CHAPTER

Twenty+ years of robotics for upper-extremity rehabilitation following a stroke

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INTRODUCTION

The ebb and flow of progress requires the convergence of several different factors, technologies, and stakeholders, and there is such a convergence of factors for what is generally described as the human-robot interface. This view on the potential of robotics was eloquently summarized by Bill Gates a couple years ago: "Imagine being present at the birth of a new industry. It is an industry based on groundbreaking new technologies, wherein a handful of well-established corporations sell highly specialized devices for business use and a fast-growing number of start-up companies produce innovative toys, gadgets for hobbyists, and other interesting niche products (like the computer industry) trends are now starting to converge and I can envision a future in which robotics devices will become a nearly ubiquitous part of our day-to-day lives. Technologies such as distributed computing, voice and visual recognition, and wireless broadband connectively will open the door to a new generation of autonomous devices that enable computers to perform tasks in the physical world on our behalf. We may be on the verge of a new era, when the PC will get up off the desktop and allow us to see, hear, touch, and manipulate objects in places where we are not physically present."

This vision might sound ambitious and similar to a tune of “old-fashioned” science fiction, but I claim it is “around the corner.” It includes a new phase of industrial revolution strongly anchored on robotic partners that will cooperate with humans in close contact. It includes widespread automation at smart homes with a multitude of automatic devices embedded in the homes to aid people with everyday activities interconnected at the Internet of things (IoT). It includes self-driving cars and the associated changes in urban development. It includes service robotics that will go

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beyond vacuuming one's carpet to rehabilitation robotics and assisting the rehabilitation process of a person with disabilities.

One cannot overstress the need for this technology. Graying of the world population is increasing the demand on caregivers, rehabilitation services, and payers and is bringing to the forefront the need for technology to assist all stakeholders. By 2050, the contingent of seniors in the United States is expected to double from 13.3% of the population or 40 million to 80 million. With this growth comes an increased incidence of age-related maladies and disease including stroke, and presently, there are already over 50 million stroke survivors worldwide, and this number is going to expand rapidly, particularly in Europe and the Pacific Rim including China. This situation creates an urgent need for new approaches to improve the effectiveness and efficiency of rehabilitation. It also creates an unprecedented opportunity to deploy technologies such as robotics to assist in the recovery process.

It should be of no surprise that large corporations are investing in "rehabilitation robots," which can be used to augment the clinician's toolbox in order to deliver meaningful restorative therapy for an aging population. Rehabilitation robotics can support and enhance the clinicians' productivity and effectiveness as they try to facilitate the individual's recovery, and it is being embraced by large corporations such as Toyota (http://www.toyota-global.com/innovation/partner_robot/family.html) with some market research studies estimating that the market will grow at a brisk pace from US $43 million in 2014 to 1.8 billion by 2020 (Wintergreen Research 2014). The industry's interest has been preceded by a growth of related research in academia as testified by the exponential increase regarding this topic in the last 20 years.

With so much excitement and work in progress, I will focus here on emerging applications of robotics to more traditional upper-extremity rehabilitation with prosthetics, assistive technology/exoskeleton, and lower-extremity rehabilitation covered in other chapters. Here, I will focus on tools to assist the clinician in promoting upper-extremity rehabilitation of an individual so that he/she can interact with the environment unassisted (rehabilitation robotics), and in particular, we will focus on stroke rehabilitation as it is the diagnosis having the largest census presently with over 50 million stroke survivors worldwide.

NEUROSCIENCE PRINCIPLES

Contrary to initial expectations, the major hindrance to the development and deployment of robots for therapy was not engineering but the lack of strong evidence supporting many current rehabilitation practices. Until the 1970s and 1980s, the perception that the brain was hardwired was prevalent. Perhaps the most well-known promoter of this view was the famous Spanish Nobel laureate Santiago Ramón y Cajal. Under Ramón's optics, beyond natural recovery, one should teach compensatory techniques, i.e., how to accomplish activities of daily living and not focus on the paretic limb or impairment. With the understanding of brain plasticity and, consequently, the objective evidence that nurture has a positive effect on nature [1,2], there was the need and the opportunity of harnessing and promoting brain plasticity with robotic tools.

However, conventional practices lacked the support of empirical evidence or any other scientific basis. As a result, there was neither clear design target for the technology nor any reliable "gold standard" against which to gauge its effectiveness. In fact, the biggest hurdle engineers faced in the development of therapeutic robotics was the validation of movement therapy per se. But every challenge is also an opportunity: robots provide an ideal platform for objective, reproducible, continuous measurement, and control of therapy. Furthermore, our research group decided against the merit of following any of the dogmatic approaches that constitute usual care practices. Instead, we took the approach that beyond natural recovery, general neuroscience-based motor learning framework could serve as a good basis for motor recovery, and consequently, we designed rehabilitation robots and its interventions around these concepts.

Kleim and Jones elegantly summarized these neuroscience principles in an easy-to-understand format shown in Table 1 [3]. However, a common mistake that we had observed is for a practitioner or researcher to build an intervention based on one of these motor learning principles without fully considering the interaction among these "10 principles." Indeed, we have demonstrated that, in many instances, embracing isolated principles that on the surface appeared to be sound and grounded proved incorrect in clinical trials.

Table 1 Ten neuroscience principles [3]

Principle	Description
1. Use it or lose it	Failure to drive specific brain functions can lead to functional degradation
2. Use it and improve it	Training that drives a specific brain function can lead to an enhancement of that function
3. Specificity	The nature of the training experience dictates the nature of the plasticity
4. Repetition matters	Induction of plasticity requires sufficient repetition
5. Intensity matters	Induction of plasticity requires sufficient training intensity
6. Time matters	Different forms of plasticity occur at different times during training
7. Salience matters	The training experience must be sufficiently salient to induce plasticity
8. Age matters	Training-induced plasticity occurs more readily in younger brains
9. Transference	Plasticity in response to one training experience can enhance the acquisition of similar behaviors
10. Interference	Plasticity in response to one experience can interfere with the acquisition of other behaviors

REHABILITATION ROBOTIC PRINCIPLES

In this section, I will discuss a few basic principles that are core for successful rehabilitation robotic technology. Of course, the goal is not to cover the engineering fundamentals but instead highlight them referring to well-founded textbooks or papers for depth. Let me mention once again that I am focusing on rehabilitation robotics and will not be discussing assistive robotics.

BACKDRIVABILITY AND PERFORMANCE

In many applications, a system has multiple operation modes that are quite distinct. For example, tug boats have to move fast to reach a ship in need and then move slowly pushing hard (in naval jargon, high bollard pull). Another example, military vessels cruise from one site to another at low speed to reduce fuel consumption but when in need move three to four times faster. Likewise, rehabilitation and assistive robotics generally require two entirely distinctive modes of operation. Typically, assistive technology is intended to provide full support for a person with disabilities; hence, an intrinsically high-impedance device is utilized. Rehabilitation robotics is at the other side of the spectrum and aims at getting out of the way to allow a weak or paretic patient to express as much movement as possible. The robots must be able to gently nudge the patient's limb toward the target, and therefore, the robots must present intrinsically low impedance. In other words, rehabilitation robotics aims at highly backdrivable devices. Closed-loop control might enhance the performance of such devices, but as a rule of thumb, we strive for a target requirement of less than 7% of a weak person's force capability to backdrive the robot. For example, in the MIT-Manus design, we considered that a weak female is capable of exerting 28 N with the arm in the horizontal plane and the robot is able to drive the patient's arm with at least 28 N. On the other hand, we want the patient to be able to express movement, and thus, we aimed at less than 2 N force to backdrive the MIT-Manus end-point friction and inertia [4].

IMPEDANCE CONTROL

An important feature of successful therapeutic robots is their interactivity, which is an essential component of effective robotic therapy. MIT designs achieve this by controlling the robot's mechanical impedance. Shaping the robot's mechanical impedance enables therapy to become directed guidance rather than imposed motion. Furthermore, stability and performance are both addressed directly when impedance control is used for controller design [5,6]. Impedance control regulates the behavior of the robot at the point where it interacts with the environment. The controller modulates the way the robot reacts to mechanical perturbation from a patient or clinician and ensures a gentle, compliant behavior. Importantly, mechanical impedance is a property of the robot alone, regardless of the environment.

Proper selection and ideal implementation of the impedance can guarantee stability with certain environments and desired transparent feel. For example, a programmer could specify a “virtual” spring connecting the patient's hand to a position that moved along a nominal trajectory. When the patient's motion is close to nominal trajectory, the robot exerts little or no force. Conversely, when the patient's hand strays, the robot pushes or pulls it back to the nominal motion; the farther the patient strays, the greater the force the robot exerts. The challenge for rehabilitation robot developers is to create devices that offer a broad range of end-point impedances that includes sufficiently low impedance for a patient to backdrive the robot with ease. This transparency quality differs from traditional factory or assistive robots, which have high impedance; it also differs from haptic devices, which typically offer a broad range of impedances but saturate at comparably low force. Note that impedance control does not specify a unique motion but rather an entire family of motions and shares the burden of producing motion with the patient. Importantly, it allows the patient to make movement errors, while it attempts to minimize the magnitude of those errors and thus is considered key to “adaptive” or “performance-based” rehabilitation. Of notice, as a rule of thumb in our adaptive algorithms, I matched the purported impedances, i.e., I selected the initial robot impedance to be of the same order of magnitude as the interacting patient's limb impedance [7,8].

ADAPTIVE CONTROL

There is no reason to believe that a “one-size-fits-all” optimal treatment exists. Fig. 1 shows examples of unassisted movement attempts to reach the same target of two different stroke patients. This figure illustrates reasonably well that different stroke lesions can lead to very different kinematic behaviors during reach. The first patient can make pretty fast but poorly aimed movements, while the second one aims well but moves very slowly. That requires an adaptive algorithm that can track the patient's needs and abilities. Our research group's performance-based adaptive algorithm explores concepts of motor learning during discrete reaching movements. We include concepts related to knowledge of results (e.g., hitting the targets) and to knowledge of performance (e.g., with every fifth repetition of the game, performance is provided in terms of initiation, aiming, deviation, power, smoothness, etc.) in order to modify the time allotted for the patient to make the move and the amount of assistance afforded. This adaptive controller guides the hand of the patient that aims poorly without holding him/her back and assists the other patient in making faster movements. While tracking allows us to tailor therapy to a particular patient's movement abilities, we need to go beyond that to continuously challenge the patient to avoid slacking.

This approach appears to be valid across different joint segments and diagnoses [7–12] and was demonstrated to work also for children with cerebral palsy making pointing movements with their impaired ankle (different populations and limb segments) [8].

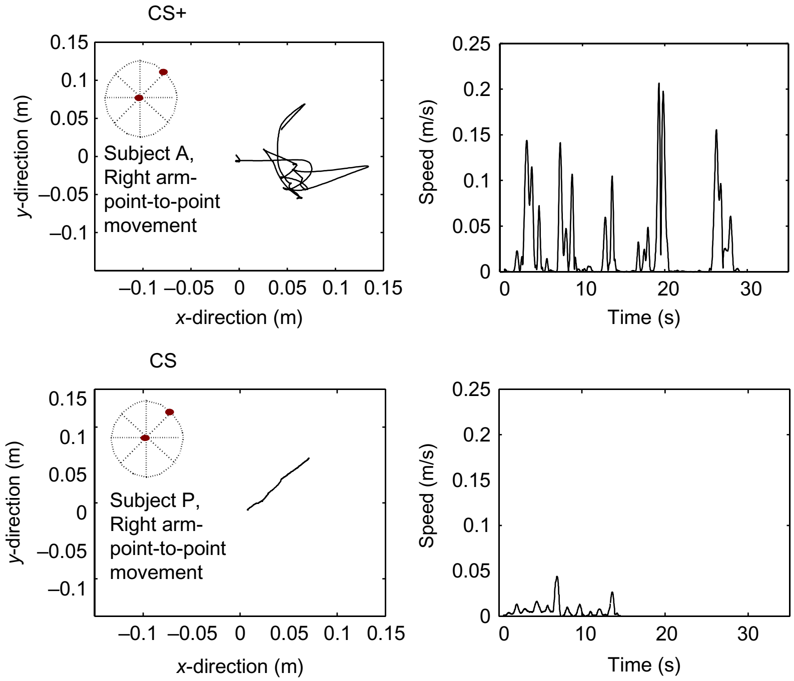

FIG. 1

Reaching movements made by patients with corpus striatum lesion (CS (8.9 cm^3)) and corpus striatum plus cortex lesion (CS + (109.9 cm^3)). The left column shows a bird view of the patients' hand path attempting a point-to-point movement. The right column shows hand speed. Patient with the large lesion (top row) could move at reasonable speed but had poor aim. The opposite holds for the patients with the small lesion (lower row).

MIT-MANUS AND OTHER REHABILITATION ROBOTICS

I will present a snapshot of a few of MIT's rehabilitation robots, discuss the results of meta-analyses for upper-extremity robotics, and finish by discussing two of our research group's exciting examples for acute and chronic stroke. This overview is not intended to offer an exhaustive list of the many other devices and researchers involved in developing rehabilitation robots.

Fig. 2 shows the gym of robots that we developed at MIT for both upper and lower extremities including the MIT-Manus for shoulder and elbow [4], antigravity [13], wrist [14], and hand [15], Anklebot [8,16], and MIT-Skywalker robots [17].

BIG PICTURE

In this chapter, I will focus on upper-extremity rehabilitation following a stroke and present a meta-analysis on the benefits of upper-extremity robotics. For the upper extremity, Kwakkel examined robotic training trials published up to October 2006 with

FIG. 2

MIT gym of robots. Top row on the left shows the MIT-Manus used to promote neurorecovery of the injured brain and control of the shoulder-and-elbow segments and on the right the antigravity device used to promote training of the shoulder against gravity. On the second row on the left, we show the wrist robot that affords training of the three degrees of freedom of the wrist and forearm and to the right the hand module for grasp and release. The third row on the left shows the combination of shoulder-and-elbow robot with the wrist module mounted at the tip of first affording training for both transport of arm and object manipulation. On the right, the alpha-prototype of the MIT-Skywalker for gait training. On the bottom row, we show pediatric populations working with the MIT-Manus and our pediatric Anklebot that provides training in dorsi-/plantarflexion and inversion/eversion.

the first generation of therapeutic robots [18]. A computerized literature search was conducted in MEDLINE, CINAHL, EMBASE, Cochrane Controlled Trial Register, DARE, SciSearch, Doconline, and PEDro, and it returned 173 hits. Only papers that compared robotic training with a control group were included. Excluded were studies that compared different forms of robotic therapy and studies on stroke that compared discharge values with admission values. The results demonstrated small but statistically significant improvements due to robot-assisted therapy, even when compared head-to-head with conventional therapy in stroke. This review demonstrated a small but substantial improvement favoring the robotic therapy group [18] (Fig. 3).

More recently, Kwakkel's team updated the meta-analysis and concluded that shoulder/elbow robotics showed small but significant effects on motor control and muscle strength, while elbow/wrist robotics had small but significant effects on motor control [19]. Our results with both studies for acute/subacute and chronic stroke patients are part of these meta-analyses, and we will discuss a few of the examples:

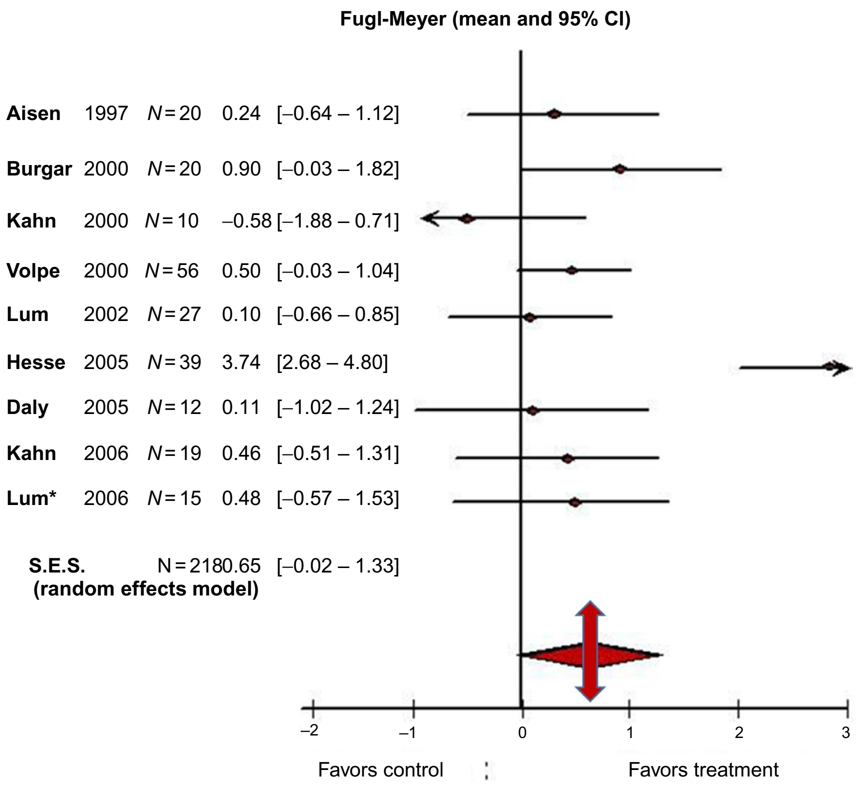

FIG. 3

Meta-analysis of robot-assisted therapy trials on motor recovery following stroke.

1990'S STUDIES: SUB-ACUTE STROKE PHASE

Volpe and colleagues reported the composite results of robotic therapy on 96 consecutive subacute stroke inpatients admitted to Burke Rehabilitation Hospital in White Plains, NY [20]. All participants received conventional neurological rehabilitation during their participation in the study. The goal of the trial was to amass initial evidence to test whether movement therapy had a measurable impact on recovery. Thus, we provided one group of patients with as much movement therapy as possible to address a fundamental question: does goal-oriented movement therapy have a positive effect on neuromotor recovery after stroke?

Patients were randomly assigned to either an experimental (robot-trained) or control (robot-exposure) group. Individuals in the robot-trained group were seen for five 1 h sessions each week and participated in at least 25 sessions of sensorimotor robotic therapy for the paretic arm. Patients were asked to perform goal-directed, planar reaching tasks that emphasized shoulder and elbow movements with their paretic arm. MIT-Manus' low impedance guaranteed that the robot would not suppress attempts to move. When a patient could not move or deviated from the desired path or was unable to reach the target, the robot provided soft guidance and assistance dictated by an impedance controller [4]. This robot action (which we dubbed "sensorimotor" therapy) was similar to the "hand-over-hand" assistance that a therapist often provides during conventional therapy.

Individuals assigned to the robot-exposure (control) group were asked to perform the same planar reaching tasks as the robot-trained group. However, the robot did not actively assist the patient's movement attempts. When the subject was unable to reach toward a target, he or she could assist with the unimpaired arm. The robot supported the weight of the limb while offering negligible resistance to motion. For this control group, the task, the visual display, the audio environment (e.g., noise from the motor amplifiers), and the therapy context (e.g., the novelty of a technology-based treatment) were all the same as for the experimental group. Patients in this group were seen for only 1 h per week during their inpatient hospitalization.

Standard clinical evaluations included the Medical Research Council motor power score for four shoulder and elbow movements (MP, maximum score = 20). Although the robot-exposure (control) and robot-trained (experimental) groups were comparable at admission based on sensory and motor evaluation and on clinical and demographic scales (enrollment into the study between 2 and 4 weeks post stroke) and both groups were inpatients in the same stroke recovery unit and received the same standard care and therapy for comparable lengths of stay, the robot-trained group demonstrated considerably greater motor improvement (higher mean interval change ± SEM) than the control group on multiple clinical scales including the MP scores. In fact, the robot-trained group improved twice as much as the control group in these measures. Though this was a modest beginning, it provided unequivocal evidence that movement therapy of the kind that might be delivered by a robot had a substantially positive impact on recovery.

We recalled these 96 stroke survivors and were able to reexamine one-third of them [20]. Most of these patients had received little therapy after discharge, yet we were able to observe two things: first, the robot-trained group maintained the advantage over the control group, and second, both groups demonstrated greater reductions in impairment. This was contrary to the existing state of knowledge at the time that indicated that the gains in motor abilities were completed after 3 months following stroke onset [21–23]. These results suggest that further improvement is possible in the chronic phase, and bolstered by these findings, we initiated trials with chronic stroke in 2000 [24–27].

2000'S STUDIES: CHRONIC STROKE

Rather than examine our results with chronic patients, we will review a publication in the New England Journal of Medicine in 2010 and related papers [28–31]. The article presented the results of a multisite, independently run, Veterans Affairs trial CSP-558: ROBOTICS involving rehabilitation robotics for the upper extremity of patients with chronic stroke employing the MIT-Manus for shoulder-and-elbow robot plus the corresponding antigravity, wrist, and hand robots. The publication was exciting for many reasons. It was a rare publication on stroke rehabilitation published by this prestigious journal. In fact, we found only one prior paper on rehabilitation following a stroke in the NEJM: "Intramuscular Injection of Botulinum Toxin for the Treatment of Wrist and Finger Spasticity after a Stroke" [32].

ROBOTICS had an unusual design, and it was comparable to a mixture of phase 2 and 3 studies. It evaluated the safety of these rehabilitation robots; they passed with flying colors. There were no serious adverse events in the robot group. A few patients mentioned muscle soreness, which is not surprising considering that they were making 1,024 movements in an hour robot session with the paretic limb (instead of the typical 45 movements in "usual care" for chronic patients) [33]. The study also evaluated efficacy and cost. The first and perhaps most understated finding of CSP-558: ROBOTICS was that usual care (three sessions per week from therapists delivering treatment as they saw fit for the upper extremity) did not reduce impairment and disability or improve quality of life in chronic stroke survivors. The usual care intervention had no measurable impact and was discontinued as futile midway through the study. While it is possible that usual care prevents further decline, we believe that delivering three therapy sessions per week for upper extremity should achieve some level of improvement beyond simple maintenance of the status quo.

The trial lasted roughly for another year and compared robotic training for the shoulder and elbow, wrist, and hand that delivered 1,024 movements three times per week with an intensive comparison training (ICT) protocol that we created to generate a positive control, in which a therapist delivered comparable movement intensity and repetition during the same period [34]. We expected that this positive control would offer an advantage to usual care, likely due to the intense movement training that required the patient to actively use the paralyzed limb for the 50 min session. We also projected that the outcome effect of these two experimental interventions would be comparable, as demonstrated in the pilot study. That result was borne out by ROBOTICS. Specifically, there was no difference between the robotic and intensive-therapy training group in motor outcome measures. However, a note of caution is required since this intervention is not conventional therapy. Given that it is very labor-intensive, it is not practical to implement as standard care in a clinic. We were able to implement this intervention because, in most cases, the VA therapists delivering this form of training were engaged in ICT on average only once per day for the robot and intensive comparison training groups during the whole duration of the trial. Red vertical arrow indicates the change in the primary outcome of the complete robot group in relation to the usual care group (Figs. 4 and 5).

There are additional important comparisons that need highlighting: (a) the comparison between the robot group and usual care involved roughly only the first half of the study, and (b) we were interested in not only the immediate or 12-week impact but also whether the changes were robust and long lasting. On this score, robotic therapy was statistically superior to usual care in Stroke Impact Scale (quality of life) at the completion of the intervention and also in the Fugl-Meyer (impairment) and Wolf Motor Function (function) 6 months following the completion of the intervention [36–39]. The results are far more impressive if we compare the whole robot group with the usual care and not just the analysis that focused on the first half of

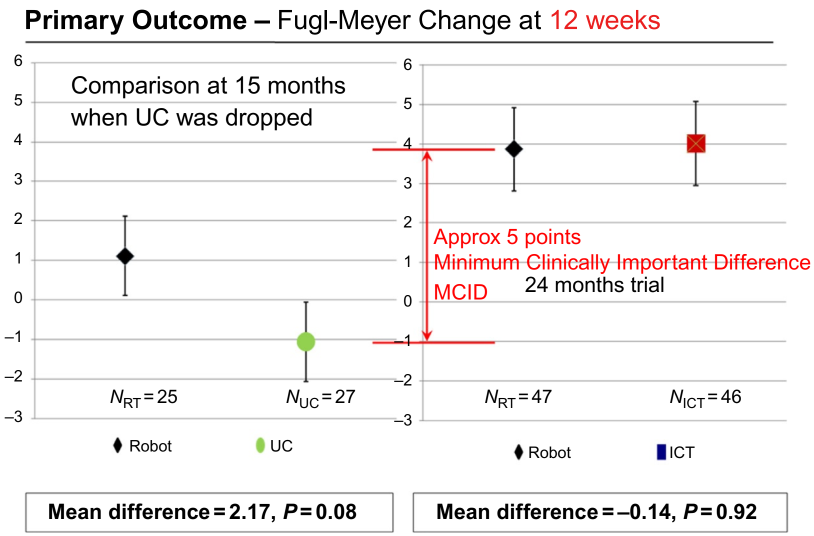

FIG. 4

ROBOTICS (CSP-558) primary results at 12 weeks (therapy completion). Left panel shows the changes in the primary outcome for the robot and usual care groups during the initial half of the trial. Right panel shows the changes in the primary outcome.

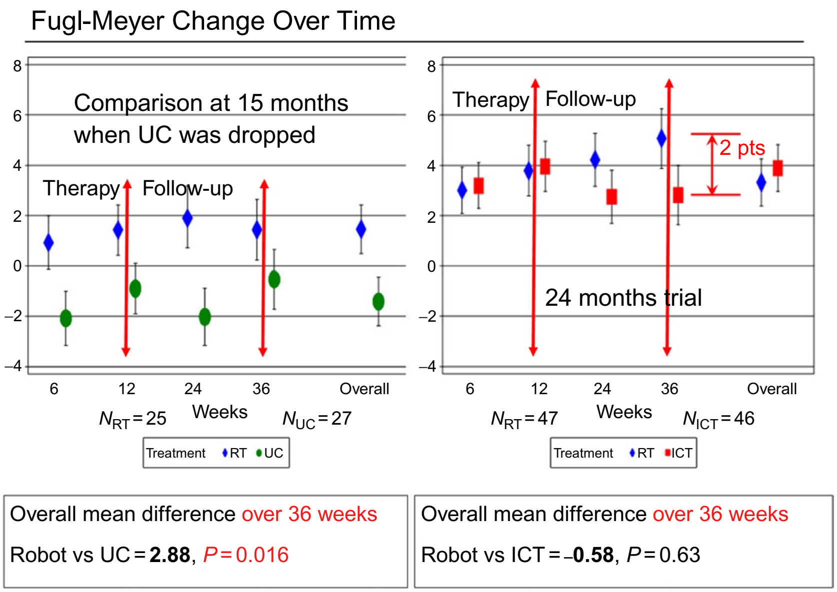

FIG. 5

ROBOTICS (CSP-558) results at 36 weeks (after 6-month follow-up). The figure shows the changes in the primary outcome over the duration of the intervention (evaluations at 6 and 12 weeks) and during the 6-month follow-up period (evaluations at 24 and 36 weeks). Each figure panel also shows the estimated changes at 36 weeks using a fixed model to fit all the data (overall). Left panel shows results for robot and usual care groups during the initial half of the study. Right panel shows results for the robot and intensive comparison training groups during the whole duration of the trial. Note that the robot group continues to improve after the intervention is completed even without further therapy (see evaluations at 24 and 36 weeks). We speculate that on average patients improved above a threshold beyond the minimum required to establish a positive reinforcement cycle [35]. Red vertical arrow indicates the actual change in the primary outcome of the complete robot group in relation to the intensive comparison training group at 36 weeks (instead of the overall fixed model estimate shown on the right).

the study. The results at 12 weeks show that the difference between the first half of the robotic treatment group and usual care was slightly over 2 Fugl-Meyer points. However, the difference between subjects receiving robotic treatment in the second half of the study and subjects receiving usual care during the first half of the study was almost 8 points in the Fugl-Meyer assessment (the total robotic group versus the total usual care showed around 5-point change [40]).

It is quite important to stress that these groups of patients with chronic stroke disability were moderately to severely impaired (admission motor impairment scales averaged 19 out of a total score of 66) and over 30% had multiple strokes. As such, the group represented a spectrum of disability burden that many studies have avoided and, in our case, represented the majority of the cases (65% of the volunteers were enrolled). Thus, even if the positive changes in the robotic therapy group might appear modest, the persistent improvement at the 6-month follow-up evaluation suggests improved robustness and perhaps an incremental advantage that prompted further improvement even without additional intervention. For example, an improvement of roughly 3 points in the Fugl-Meyer scale would enable a very severe patient to start to raise the arm and to bathe independently or to start to stretch the formerly paralyzed arm so that independent dressing could take place. It might enable a more moderate stroke patient to start to tuck in the shirt or to hike the pants independently or to start to reach overhead and actively grasp an object.

More recently, the VA team published part of the secondary analysis adjusted to comorbidities and other factors [31]. Table 2 shows that compared with usual care, the robotic therapy improved 4.2 points in the Fugl-Meyer Assessment (FMA), reduced 7.6 s in completing the Wolf Motor Function Test (WMFT), and improved by 8.3 points in the Stroke Impact Scale (SIS) at completion of training, and these changes were all highly significant. At 6-month follow-up, the robot group advantage was sustained with the robotic therapy, improved 4.6 points in the FMA, reduced 7.8 s in the WMFT, and improved by 3.2 points in the SIS. Even more interesting is the tree analysis breaking down the impact of different cofactors. The younger group of veterans, less than 55 years of age, who had their stroke less than a year at enrollment (i.e., enrollment occurred between 6 and 12 months), were the ones that improved the most. Note that usual care group improved very little independent of age. One note of caution in interpreting this result is that one-third of these veterans had multiple strokes and the VA did not conduct an analysis based on number of strokes. I speculate that age and number of strokes correlate well.

In this era of cost containment, a further important result arose from a cost-benefit analysis. While the active interventions added cost as compared with the usual care (e.g., the added cost of the robotic equipment and the expense of an additional therapist cost the VA approximately $5,000 per patient for 36 months), when we compared with total health-care utilization cost that includes all the clinical care needed to take care of these veterans, there were no significant differences between active interventions and usual care. The robot-trained group consumed $17,831, while the usual care group consumed $19,098 [29]. In other words, the usual care group used the rest of the health-care system for clinical care far more often than the robotic intervention group. This suggests better care for the same or slightly lower total cost. In lieu of this result, the National Health Service in the United Kingdom initiated through its Health Technology Assessment program the largest trial on rehabilitation robotics "RATULS [41]" targeting approximately 800 stroke patients to determine both efficacy and efficiency[1]. One might assume that this trial employing MIT technology will significantly address most of the key questions to allow us to tailor therapy for a particular patient's needs.

[1] The trial is on target for completion at the end of 2018 with 651 stroke patients completed so far.

Table 2 Secondary analysis of VA ROBOTICS

	12 weeks				36 weeks			
	UC	**IT**	**Mean Δ**	***P*-value**	**UC**	**IT**	**Mean Δ**	***P*-value**
Outcome	Mean ± SEM	Mean ± SEM			Mean ± SEM	Mean ± SEM		
FMA	0.03 ± 1.5	4.0 ± 1.3	4	0.005	0.4 ± 1.8	3.8 ± 1.6	3.4	0.051
WMFT	1.4 ± 4.3	−6.4 ± 3.7	−7.8	0.052	−0.2 ± 3.4	−7.7 ± 2.9	−7.5	0.022
SIS	0.003 ± 2.5	7.4 ± 2.2	7.4	0.002	2.3 ± 2.8	4.7 ± 2.4	2.4	0.4
	UC	**RT**	**Mean Δ**	***P*-value**	**UC**	**RT**	**Mean Δ**	***P*-value**
Outcome	Mean ± SEM	Mean ± SEM			Mean ± SEM	Mean ± SEM		
FMA	−0.6 ± 1.6	3.6 ± 1.8	4.2	0.005	0.4 ± 2.1	5.0 ± 2.4	4.6	0.026
WMFT	3.3 ± 4.3	−4.3 ± 4.6	−7.6	0.046	1.2 ± 4.3	−6.6 ± 4.7	−7.8	0.051
SIS	−1.6 ± 3.1	6.8 ± 3.4	8.3	0.005	0.5 ± 3.3	3.8 ± 3.7	3.2	0.3
	UC	**ICT**	**Mean Δ**	***P*-value**	**UC**	**ICT**	**Mean Δ**	***P*-value**
Outcome	Mean ± SEM	Mean ± SEM			Mean ± SEM	Mean ± SEM		
FMA	0.6 ± 1.6	4.9 ± 1.5	4.2	0.007	0.8 ± 1.9	3.4 ± 1.8	2.6	0.2
WMFT	−2.3 ± 5.2	−10.2 ± 4.7	−7.8	0.1	−2.2 ± 3.3	−10 ± 3.1	−7.8	0.016
SIS	2.7 ± 2.7	9.5 ± 2.4	6.7	0.008	4.8 ± 2.7	7.4 ± 2.6	2.5	0.3

UC, usual care; IT, intensive therapy, which includes both the robot and intensive comparison therapy; RT, robot-assisted therapy; ICT, intensive comparison therapy; FMA, Fugl-Meyer Assessment; WMFT, Wolf Motor Function Test; SIS, Stroke Impact Scale; SEM, standard error measurement. Note that the values at baseline were adjusted according to the Comorbidity Disease Index score, the medical center, baclofen administration, and concomitant physical therapy.

CONCLUSION

In summary, I believe that robotic therapy that involves an interactive high-intensity, intention-driven therapy based on motor learning principles and the assist-as-needed principle leads to better outcomes than usual care in acute/subacute and chronic stroke and so do many health-care associations in their clinical guidelines. For example, in 2010, the American Heart Association (AHA) issued "The Comprehensive Overview of Nursing and Interdisciplinary Rehabilitation Care of the Stroke Patient: A Scientific Statement from the American Heart Association" [42]. It recommended that "Robot-assisted therapy offers the amount of motor practice needed to relearn motor skills with less therapist assistance. Most robots for motor rehabilitation not only allow for robot assistance in movement initiation and guidance but also provide accurate feedback; some robots additionally provide movement resistance. Most trials of robot-assisted motor rehabilitation concern the upper extremity (UE), with robotics for the lower extremity (LE) still in its infancy… Robot-assisted UE therapy, however, can improve motor function during the inpatient period after stroke." AHA suggested that robot-assisted therapy for the UE has already achieved class I, level of evidence A for stroke care in the outpatient setting and care in chronic care settings. It suggested that robot-assisted therapy for UE has achieved class IIa, level of evidence A for stroke care in the inpatient setting. Class I is defined as "Benefit >>> Risk. Procedure/Treatment SHOULD be performed/administered"; Class IIa is defined as: "Benefit >> Risk, IT IS REASONABLE to perform procedure/administer treatment"; Level A is defined as "Multiple populations evaluated: Data derived from multiple randomized clinical trials or meta-analysis." The 2010 Veterans Administration/Department of Defense guidelines for stroke care came to the same conclusion endorsing the use of rehabilitation robots for the upper extremity, but not yet for the lower extremity [43]. The 2016 AHA guidelines came to the same conclusion albeit there was no separation between the inpatient (subacute) or outpatient (chronic) setting and hence UE received a Class IIa [44].

Acknowledgment

Dr. H. I. Krebs is a coinventor in several MIT-held patents for the robotic technology. He was the founder of Interactive Motion Technologies and 4Motion Robotics.

REFERENCES

[1] Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. Science 1996;272(5269):1791–4.
[2] Jenkins WM, Merzenich MM. Reorganization of neocortical representations after brain injury: a neurophysiological model of the bases of recovery from stroke. Prog Brain Res 1987;71:249–66.
[3] Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. J Speech Lang Hear Res 2008;51(1):S225–239.

[4] Krebs HI, Hogan N, Aisen ML, Volpe BT. Robot-aided neurorehabilitation. IEEE Trans Rehabi Eng 1998;6(1):75–87.
[5] Hogan N. Impedance control: an approach to manipulation. ASME J Dyn Syst Meas Control 1985;107:1–24.
[6] Hogan N, Buerger SP. Impedance and interaction control. In: Kurfess TR, editor. Robotics and automation handbook. Boca Raton, FL: CRC Press; 2004. 19-11 to 19-24.
[7] Krebs HI, Palazzolo JJ, Dipietro L, et al. Rehabilitation robotics: performance-based progressive robot-assisted therapy. auton robot 2003;15(1):7–20.
[8] Michmizos K, Rossi S, Castelli E, Cappa P, Krebs H. Robot-aided neurorehabilitation: a pediatric robot for ankle rehabilitation. IEEE Trans Neural Syst Rehabil 2015;23(6):1056–67.
[9] Colombo R, Sterpi I, Mazzone A, Delconte C, Pisano F. Development of a progressive task regulation algorithm for robot-aided rehabilitation. IEEE Eng Med Biol Soc Conf 2011;2011:3123–6.
[10] Colombo R, Pisano F, Mazzone A, et al. Design strategies to improve patient motivation during robot-aided rehabilitation. J Neuroeng Rehabil 2007;4:3.
[11] Emken JL, Benitez R, Sideris A, Bobrow JE, Reinkensmeyer DJ. Motor adaptation as a greedy optimization of error and effort. J Neurophysiol 2007;97(6):3997–4006.
[12] Emken JL, Reinkensmeyer DJ. Robot-enhanced motor learning: accelerating internal model formation during locomotion by transient dynamic amplification. IEEE Trans Neural Syst Rehabil Eng 2005;13(1):33–9.
[13] Krebs HI, Ferraro M, Buerger SP, et al. Rehabilitation robotics: pilot trial of a spatial extension for MIT-Manus. J Neuroeng Rehabil 2004;1(1):5.
[14] Krebs HI, Volpe BT, Williams D, et al. Robot-aided neurorehabilitation: a robot for wrist rehabilitation. IEEE Trans Neural Systems Rehabil Eng 2007;15(3):327–35.
[15] Masia L, Krebs HI, Cappa P, Hogan N. Design and characterization of hand module for whole-arm rehabilitation following stroke. IEEE/ASME Trans Mechatron 2007;12(4):399–407.
[16] Roy A, Krebs HI, Williams DJ, Bever CT, Forrester LW, Macko RM, et al. Robot-aided neurorehabilitation: a novel robot for ankle rehabilitation. IEEE Trans Robotics 2009;25(3):569–82.
[17] Susko T, Swaminathan K, Krebs HI. MIT-skywalker: a novel gait neurorehabilitation robot for stroke and cerebral palsy. IEEE Trans Neural Syst Rehabil Eng 2016; 24(10):1089–99.
[18] Kwakkel G, Kollen BJ, Krebs HI. Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. Neurorehabil Neural Repair 2008;22(2):111–21.
[19] Veerbeek JM, Langbroek-Amersfoort AC, van Wegen EE, Meskers CG, Kwakkel G. Effects of robot-assisted therapy for the upper limb after stroke. Neurorehabil Neural Repair 2017;31(2):107–21.
[20] Volpe BT, Krebs HI, Hogan N. Is robot-aided sensorimotor training in stroke rehabilitation a realistic option? Curr Opin Neurol 2001;14(6):745–52.
[21] 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.
[22] Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS. Outcome and time course of recovery in stroke. Part I: Outcome. The Copenhagen Stroke Study. Arch Phys Med Rehabil 1995;76(5):399–405.

[23] Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS. Outcome and time course of recovery in stroke. Part II: time course of recovery. The Copenhagen Stroke Study. Arch Phys Med Rehabil 1995;76(5):406–12.

[24] Ferraro M, Palazzolo JJ, Krol J, Krebs HI, Hogan N, Volpe BT. Robot-aided sensorimotor arm training improves outcome in patients with chronic stroke. Neurology 2003;61(11):1604–7.

[25] Fasoli SE, Krebs HI, Stein J, Frontera WR, Hogan N. Effects of robotic therapy on motor impairment and recovery in chronic stroke. Arch Phys Med Rehabil 2003;84(4):477–82.

[26] Stein J, Krebs HI, Frontera WR, Fasoli SE, Hughes R, Hogan N. Comparison of two techniques of robot-aided upper limb exercise training after stroke. Am J Phys Med Rehabil 2004;83(9):720–8.

[27] Fasoli SE, Krebs HI, Stein J, Frontera WR, Hughes R, Hogan N. Robotic therapy for chronic motor impairments after stroke: follow-up results. Arch Phys Med Rehabil 2004;85(7):1106–11.

[28] Lo AC, Guarino PD, Richards LG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med 2010;362(19):1772–83.

[29] Wagner TH, Lo AC, Peduzzi P, et al. An economic analysis of robot-assisted therapy for long-term upper-limb impairment after stroke. Stroke 2011;42(9):2630–2.

[30] Lo AC, Guarino P, Krebs HI, et al. Multicenter randomized trial of robot-assisted rehabilitation for chronic stroke: methods and entry characteristics for VA ROBOTICS. Neurorehabil Neural Repair 2009;23(8):775–83.

[31] Wu X, Guarino P, Lo AC, Peduzzi P, Wininger M. Long-term effectiveness of intensive therapy in chronic stroke. Neurorehabil Neural Repair 2016;30(6):583–90.

[32] Brashear A, Gordon MF, Elovic E, et al. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. N Engl J Med 2002;347(6):395–400.

[33] Lang CE, Macdonald JR, Reisman DS, et al. Observation of amounts of movement practice provided during stroke rehabilitation. Arch Phys Med Rehabil 2009;90(10):1692–8.

[34] Volpe BT, Lynch D, Rykman-Berland A, et al. Intensive sensorimotor arm training mediated by therapist or robot improves hemiparesis in patients with chronic stroke. Neurorehabil Neural Repair 2008;22(3):305–10.

[35] Schweighofer N, Han CE, Wolf SL, Arbib MA, Winstein CJ. A functional threshold for long-term use of hand and arm function can be determined: predictions from a computational model and supporting data from the extremity constraint-induced therapy evaluation (EXCITE) trial. Phys Ther 2009;89(12):1327–36.

[36] Fugl-Meyer AR, Jaasko L, Norlin V. The post-stroke hemiplegic patient. II. Incidence, mortality, and vocational return in Goteborg, Sweden with a review of the literature. Scand J Rehabil Med 1975;7(2):73–83.

[37] Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. J Am Med Assoc 2006;296(17):2095–104.

[38] Duncan PW, Bode RK, Min Lai S, Perera S. Glycine antagonist in neuroprotection Americans I. Rasch analysis of a new stroke-specific outcome scale: the stroke impact scale. Arch Phys Med Rehabil 2003;84(7):950–63.

[39] Duncan PW, Lai SM, Bode RK, Perera S, DeRosa J. Stroke Impact Scale-16: a brief assessment of physical function. Neurology 2003;60(2):291–6.

[40] Page SJ, Fulk GD, Boyne P. Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. Phys Ther 2012;92(6):791–8.

[41] Rodgers H, Shaw L, Bosomworth H, et al. Robot assisted training for the upper limb after stroke (RATULS): study protocol for a randomised controlled trial. Trials 2017;18(1):340.

[42] Miller EL, Murray L, Richards L, et al. Comprehensive overview of nursing and interdisciplinary rehabilitation care of the stroke patient: a scientific statement from the American Heart Association. Stroke 2010;41(10):2402–48.

[43] Management of Stroke Rehabilitation Working G. VA/DOD Clinical practice guideline for the management of stroke rehabilitation. J Rehabil Res Dev 2010;47(9):1–43.

[44] Winstein CJ, Stein J, Arena R, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2016;47(6):e98–e169.