday tasks. Rather than utilising motors to aid mobility, the ArmeoSpring, uses springs to balance the equipment's and patient's upper extremity weight which is similar type of product as that of Armeo Power. The Armeo Power improves at patient participation, promoting repeated movement with strong visuals and simple, yet intriguing activities. The programme allows the physician to choose the right task by adjusting the visual field's complexity, specifying the range of motion necessary, and setting the game's tempo [27, 28]. The Power, like the MIT-MANUS, uses an assist-as-needed paradigm, which allows the therapist to give the best task at all stages of recoveries. Furthermore, this innovations allows for the stabilisation of certain joints during games, allowing the physician to choose between a modular or composite therapy strategies. A research evaluating Armeo Power the effectiveness in a multi-locations randomised trial was released in 2014. A total of 77 patients of post - stroke with moderate to severe paralysis were randomly assigned to either robotic or traditional surgery. The researchers discovered that while all individuals improved their motor skills, those in the robotic treatment center improved their motor skills more than those in the dose-matched traditional upper extremity treatment center, with 0.78 points a mean difference on the Fugl-Meyer scale. While the variation among robotic and dose-matched traditional treatment was clinically meaningful, it was not statistically significant. Furthermore, the intensity of the cumulative motor enhancement is of slight statistical importance (3.25 points on the upper extremities on scale of Fugl-Meyer), related to other research of upper extremity robotic treatment for patient with severe hemiplegia, compared to the least clinically significant variation for mild to moderate disable patients, of about five points. SMARTS 2, a multicenter experiment that combines suspension mode of the exoskeleton with a unique software programme meant to evoke motor investigation via a game managing an animated dolphin, is under underway. The research looks at the effects of dose-matched, intense training (both traditional and robotic) in the acute period of recoveries, with individuals starting therapy no later than 6 weeks after a stroke [29-31].

Bi-Manu-Track robotic arm trainer: Bilateral devices

A bilateral treatment method provides an option to upper extremity robotic therapy. The Bi-Manu-Track (RehaStim, Germany) that comprises of two forearm troughs installed on a desktop workplace, is an example of this method. The BiManu-Track allows for replicated upper motions such as, metacarpo phalangeal extension, wrist extension/flexion, and forearm supination/pronation. The device can offer passive bilateral mobility, mimic arm motions of unaffected/affected, or give resistance to mobility. In chronic stroke patients, a randomised controlled study (n=20) compared treatment of Bi-Manu-Track combined with operational exercise to dose-matched traditional treatments. When compared to the control group, the robot-assisted treatment group showed substantially improved motor function, hemiparesis arm movement (as judged by self-reported operational capacities), and bilateral arm harmony after 4 weeks of intense treatment (5 days/week for 90–105 min.,) [32-34].

DIEGO

Cables are utilised to support and mobilise the upper extremities in a 3rd, less commonly used form idea in workstation robots. The DIEGO (Tyromotion, Graz, Austria) is a widely marketed device that uses an overhead boom with four hanging wires that link to slings at the elbow and wrist. The device, similar to a movable arm support, may be used bilaterally or unilaterally and uses "intelligent gravity correction" to unweight the limb and allow mobility in 3D. As users go from passive to active treatment methods, assistance can be reduced over time. The DIEGO builds on the notion of gaming as a way to involve patients by using specifically created cognitive games that combine upper-limb exercise with cognitive rehabilitation. Most importantly, the gadget may be used to facilitate the execution of genuine tabletop functional activities [35, 36].

The DIEGO's architecture allows it to provide the variety and speed of an end-effector device while also allowing for direct application to functional tasks. This one-of-a-kind capability exemplifies a novel approach to robotic treatment: combining robotic assistance with real-world task practise. In some ways, the Armeo Boom (Hocoma) is comparable, albeit it depends only on mechanical upper extremity assistance instead of robotic controls [37].

Amadeo

Because of the hand's dimensions as well as mechanical complexities, rehabilitation of the hand is a significant barrier for robotic equipment. Tyromotion's Amadeo is a hand-designed end-effector device is one of the limited choices now present on the retail market. The Amadeo is made up of individual digit actuators and a forearm trough that are attached to the fingers using magnets. To flex and extend the digits, the single digit supports travel down a track [38].

In the prolonged period, the Amadeo has shown practicality and tentative effectiveness for stroke. Conventional occupational treatment was compared to Amadeo robotic treatment in a recent randomised controlled trial of 17 individuals. Both groups improved significantly after 40 sessions, but the robotic therapy had a greater impact sizes on the Motricity Index and Fugl-Meyer in terms of function of hand [39].

Hand of Hope

A semi-wearable hand exoskeletal device developed by Rehab-Robotics, Hong Kong is "Hand of Hope." A biofeedback method utilized by the Hand of Hope to sense a patient's intent via surface electromyography and reply with an exoskeleton-driven grip or relieve. A training programme utilising the Hand of Hope resulted in substantially meaningful enhancements in operational efficiency and increased muscular harmony, as evaluated by EMG, in 10 patients with severe stroke [40].

Other devices

The Proficio, the Kinarm (BKIN), Hand Mentor Pro (Motus Nova), and ReoGo (Motorika), are some of the other currently marketed upper extremity workstation equipment (Barrett). While a full examination of these equipment is far away the objective of this article, each has unique design elements that may provide them an edge over rival equipment in certain situations [41].

Robots for lower limb exercise

Lokomat

The Lokomat is the very extensively researched robotic gait learning tool available. A treadmill, bilateral exoskeletal components and support system of a bodyweight, providing actuation at the knees and hips make up this workstation gadget. Elastic foot lifters, which are optional, give additional ankle support if needed. A number of "guidance" parameters are supported by the Lokomat programme. The Device, at its most advanced level, directs the limbs through a preset mobility style based on research of natural gait. As the device's instructions is decreased, it allows for more departure from the trajectory before giving help. The use of Lokomat exercise to complement the benefits of traditional therapy has been supported in studies in the stroke population. A short research (n = 30) comparing a 4 week regimen of Lokomat exercise with physiotherapy to dose-matched physical therapy in patients with stroke revealed similar increases in functional gait [42, 43]. Through over ambulation, the Lokomat group also showed better gait features, including a substantially lengthy single stance stage on the paretic leg. A bigger research (n=67) comparing these exercise models in the subacute stage revealed that the Lokomat group had better functional and motor results following a six-week training period. These results are echoed in studies of people who have had a persistent stroke. In a 2014 research (n=107) of both acute and severe patients who participated in an intense exercise programme including traditional physiotherapy, robotic treatment, and physical therapy, the Lokomat group had better results. Moreover, a small research of severe stroke patients contrasted combination therapy with regular treadmill training in an intense four-week protocol found that robotic therapy was superior to normal treatment, with substantial enhancements in balance, step length, cadence, and gait speed. The duration of double limb support was also observed to be considerably shorter in Lokomat treatment patients. Lokomat training has been shown in other research to be less efficient than dose-matched gait training. After a 12-session programme, Hornby and colleagues discovered that single therapist-assisted locomotor therapy was more successful than dose-matched robotic therapy in terms of symmetry and gait speed [44, 45]. The Lokomat gadget is essentially a robotic application of body-weight assisted treadmill training, which is traditionally done by a physiotherapist manually. According to new data, this training approach is not the best for those who have had a stroke. Although what appears to have a solid theoretical framework, body-weight assisted treadmill training has failed in a large clinical experiment. For 408 individuals with acute stroke, the LEAPS study investigated the effectiveness of therapist-assisted, bodyweight aided locomotor rehabilitation. One year after the stroke, the researchers found that therapist-assisted weight-bearing exercise was no more beneficial than the therapist-led home exercise program that emphasized mobility and balance. While this research did not explicitly compare the effectiveness of a related robotic rehabilitation, like the Lokomat, it does cast doubt on the validity of body-weight assisted locomotor exercise as a proof-based treatment following a stroke. As a outcome, this treatment is currently underutilised. The scientist found that initial conceptual research, instead of expensive mass-production of complicated gadgets, might speed up the creation of innovative therapies with higher efficacy. They also argue that workstation robotic equipment could be inadequate in the long run to replicate the habitat and overground training task-specific benefits in a natural setting [46, 47].

G-E O system

Reha Technologies' Robot of G-EO System is an available saleswise, system of end-effector designed particularly for stroke therapy. The gadget is comparable to an athletic machine in principle, with 2

footplates that glide along a predetermined course and support system of a bodyweight. The equipment senses the user's attempt to walk and generates the appropriate gait pattern. It also has a partial mobility mode that allows gait components to be isolated and repeated. Customizing ambulation characteristics like foot angles, height and length of step during toe off and early touch is possible with the G-EO. The G-EO builds on the efforts of the HapticWalker research equipment, offering the 1st commercialized robotic treadmill capability of mimicking steps-climbing in a manner that can be used in a therapeutic setting. The gadget permits muscular activation patterns in ambulatory stroke patients that are comparable to patterns documented during actual steps climbing exercises, according to preliminary research into this steps climbing mode [48-50]. While no randomised controlled studies with this innovation have been done as yet, preliminary data show that the G-EO may be practical and helpful for the subacute population's gait and stair climbing abilities. In addition, a current uncontrolled multicenter trial shows that the G-EO is feasible for chronic stroke patients in terms of gait recovery.

TPAD

A research equipment, TPAD-Tethered Pelvic Assist Device that delivers stresses to a patient's pelvic belt during treadmill training through cables connected to the belt. The device determines the optimal degree of force for a patient using force plate and motion capture data and distributes forces along an adjustable vector during specified gait phases. This innovation has been used in initial experiments to help people with hemiparesis transfer their weight or burden their afflicted leg. The TPAD illustrates how robotic gadgets may be used as a signal of training, delivering haptic signals to the patient without requiring significant physical help at the same time. This could be configured in a "help as required" method, identical to other robotic equipment or in an error addition method to evoke a user-adaptive reaction. This adaptability is useful for researching alternative types of stimulus feedback throughout post-stroke gait training that might lead to the development of more effective techniques for improving motor learning after a stroke [51, 52].

Other devices

Other lower extremity workstation equipment are available saleswise, such as Walkbot (P&S Mechanics), and KineAssist-MX (HDT Global), but do not fall within the scope of this article [53, 54].

New frontiers

Rigid materials have always been used in robotic rehabilitation equipment because of their physical robustness and consistent functionality. Soft robotics, a new discipline that draws inspiration from the biological architecture of nimble species like the octopus, aims to turn this concept on its head. Soft robotic components are more similar to the anatomy and features of the human body, potentially improving safety of patients, fit, and movement. Soft robotics may provide joint function human-like and greater flexibility for accurate operational activities like grasping in the rehabilitative environment. Nonetheless, there are a number of obstacles to overcome in this young sector. Soft components including silicone rubber, provide unique mechanical problems since the degrees of freedom they provide are both attractive for rehabilitation treatments and extremely difficult to regulate. Soft robotics also frequently use hydraulic or pneumatic control systems that are susceptible to sluggish actuation rates and necessitate the use of pumps or pools [55-57]. Soft technologies are now controlled mostly through "hard" electronic platforms, which limits their applicability. Soft electronics, on the other hand, have recently received a lot of interest in the scientific community, allowing the potential of a various innovations like perpetual stretch sensors, being integrated into stroke therapy in the future. In the not-too-distant future, alternative innovations like as computer-brain interactions and software of information processing can provide highly inherent control methods for patients. The capacity of rehabilitation robots to capture huge quantities of information on movement kinematics and other elements is one of the most intriguing aspects of the technology [58, 59]. As a result, robotic gadgets might be able to assist us address some of the numerous concerns

we have about stroke rehabilitation. Many traditional stroke recovery tests focus on particular patterns of movement or random functional tasks, with the capacity to distinguish real motor recoveries from learnt compensation being restricted. While kinematic information gives a precise assessment that can be used to deduce novel information on stroke recoveries [60, 61].

Conclusions

The entrance of robotic equipment into the area of stroke therapy has been hailed in a number of current research. Many studies have documented the effectiveness of robot-assisted treatment in restoring motor and ambulatory performance in stroke patients. Yet, the development of double-blind randomised controlled investigations of robot-assisted treatment in stroke patients is hampered by both legal and methodological restrictions. Additionally, there are just a few thorough evaluations of robot-assisted treatment that are well-organized. Because of the variety of robotic equipment and user variables as well as the diversity of study methods in the research meta-analysis of robot-assisted treatment is extremely difficult. As a result, in order to get the best findings, it is critical to include expert opinion as well as study facts. We examined the impact of several types of robotic gadgets on upper extremity and hand motor function, as well as gait function, in this article. In conclusion, robot-assisted treatment in stroke rehabilitation is presently used as an addition to rather than a substitute for traditional rehabilitation. To develop robot-assisted treatment as an important element of stroke rehabilitation, well-designed trials with huge numbers of subjects will be required.

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References

1. A. Adomavičienė, K. Daunoravičienė, R. Kubilius, L. Varžaitytė, J. Raistenskis, Influence of New Technologies on Post-Stroke Rehabilitation: A Comparison of Armeo Spring to the Kinect System, *Medicina (Kaunas, Lithuania)*, 55 (2019).
2. I. Aprile, M. Germanotta, A. Cruciani, S. Loreti, C. Pecchioli, F. Cecchi, A. Montesano, S. Galeri, M. Diverio, C. Falsini, G. Speranza, E. Langone, D. Papadopoulou, L. Padua, M.C. Carrozza, Upper Limb Robotic Rehabilitation After Stroke: A Multicenter, Randomized Clinical Trial, *Journal of neurologic physical therapy : JNPT*, 44 (2020) 3-14.
3. K. Baur, F. Speth, A. Nagle, R. Riener, V. Klamroth-Marganska, Music meets robotics: a prospective randomized study on motivation during robot aided therapy, *Journal of neuroengineering and rehabilitation*, 15 (2018) 79.
4. M. Belas Dos Santos, C. Barros de Oliveira, A. Dos Santos, C. Garabello Pires, V. Dylewski, R.M. Arida, A Comparative Study of Conventional Physiotherapy versus Robot-Assisted Gait Training Associated to Physiotherapy in Individuals with Ataxia after Stroke, *Behavioural neurology*, 2018 (2018) 2892065.
5. J. Bergmann, C. Krewer, P. Bauer, A. Koenig, R. Riener, F. Müller, Virtual reality to augment robot-assisted gait training in non-ambulatory patients with a subacute stroke: a pilot randomized controlled trial, *European journal of physical and rehabilitation medicine*, 54 (2018) 397-407.
6. R. Bertani, C. Melegari, M.C. De Cola, A. Bramanti, P. Bramanti, R.S. Calabrò, Effects of robot-assisted upper limb rehabilitation in stroke patients: a systematic review with meta-analysis, *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, 38 (2017) 1561-1569.

7. H. Bosomworth, H. Rodgers, L. Shaw, L. Smith, L. Aird, D. Howel, N. Wilson, N. Alvarado, S. Andole, D.L. Cohen, J. Dawson, C. Fernandez-Garcia, T. Finch, G.A. Ford, R. Francis, S. Hogg, N. Hughes, C.I. Price, L. Ternent, D.L. Turner, L. Vale, S. Wilkes, H.I. Krebs, F. van Wijck, Evaluation of the enhanced upper limb therapy programme within the Robot-Assisted Training for the Upper Limb after Stroke trial: descriptive analysis of intervention fidelity, goal selection and goal achievement, *Clinical rehabilitation*, 35 (2021) 119-134.
8. M.F. Bruni, C. Melegari, M.C. De Cola, A. Bramanti, P. Bramanti, R.S. Calabrò, What does best evidence tell us about robotic gait rehabilitation in stroke patients: A systematic review and meta-analysis, *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia*, 48 (2018) 11-17.
9. K.D. Bui, M.J. Johnson, Designing robot-assisted neurorehabilitation strategies for people with both HIV and stroke, *Journal of neuroengineering and rehabilitation*, 15 (2018) 75.
10. K.D. Bui, M.J. Johnson, Towards Robot-Based Cognitive and Motor Assessment Across the HIV-Stroke Spectrum, Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference, 2018 (2018) 3618-3621.
11. K. Bustamante Valles, S. Montes, J. Madrigal Mde, A. Burciaga, M.E. Martínez, M.J. Johnson, Technology-assisted stroke rehabilitation in Mexico: a pilot randomized trial comparing traditional therapy to circuit training in a Robot/technology-assisted therapy gym, *Journal of neuroengineering and rehabilitation*, 13 (2016) 83.
12. I. Carpinella, T. Lencioni, T. Bowman, R. Bertoni, A. Turolla, M. Ferrarin, J. Jonsdottir, Effects of robot therapy on upper body kinematics and arm function in persons post stroke: a pilot randomized controlled trial, *Journal of neuroengineering and rehabilitation*, 17 (2020) 10.
13. W.T. Chien, Y.Y. Chong, M.K. Tse, C.W. Chien, H.Y. Cheng, Robot-assisted therapy for upper-limb rehabilitation in subacute stroke patients: A systematic review and meta-analysis, *Brain and behavior*, 10 (2020) e01742.
14. J.E. Cho, J.S. Yoo, K.E. Kim, S.T. Cho, W.S. Jang, K.H. Cho, W.H. Lee, Systematic Review of Appropriate Robotic Intervention for Gait Function in Subacute Stroke Patients, *BioMed research international*, 2018 (2018) 4085298.
15. S.S. Conroy, G.F. Wittenberg, H.I. Krebs, M. Zhan, C.T. Bever, J. Whitall, Robot-Assisted Arm Training in Chronic Stroke: Addition of Transition-to-Task Practice, *Neurorehabilitation and neural repair*, 33 (2019) 751-761.
16. F. Cordella, F. Scotto Di Luzio, M. Bravi, F. Santacaterina, F. Bressi, L. Zollo, Hand motion analysis during robot-aided rehabilitation in chronic stroke, *Journal of biological regulators and homeostatic agents*, 34 (2020) 45-52. *Technology in Medicine*.
17. M. Coscia, M.J. Wessel, U. Chaudary, J.D.R. Millán, S. Micera, A. Guggisberg, P. Vuadens, J. Donoghue, N. Birbaumer, F.C. Hummel, Neurotechnology-aided interventions for upper limb motor rehabilitation in severe chronic stroke, *Brain : a journal of neurology*, 142 (2019) 2182-2197.
18. K. Daunoraviciene, A. Adomaviciene, A. Grigonyte, J. Griškevičius, A. Juocevicius, Effects of robot-assisted training on upper limb functional recovery during the rehabilitation of poststroke patients, *Technology and health care : official journal of the European Society for Engineering and Medicine*, 26 (2018) 533-542.
19. S. Dehem, M. Gilliaux, G. Stoquart, C. Detrembleur, G. Jacquemin, S. Palumbo, A. Frederick, T. Lejeune, Effectiveness of upper-limb robotic-assisted therapy in the early rehabilitation phase after stroke: A single-blind, randomised, controlled trial, *Annals of physical and rehabilitation medicine*, 62 (2019) 313-320.
20. G.J. Everard, K. Ajana, S.B. Dehem, G.G. Stoquart, M.G. Edwards, T.M. Lejeune, Is cognition considered in post-stroke upper limb robot-assisted therapy trials? A brief systematic review, *International journal of rehabilitation research. Internationale Zeitschrift für*

- Rehabilitationsforschung. *Revue internationale de recherches de readaptation*, 43 (2020) 195-198.
21. M. Franceschini, M. Goffredo, S. Pournajaf, S. Paravati, M. Agosti, F. De Pisi, D. Galafate, F. Posteraro, Predictors of activities of daily living outcomes after upper limb robot-assisted therapy in subacute stroke patients, *PloS one*, 13 (2018) e0193235.
 22. M. Franceschini, S. Mazzoleni, M. Goffredo, S. Pournajaf, D. Galafate, S. Criscuolo, M. Agosti, F. Posteraro, Upper limb robot-assisted rehabilitation versus physical therapy on subacute stroke patients: A follow-up study, *Journal of bodywork and movement therapies*, 24 (2020) 194-198.
 23. R. Gassert, V. Dietz, Rehabilitation robots for the treatment of sensorimotor deficits: a neurophysiological perspective, *Journal of neuroengineering and rehabilitation*, 15 (2018) 46.
 24. Y. Iwamoto, T. Imura, T. Suzukawa, H. Fukuyama, T. Ishii, S. Taki, N. Imada, M. Shibukawa, T. Inagawa, H. Araki, O. Araki, Combination of Exoskeletal Upper Limb Robot and Occupational Therapy Improve Activities of Daily Living Function in Acute Stroke Patients, *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*, 28 (2019) 2018-2025.
 25. I. Jakob, A. Kollreider, M. Germanotta, F. Benetti, A. Cruciani, L. Padua, I. Aprile, Robotic and Sensor Technology for Upper Limb Rehabilitation, *PM & R : the journal of injury, function, and rehabilitation*, 10 (2018) S189-s197.
 26. W. Kakuda, [Future directions of stroke rehabilitation], *Rinsho shinkeigaku = Clinical neurology*, 60 (2020) 181-186.
 27. A.B. Keeling, M. Piitz, J.A. Semrau, M.D. Hill, S.H. Scott, S.P. Dukelow, Robot enhanced stroke therapy optimizes rehabilitation (RESTORE): a pilot study, *Journal of neuroengineering and rehabilitation*, 18 (2021) 10.
 28. G.J. Kim, M. Taub, C. Creelman, C. Cahalan, M.W. O'Dell, J. Stein, Feasibility of an Electromyography-Triggered Hand Robot for People After Chronic Stroke, *The American journal of occupational therapy : official publication of the American Occupational Therapy Association*, 73 (2019) 7304345040p7304345041-7304345040p7304345049.
 29. H.Y. Kim, J.H. Shin, S.P. Yang, M.A. Shin, S.H. Lee, Robot-assisted gait training for balance and lower extremity function in patients with infratentorial stroke: a single-blinded randomized controlled trial, *Journal of neuroengineering and rehabilitation*, 16 (2019) 99.
 30. P. Kiper, A. Szczudlik, M. Agostini, J. Opara, R. Nowobilski, L. Ventura, P. Tonin, A. Turolla, Virtual Reality for Upper Limb Rehabilitation in Subacute and Chronic Stroke: A Randomized Controlled Trial, *Archives of physical medicine and rehabilitation*, 99 (2018) 834-842.e834.
 31. V. Klamroth-Marganska, Stroke Rehabilitation: Therapy Robots and Assistive Devices, *Advances in experimental medicine and biology*, 1065 (2018) 579-587.
 32. K.D. Knepley, J.Z. Mao, P. Wiczorek, F.O. Okoye, A.P. Jain, N.Y. Harel, Impact of Telerehabilitation for Stroke-Related Deficits, *Telemedicine journal and e-health : the official journal of the American Telemedicine Association*, 27 (2021) 239-246.
 33. H.C. Lee, F.L. Kuo, Y.N. Lin, T.H. Liou, J.C. Lin, S.W. Huang, Effects of Robot-Assisted Rehabilitation on Hand Function of People With Stroke: A Randomized, Crossover-Controlled, Assessor-Blinded Study, *The American journal of occupational therapy : official publication of the American Occupational Therapy Association*, 75 (2021) 7501205020p7501205021-7501205020p7501205011.
 34. H.J. Lee, S.H. Lee, K. Seo, M. Lee, W.H. Chang, B.O. Choi, G.H. Ryu, Y.H. Kim, Training for Walking Efficiency With a Wearable Hip-Assist Robot in Patients With Stroke: A Pilot Randomized Controlled Trial, *Stroke*, 50 (2019) 3545-3552.
 35. M.J. Lee, J.H. Lee, S.M. Lee, Effects of robot-assisted therapy on upper extremity function and activities of daily living in hemiplegic patients: A single-blinded, randomized, controlled trial, *Technology and health care : official journal of the European Society for Engineering and Medicine*, 26 (2018) 659-666.

36. M.J. Leem, G.S. Kim, K.H. Kim, T.I. Yi, H.I. Moon, Predictors of functional and motor outcomes following upper limb robot-assisted therapy after stroke, *International journal of rehabilitation research. Internationale Zeitschrift fur Rehabilitationsforschung. Revue internationale de recherches de readaptation*, 42 (2019) 223-228.
37. D.J. Lin, S.P. Finklestein, S.C. Cramer, New Directions in Treatments Targeting Stroke Recovery, *Stroke*, 49 (2018) 3107-3114.
38. K. Lo, M. Stephenson, C. Lockwood, Effectiveness of robotic assisted rehabilitation for mobility and functional ability in adult stroke patients: a systematic review, *JBI database of systematic reviews and implementation reports*, 15 (2017) 3049-3091.
39. A. Mayr, E. Quirbach, A. Picelli, M. Kofler, N. Smania, L. Saltuari, Early robot-assisted gait retraining in non-ambulatory patients with stroke: a single blind randomized controlled trial, *European journal of physical and rehabilitation medicine*, 54 (2018) 819-826.
40. S. Mazzoleni, E. Battini, R. Crecchi, P. Dario, F. Posteraro, Upper limb robot-assisted therapy in subacute and chronic stroke patients using an innovative end-effector haptic device: A pilot study, *NeuroRehabilitation*, 42 (2018) 43-52.
41. [41] A.C. McConnell, R.C. Moiola, F.L. Brasil, M. Vallejo, D.W. Corne, P.A. Vargas, A.A. Stokes, Robotic devices and brain-machine interfaces for hand rehabilitation post-stroke, *Journal of rehabilitation medicine*, 49 (2017) 449-460.
42. J. Mehrholz, M. Pohl, T. Platz, J. Kugler, B. Elsner, Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke, *The Cochrane database of systematic reviews*, 9 (2018) Cd006876.
43. J. Mehrholz, S. Thomas, C. Werner, J. Kugler, M. Pohl, B. Elsner, Electromechanical-assisted training for walking after stroke, *The Cochrane database of systematic reviews*, 5 (2017) Cd006185.
44. S. Micera, M. Caleo, C. Chisari, F.C. Hummel, A. Pedrocchi, Advanced Neurotechnologies for the Restoration of Motor Function, *Neuron*, 105 (2020) 604-620.
45. M. Mohan, R. Mendonca, M.J. Johnson, Towards quantifying dynamic human-human physical interactions for robot assisted stroke therapy, *IEEE ... International Conference on Rehabilitation Robotics : [proceedings]*, 2017 (2017) 913-918.
46. G. Morone, I. Cocchi, S. Paolucci, M. Iosa, Robot-assisted therapy for arm recovery for stroke patients: state of the art and clinical implication, *Expert review of medical devices*, 17 (2020) 223-233.
47. N. Norouzi-Gheidari, P.S. Archambault, J. Fung, Robot-Assisted Reaching Performance of Chronic Stroke and Healthy Individuals in a Virtual Versus a Physical Environment: A Pilot Study, *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society*, 27 (2019) 1273-1281.
48. J. Park, Y. Chung, The effects of robot-assisted gait training using virtual reality and auditory stimulation on balance and gait abilities in persons with stroke, *NeuroRehabilitation*, 43 (2018) 227-235.
49. S.W. Park, J.H. Kim, Y.J. Yang, Mental practice for upper limb rehabilitation after stroke: a systematic review and meta-analysis, *International journal of rehabilitation research. Internationale Zeitschrift fur Rehabilitationsforschung. Revue internationale de recherches de readaptation*, 41 (2018) 197-203.
50. D. Iyer, B.K. Sharma, U.K. Patil, Isolation of bioactive phytoconstituent from *Alpinia galanga* L. with anti-hyperlipidemic activity, *Journal of dietary supplements*, 10 (2013) 309-317.
51. R. Ranzani, O. Lamercy, J.C. Metzger, A. Califfi, S. Regazzi, D. Dinacci, C. Petrillo, P. Rossi, F.M. Conti, R. Gassert, Neurocognitive robot-assisted rehabilitation of hand function: a randomized control trial on motor recovery in subacute stroke, *Journal of neuroengineering and rehabilitation*, 17 (2020) 115.
52. C. Ridler, Stroke: Wearable robot aids walking after stroke, *Nature reviews. Neurology*, 13 (2017) 576-577.

53. H. Rodgers, H. Bosomworth, H.I. Krebs, F. van Wijck, D. Howel, N. Wilson, L. Aird, N. Alvarado, S. Andole, D.L. Cohen, J. Dawson, C. Fernandez-Garcia, T. Finch, G.A. Ford, R. Francis, S. Hogg, N. Hughes, C.I. Price, L. Ternent, D.L. Turner, L. Vale, S. Wilkes, L. Shaw, Robot assisted training for the upper limb after stroke (RATULS): a multicentre randomised controlled trial, *Lancet* (London, England), 394 (2019) 51-62.
54. V.K. Sharma, P.P. Sharma, B. Mazumder, A. Bhatnagar, V. Subramaniyan, S. Fuloria, N.K. Fuloria, Mucoadhesive microspheres of glutaraldehyde crosslinked mucilage of Isabgol husk for sustained release of gliclazide, *Journal of biomaterials science. Polymer edition*, 32 (2021) 1420-1449.
55. H. Rodgers, L. Shaw, H. Bosomworth, L. Aird, N. Alvarado, S. Andole, D.L. Cohen, J. Dawson, J. Eyre, T. Finch, G.A. Ford, J. Hislop, S. Hogg, D. Howel, N. Hughes, H.I. Krebs, C. Price, L. Rochester, E. Stamp, L. Ternent, D. Turner, L. Vale, E. Warburton, F. van Wijck, S. Wilkes, Robot Assisted Training for the Upper Limb after Stroke (RATULS): study protocol for a randomised controlled trial, *Trials*, 18 (2017) 340.
56. A. Schicketmueller, J. Lamprecht, M. Hofmann, M. Sailer, G. Rose, Gait Event Detection for Stroke Patients during Robot-Assisted Gait Training, *Sensors* (Basel, Switzerland), 20 (2020).
57. R. Malviya, A. Tyagi, S. Fuloria, V. Subramaniyan, K. Sathasivam, S. Sundram, S. Karupiah, O. Porwal, D. Meenakshi, N. Gupta, M. Sekar, K. Sudhakar, N. Fuloria, U.M. Dhana Lekshmi, Fabrication and Characterization of Chitosan-Tamarind Seed Polysaccharide Composite Film for Transdermal Delivery of Protein/Peptide, *Polymers*, 13 (2021) 1531.
58. J. Schröder, S. Truijen, T. Van Crieking, W. Saeys, Feasibility and effectiveness of repetitive gait training early after stroke: A systematic review and meta-analysis, *Journal of rehabilitation medicine*, 51 (2019) 78-88.
59. C.K. Sen, S. Khanna, H. Harris, R. Stewart, M. Balch, M. Heigel, S. Teplitsky, S. Gnyawali, C. Rink, Robot-assisted mechanical therapy attenuates stroke-induced limb skeletal muscle injury, *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*, 31 (2017) 927-936.
60. J.S. Seo, H.S. Yang, S. Jung, C.S. Kang, S. Jang, D.H. Kim, Effect of reducing assistance during robot-assisted gait training on step length asymmetry in patients with hemiplegic stroke: A randomized controlled pilot trial, *Medicine*, 97 (2018) e11792.
61. R. Dahiya, S. Dahiya, N.K. Fuloria, S. Jankie, A. Agarwal, V. Davis, V. Sahadeo, V. Radhay, Y. Ramsubhag, W. Mullings, Z. Langford, Z. Bedassie, S. Fuloria, Natural Thiazoline-Based Cyclodepsipeptides from Marine Cyanobacteria: Chemistry, Bioefficiency and Clinical Aspects, *Curr Med Chem*, 28 (2021) 7887-7909.