Robotic Assistance for Upper Extremity Training after Stroke

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Abstract. There has been a rapid increase in the past decade in the number of robotic devices that are being developed to assist in movement rehabilitation of the upper extremity following stroke. Many of these devices have produced positive clinical results. Yet, it is still not well understood how these devices enhance movement recovery, and whether they have inherent therapeutic value that can be attributed to their robotic properties per se. This chapter reviews the history of robotic assistance for upper extremity training after stroke and the current state of the field. Future advances in the field will likely be driven by scientific studies focused on defining the behavioral factors that influence motor plasticity.

Keywords. upper extremity, rehabilitation, robotics, motor control, plasticity

Introduction

In the early 1990's there were a handful of robotic devices being developed for upper extremity training after stroke. Today there are tens of prototypes and several companies selling commercial devices [1]. However, use of robotic devices in rehabilitation clinics is still rare. This chapter reviews the history of the field, and identifies factors that limit clinical acceptance and important directions for future scientific research. Section 1 reviews why engineers started investigating robots for use in rehabilitation therapy, and initial reactions by clinicians to these efforts. Section 2 reviews key design decisions that had to be made for the first robotic therapy devices, which in some ways defined the flow of the field. Section 3 reviews clinical results from the field and two important scientific questions that these results have raised.

Section 4 discusses recent developments in robotic assistance for the upper extremity. The chapter concludes by suggesting directions for future research.

1. Robotic Assistance: Beginnings and Therapist Response

1.1. Precursors from Therapists

The development of robotic devices for rehabilitation therapy can be seen as the logical progression of a stream of technological development activity begun by therapists

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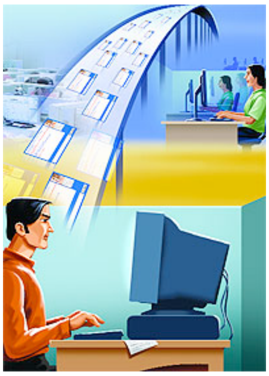

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Figure 1. Pre-cursors of robotic therapy devices. The three devices on the left (Swedish sling, arm skateboard, and JAECO mobile arm support) are designed to provides assistance for arm movement without using actuators. The device on the right is the Biodex Active Dynamometer, which is a single degree-of-freedom robot that can be adjusted to assist or resist movement around different joints.

themselves. Rehabilitation professionals have long taken an active interest in developing and using technology to assist in rehabilitation (Figure 1). Therapy catalogs such as the Sammons-Preston catalog (http://www.sammonspreston.com/) contain dozens of devices designed to assist in upper extremity therapy after stroke. Much of this technology tries to meet one or more of three goals: increasing activity, providing assistance, and assessing outcomes (Table 1).

Implicit in the development of this technology was the idea of *partial automation*; that is, the technology might allow patients to practice some of the repetitive aspects of rehabilitation therapy on their own, without the continuous presence of the rehabilitation therapist.

1.2. Enter the Engineers

In the late 1980’s and early 1990’s engineers began to realize that robotic devices could potentially be adapted to better fulfill these same goals [2, 3]. This work was a logical continuation of work on what were probably the first robotic devices for rehabilitation therapy: the active dynamometers, such as the Lido and Biodex machines,

Table 1. Typical goals of older, simpler therapy technology, and how robotic devices further these goals.

Goals of therapy technology	Example of simple, existing technology	How robotic devices further these goals
Increase Activity: provide activities that allow stroke patients to independently exercise and practice functional tasks.	therabands, pegboards, blocks	Robots can simulate a variety of computerized activities and quickly and automatically switch between them.
Provide Assistance: assist patients in positioning or moving the hand or arm with a therapeutic goal.	Splints, arm supports	Robots can generate arbitrary patterns of assistance or resistance force against the patient’s limb, and automatically adjust this force based on performance.
Assess Outcomes: measure the movement performance of patients.	Grip force measurement devices, electrogoniometers, timers	Robots can assess performance in an integrated and objective way using their sensors.

Figure 2. Some of the first robotic therapy devices for the arm to undergo clinical testing (left to right: MIT-MANUS [2], MIME [4], the ARM Guide [5]). These devices were designed to provide active assistance to patients during reaching movements with the arm.

developed in the late 1970’s and early 1980’s (Figure 1). Here we define a robot to be a device that can move in response to commands (cf. American Heritage Dictionary). Active dynamometers incorporate a computer-controlled motor, and thus fit this general definition of a robot. They include a kit of levers and bars that can be attached to the motor. The levers are designed to work with different limbs and joints (e.g. elbow flexion/extension, or should abduction/adduction), allowing patients to exercise a joint while the motor resists or assists movement. The dynamometer senses the torque and limb rotation that the patient generates, and displays this information to the patient and therapist for visual feedback and outcomes documentation.

Robotics engineers realized that not only one-joint robotic devices with simple controllers like active dynamometers could be used in therapy, but also more sophisticated robotic mechanisms with more than one joint and more sophisticated controllers (Figure 2). Engineers began to delineate possible benefits of robots, in a way that aligned with many of the therapists’ technological goals defined above (Table 1). Engineers also explicitly promoted the goal of *partial automation*: robots had the potential to allow the patient to practice some of the repetitive aspects of rehabilitation therapy on their own, without the continuous presence of the rehabilitation therapist.

1.3. A Skeptical Reception by Some Clinicians, and a Collaborative Approach by Others

Some clinicians expressed skepticism toward the idea that robots could help them meet rehabilitation goals. Skeptical clinicians had good reasons to be skeptical that included the following points:

1) *Robots cannot match therapists’ expertise and skill.* Therapy involves manual skills that are learned over the course of years by experience under the guidance of expert mentors. Some of these skills require sophisticated manual manipulations of complex joints (e.g. mobilizing the patient’s scapula). An alert and perceptive therapist alters her therapy goals and assistance based on a complex, ongoing consideration of the patient’s state and progress. In brief: hands-on therapy requires expertise and is complex; it seems doubtful that a robot could replicate hands-on therapy effectively.
2) *Robots are unsafe:* robots are dangerous because they can move patient’s limbs but are not intelligent and sensitive to contra-indications to imposed movement like human therapists. They could move a patient in a harmful way.
3) *Robots might replace therapists.* Also implicit in the dubious reception by some therapists was a concern that robots might replace therapists, just as

> robots had replaced assembly workers in factories. Indeed, another definition of a robot is “a machine designed to replace human beings in performing a variety of tasks, either on command or by being programmed in advance.” (American Heritage Science Dictionary). Most engineers interested in robotic therapy probably never assumed that a robot could replace a therapist, because the job of a therapist is multifaceted and interpersonal, involving much more than just rotely moving limbs. Rather, the goal in the mind of most engineers was consistent with that of therapists’ own previous technological developments (Figure 1): to provide a means for patients to practice therapy on their own so that they could get more therapy at less cost *(i.e. partial automation).*

Other clinicians were of course more receptive to the idea or robot-assisted therapy, perhaps because they saw robotic therapy devices as the logical evolution of technology already being used in therapy. Robotic devices were an opportunity to try to improve on the forms of technology already used in clinics to partially automate repetitive aspects of therapy.

1.4. Incentives for Forging Ahead

Several research groups went ahead and developed robotic therapy devices for the arm, notably, MIT-MANUS [2], MIME [4], and the ARM Guide [5] (Figure 2), collaborating with the rehabilitation professionals who saw potential for these devices. These engineering teams were perhaps bolstered by the insights that robotics, control theory, and computational approaches were giving to the understanding of human motor control in the 1980’s (e.g. [6]). If engineering concepts and technology could help improve understanding of normal human motor control, could they also improve understanding of motor control after neurologic injury? The prospect of developing computational models of motor plasticity using robotic tools was intriguing.

Another motivation in most research team’s minds was the possible business opportunity presented by robotic therapy: more people than ever before were in need of rehabilitation after stroke because of the demographics of aging in industrialized nations and the increased stroke survival rates, and this trend was expected to continue. At the same time, rehabilitation units were being forced to deliver less repetitive therapy because of cost-saving attempts in the health care industry. For example, the average length of stay for stroke survivors in inpatient rehabilitation facilities in the U.S. decreased from 31 days to 14 days after prospective payment system reimbursement was instituted in 1983 [7]. And yet rehabilitation science was finding with increasing certainty that recovery could be influenced by activity: training enhanced use-dependent plasticity (e.g. [8, 9]). Developers of robotic therapy devices thought that robots might help people with a stroke by allowing them access to a greater quantitative of repetitive therapy at less cost than would be possible with one-on-one interactions with a clinician. This access might allow the creation of new businesses, providing an additional incentive to pursue device development.

2. Initial Design Decisions

2.1. But what should the robot do?

To this point, I have spoken of “robot assistance” in general terms – the robot assists the therapist and patient in some way that promotes rehabilitation. When it came time to actually build robotic therapy devices, however, engineers had to determine exactly what the robots were to do – for example, they had to write the computer program that controlled the motors on the robot. Here, engineers encountered a problem: we discovered that the specific movement and assistance patterns that were effective for therapy were relatively unknown. Despite a history of over one hundred years, and the presence of somewhat dogmatic schools of therapy (e.g. Neurodevelopmental Treatment, Brunstrom Technique, Proprioceptive Neural Facilitation [10]), the field of rehabilitation science had at that time few randomized controlled trials that defined the elements of therapy that specifically aided recovery [11]. Clinical practice varied widely, with details of therapeutic techniques sometimes in opposition to each other in different clinics (e.g. should the therapist promote movement within synergy or avoid it? Is movement against resistance therapeutic, or does it increase spasticity?), depending on which school of therapy the clinic’s therapists had been educated in. The general lack of evidence for specific motions to be practiced or assistance patterns to be applied had the practical result that there was not a well-defined scientific basis on which the design of robots and computer algorithms for movement training could be based.

2.2. A Logical Target: Active Assist Exercise

Despite this uncertainty, or perhaps because of it, the therapeutic target that the robotic therapy research teams chose for MIT-MANUS, MIME, and the ARM Guide was the same: active assist exercise, and, indeed, this technique has continued to be the primary target for robotic therapy devices. In this technique, the therapist manually assists the patient in achieving desired movements. The “active” refers to the patient being active and engaged; i.e. the patient tries to move during the exercise. The “assist” refers to the therapist manually assisting the patient, but only as much as needed. Researchers chose this technique as a target because most of the schools of therapy seemed to incorporate active assist exercise as an element [10]. As a result, application of this technique could be witnessed on almost any day on a visit to almost any rehabilitation clinic. The technique was also amenable to robotic implementation – assisting movement was something robots could do.

It was also straightforward to conceive of a scientific rationale for active assist therapy, although the rationale was speculative rather than verified:

1) *Suppleness Enhancement:* at the lowest level of motor control of biomechanics and reflexes, active assist exercise stretches soft tissue and muscles, which might be helpful for preventing contracture and reducing spasticity.
2) *Plasticity Enhancement*: at a middle level of motor control, active assist exercise provides the patient’s motor system with somatosensory stimulation that would normally not be available because the patient is paretic. Somatosensory input had recently been shown to drive cortical plasticity [12].

3) *Motivation Enhancement:* at a high level of the motor system, active assist exercise may motivate patients to exercise. If a patient cannot move well on his own, he are she may be disinclined to try to move. Active assist exercise allows the patient to be successful in achieving a desired movement, presumably motivating practice and effort [13]. However, it should be noted, assisting too much with a robot may decrease effort [14].

As stated earlier, the field of rehabilitation science was not well established and none of these rationales was scientifically proven at the time. They still remain largely unproven today, even though most robotic therapy devices still focus on implementing active assist exercise.

2.3. But what joints?

A decision also had to be made about which joints of the upper extremity to focus on, as development of a robotic exoskeleton that can assist in all joint movements of the upper extremity was and remains an unsolved problem, especially for the hand and shoulder complex. The first robotic therapy devices for the upper extremity that were clinically tested (i.e. MIT-MANUS, MIME, and the ARM Guide, Figure 2) focused on providing active assist exercise for elbow flexion/extension and for limited shoulder movements (e.g. shoulder flexion below 90 degrees and limited external rotation). Three reasons for this choice were:

1) *Simplicity:* these joints were viewed as simpler than the hand, wrist, and complex shoulder movements.
2) *Availability of tools:* robots had already been developed to study motor control at these joints, and thus there were technological precedents and scientific concepts from which to build. For example, MIT-MANUS was essentially the same robot that was concurrently being used in early, influential studies of motor adaptation [15]. MIME used an industrial robot that had the scale of human arm movements.
3) *Pragmatism:* the hand often appears to be hopelessly impaired following stroke, and shoulder problems such as subluxation are governed by complex biomechanical and neurological mechanisms which would be very difficult for a robot to address. Reaching movements with the arm are needed for a lot of functional activities. Robotic therapy research teams therefore aimed to achieve functional improvements by making robots that focused on reaching movements with the arm.

It is worth noting that it is still unclear which joints to focus on for an optimal therapeutic result because of a lack of clinical trials addressing this question. Intriguingly, a device focused on simple wrist and forearm movements, the BiManuTrac, has produced the largest changes in impairment observed with robotic therapy to date [16].

2.4. And what types of movements?

Finally a related decision had to made about what types of movements the patient would perform with robot assistance. Should the movements be single-joint or multiple joint? Should they be fast-as-possible or slow? Should they avoid abnormal synergy patterns or work to build strength in those patterns? Bimanual, with two robots, or unimanual? Should they have a functional goal?

The motions used by MIT-MANUS in the first clinical trials were unimanual pointing movements in the horizontal plane [17]. The patient was instructed to move a cursor to a target. After attaining the target, the target moved to a new location. The robot helped the patient to make the movement to the target, following a normative trajectory (minimum jerk trajectory) [17]. This type of paradigm had been used often previously in motor control research. It required multiple-joint coordination, and was functional in a sense, since pointing (or reaching) is a component of many activities of daily living. MIME and the ARM Guide also focused on unimanual reaching movements. MIME incorporated some bimanual reaching exercises also.

3. Initial Clinical Tests and the Questions they Raised

3.1. First Clinical Results

The basic findings of the initial clinical tests with the first three robotic therapy devices for the arm (MIT-Manus, MIME, and the ARM Guide) were as follows (for detailed reviews, see: [1, 9, 18]):

1. *Statistically Significant Motor Gains:* An additional dose of active assist exercise, delivered with a robotic device with an intensity of several hours per week for several weeks, significantly (in a statistical sense) improved motor recovery in the acute or chronic stage following a stroke, as measured with quantitative measures of range of motion or strength, or clinical impairment scales (Figure 3). Patients typically maintained this improvement at long-term follow-up (i.e. months later).
2. *Modest Motor Gains:* While statistically significant, the gains due to robotic therapy were small – typically 2-6 points on the upper extremity Fugl-Meyer scale [19], which ranges from 0-66 (Figure 3). Functional gains, as measured with clinical ADL scales, typically were even smaller and sometimes not significant [19].
3. *Comparable Motor Gains:* The gains due to robotic therapy were roughly the same size as those due to a matched amount of conventional rehabilitation therapy, or to unassisted rehabilitation practice, as well as comparable between the different robots used (Figure 3). In other words, comparisons between different types of therapy often led to statistically inconclusive results.

Clinical testing of second generation robotic therapy devices has essentially been confirmatory of these findings, as reviewed in a recent systematic review [19].

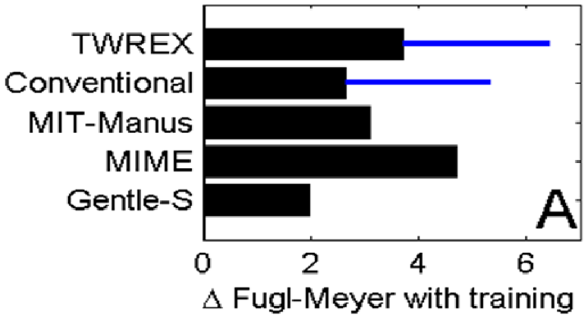

Figure 3. Change in Fugl-Meyer Upper-Extremity Score with one to two months of training several hours per week after chronic stroke, for three robotic devices (MIT-MANUS [17], MIME [4], and Gentle-S [20]), and with conventional table-top exercise [21] and with the TWREX non-robotic exoskeleton [21] (see Figure 4). The Fugl-Meyer score varies from 0 (complete paralysis) to 66 (normal movement ability).

3.2. Questions Raised by Initial Clinical Testing

This initial clinical testing raised two important questions:

1. *The Question of Necessity:* Was the robot necessary for the observed therapeutic benefit? I think the clearest way to express this question is as follows [22]: Consider a control group for which the motors of the robot are removed but the joints are allowed to move freely such that the robot allows movement but does not assist movement. The unactuated robot provides the same audiovisual stimulation, and the control group undergoes a matched duration of unactuated therapy. Would this control group recover less than a group that exercised with the actuated robot? If not, this would suggest that the robotic properties themselves (i.e. the programmable actuators) were superfluous. This result is scientifically plausible because, with regards to motor plasticity after stroke, we know that practice is a key (or perhaps *the* key) stimulant for motor plasticity.
2. *The Question of Optimization*. If one accepts that the robotic properties of robotic therapy are helpful for enhancing recovery, a logical question is how sensitive are therapeutic benefits to the optimization of the robotic parameters? The first robotic therapy devices elicited therapeutic benefits comparable to each other, even though they were fairly different in their design and approach (e.g. number of degrees of freedom, details of the form of assistance provided, stiffness levels). Can tuning the robot geometry and control algorithm increase the therapeutic benefits? Or will any reasonable robot (or non-robotic therapy) give approximately the same result?

4. State of the Field Today

4.1. Progress in answering questions about the necessity and optimization of robotic actuation

Few randomized controlled trials have yet addressed whether robotic actuation is necessary for therapeutic benefit and how much it can be optimized. A recent exception was a study that found that chronic stroke patients who received a fixed dose of active assist therapy for the hand from a robotic device (HWARD) recovered significantly better than a group that received half as much active assist therapy [23]. The number of patients included in this study was small (n = 13) and the baseline characteristics of the subjects were slightly mismatched, however, so the result needs to be examined with a larger study. The additional advantage due to more active assist therapy was moderate (about 3 extra Fugl-Meyer points).

Notably, the process of answering the necessity and optimization questions is theoretically endless because of the problem of “unlimited alternatives”. That is, even if a randomized controlled trial demonstrates that the robotic properties being tested were unnecessary to generate the observed benefits (i.e. a group trained with an unactuated technique at similar dosage receives similar therapeutic benefits), or even if an interesting tweak of a robot’s parameters does not substantially alter the clinical outcomes, such a negative finding would of course only be for one particular instantiation of robot therapy. Other robots or different control algorithms, some maybe as yet unconceived, may produce better results. Since there are an infinite number of possible robots and robot control algorithms, it may be impossible to provide definitive answers to these questions. In addition, establishing negative results (i.e. no difference between therapy groups) with a high level of precision requires large subject populations because of the high inter-subject variability in stroke patients and the nature of statistical power, again adding effort, cost, and time to the process.

4.2. Trends in the Field

If the field has not focused on answering the necessity and optimization questions with clinical trials, what has it focused on? Three trends mark the field of robotic therapy for the upper extremity today:

1. *Rapid Proliferation of Innovative Hardware.* Many cleverly designed robotic devices have been or are being developed to assist at different joints, at more joints, or at the same joints as before with improved weight, mass, or control properties (Figure 4, see review: [1]). Non-robotic approaches are also being developed, such as devices that passively relieve the weight of the arm [21, 24]. Initial testing suggests that passive devices may have similar clinical benefits with lower cost and theoretically-better safety [21] (Figure 4). Several companies are now selling upper extremity devices, and sales of these devices number in the hundreds.
2. *Development of New Control Strategies.* Most current research on control strategies still focuses on active assist exercise. To improve active assistance algorithms, researchers are exploring several strategies, including:

Figure 4. Recently developed robotic and non-robotic therapy devices. *Upper left*: NeReBot: a 5 DOF cable robot that can be used next to a patient's bed [27]. *Bottom left*: ArmIn: a highly responsive robot that allows naturalistic arm movement, including shoulder translation [28]. *Middle top*: Rupert: a lightweight exoskeleton actuated with pneumatic muscles, which can be worn by the subject [29]. *Middle bottom*: T-WREX – a non-robotic arm support device [21]. *Upper right*: HWARD – a 3 DOF hand and wrist robot [23]. *Lower right*: A cable driven glove that can be worn, and driven by a motor or the patients shoulder shrugs [30].

- *Improved Compliance and Feedforward Control:* These efforts include methods to make robots more compliant but still able to assist in spatial movement, by incorporating feedforward control [25, 26]. Compliance may have the advantage of making the patient feel more in control of therapy, and thus more engaged. It also preserves the relationship between motor commands that the patient generates and actual movement direction, which may allow patients to better optimize motor commands, since they receive accurate information about the results of a change in their motor command, whereas a stiff robot will always enforce the same trajectory.
- *Adaptive Control:* Several groups are making the controller adaptive, so that the robot changes its assistance based on ongoing sensing of patient performance [25, 31, 32]. The key concept here is that patient ability changes during therapy, and it would theoretically be best to keep the patient appropriately challenged, for provoking motor learning.
- *Optimization:* Optimization theory allows the goals of the therapy to be expressed as a high-level control objective. For example, for active assistance, my research group has proposed to minimize a weighted sum of patient movement error and robot assistance force [33]. Minimization of this cost function thus helps the patient achieve a desired trajectory, but with as little robot force as possible (Assistance-as-needed). Optimization theory provides a means to derive the robot therapy controller that mathematically optimizes the cost function. Within an optimization framework, robotic therapy controllers can be rigorously proven to satisfy a "high level" goal, rather than being based on ad hoc strategies devised by the research team.

- *Neuro-Computational Modeling:* My own research group has also begun to develop computational models that model what the patient's brain is computing during therapy to gain insight into how better to design robotic therapy controllers [34, 35]. The concept here is that if we can mathematically model how behavioral signals drive adaptation, then we should be able to design control strategies that mathematically optimize adaptation.

Other therapeutic paradigms besides active assistance are also being explored including:

- *Error amplification strategies* [36, 37]: The concept behind this approach is that movement errors drive motor adaptation, and thus assistance may be the wrong approach to take if the goal is to enhance motor adaptation, since assistance reduces movement errors. Amplifying errors may improve the rate or extent of motor adaptation by better provoking motor plasticity. Clinically, this technique has only been shown to be effective in reducing curvature errors during supported-arm reaching in the short-term [38].
- *Virtual environments (see review:* [39]*)* Another alternate therapeutic paradigm that differs from the active assistance paradigm that dominates the field is to use the robot to create a virtual environment that simulates different therapeutic activities. In this paradigm, the robot may not physically assist or resist movement, but instead just provide a training environment that simulates reality. Potential advantages of training in a haptic environment over training in physical reality include: a haptic simulator can create many different interactive environments simulating a wide range of real-life situations; quickly switch between these environments without a "set-up" time, automatically grade the difficulty of the training environment by adding or removing virtual features; make the environments more interesting than a typical rehabilitation environment; automatically "reset" itself if virtual objects are dropped or misplaced; and provide novel forms of visual and haptic feedback regarding performance. In this haptic simulation framework, robotics may benefit rehabilitation therapy not by provoking motor plasticity with special assisting or resisting control schemes, but rather by providing a diverse, salient, and convenient environment for semi-autonomous training.

3. Rehabilitation Therapists are Accepting Robots as Scientific but not Clinical Tools. A third trend is that while rehabilitation therapists are not widely incorporating commercial robotic therapy devices for clinical use, they are using robots in their research. The research therapists in the conference that led to this book are setting the pace: they are doing groundbreaking scientific work using robotics and related technology, as can be read in this book's other chapters (see chapter by Mataric, for example).

5. Conclusion

As mentioned in the Introduction, in the early 1990's there were only a handful of robotic devices being developed for upper extremity training after stroke. In 2008, there are dozens of devices being developed. However, robotic therapy has not become a standard therapeutic treatment in most clinics. What impedes clinical acceptance?

One important factor is that the therapeutic benefits of robotic therapy are modest, and have not been shown to be decisively better than other, less expensive approaches that can partially automate therapy (Figure 1). In other words, the necessity question remains unanswered. There is little motivation for most clinics to buy expensive robots until it is proven that the robots yield therapeutic or cost benefits that are substantially better than current approaches.

The field seems to be investing the majority of its resources in developing new devices, rather than in understanding and optimizing the content of robotic therapy. One explanation for this phenomenon is that there is a lack of devices for certain movements and applications, such as hand movement and naturalistic arm movement, and the new technology addresses this lack, as well as improving features such as portability and force control response (Figure 4). But another possible factor is that engineers like to build devices and are good at it. Engineers' motivation and expertise for scientifically exploring the clinical effects of their devices is more limited, and this may signal the need for an even greater role by clinician scientists.

The field will likely have to evolve to place more focus on scientific studies of the mechanisms of motor plasticity to optimize technology, improve the benefits of robotic therapy, and determine if routine clinical use makes sense. The question of "What are the maximum benefits that we can obtain with robotic therapy?" can be illustrated by a boy playing with a stomp rocket (Figure 5). A dose of robotic therapy is like stomping on the air bladder. The altitude that the rocket reaches is like the resulting improvement in motor control. The boy can increase the rocket altitude by stomping harder, just like a robotic device can increase recovery if it uses an optimal training paradigm, but there is a limit to how the rocket, and likely recovery also, can go. For upper extremity recovery, the limit is probably dictated by the number of spared corticospinal neurons following stroke. The limit for the rocket is well short of the Eiffel tower, despite the perspective shown in Figure 5. Does a trick of perspective make us think that the limits for recovery enhancement that are possible with robotic therapy are higher than they really are, if indeed the amount of cell loss defines them?

Addressing the following two key questions would help answer this question, and advance robotic therapy development:

1. *What behavioral signals provoke plasticity during rehabilitation*? Knowing these signals would allow us to design robots that optimally influence those signals. This would provide answers to questions like "What type of forces (error attenuating or error amplifying)?, "What joints?", "What movements?", and "What type of feedback?".
2. *What are the fundamental limits to the plasticity that can be provoked with behavioral signals?* Answering this question would define the limits we should expect of robotic therapy optimization. It would thus allow us to determine how much time to invest in optimizing robotic therapy itself. If the cost function is relatively flat and we are already close to an optimum, it may

Figure 5. What are the maximum benefits that we can obtain with robotic therapy?

make sense to focus more attention on approaches that combine cell- or molecule based regeneration techniques with robotic therapy, in search for a synergy that improves clinical results beyond that achievable with either robots or regeneration alone.

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