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UNIVERSITY OF CALIFORNIA,
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Effects of Robotic Challenge Level on Motor Learning, Rehabilitation, and Motivation:
The Real-World Challenge Point Framework

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY
in Mechanical and Aerospace Engineering

by

Jaime E. Duarte

Dissertation Committee:
David J. Reinkensmeyer, Chair
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2014

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DEDICATION

To my mom and dad for their unconditional love and support.
To my sister for always being my best friend.

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ABSTRACT OF THE DISSERTATION

Effects of Robotic Challenge Level on Motor Learning, Rehabilitation, and Motivation:
The Real-World Challenge Point Framework

By

Jaime E. Duarte

Doctor of Philosophy in Mechanical and Aerospace Engineering

University of California, Irvine, 2014

David J. Reinkensmeyer, Chair

Robotic devices have emerged as promising solutions to support motor training in physical rehabilitation, surgery, and sports, but the optimal control strategies for robotic motor training are still unclear. This dissertation focuses on the development and evaluation of algorithms that modulate the challenge level experienced by a trainee in order to optimize training. Challenge level has been proposed to affect both motor learning and motivation, but these effects, in the context of robotic-based training, are not well understood. To understand these effects, we developed three novel experimental paradigms and studied motor learning of a complex motor skill in humans, and motor rehabilitation after spinal cord injury in a rat and in a non-human primate model.

The first experiment focused on motor learning in humans without impairment. We modulated the difficulty of a virtual golf task by either reducing or augmenting kinematic errors with a haptic robot while participants putted to two target locations. We found that the training conditions had mixed effects on learning, but significantly affected participants' subjective experiences of training. Specifically, robotically reducing errors improved self-reports of competence and satisfaction, while augmenting

errors worsened reports. These effects persisted days after the robotic manipulations ceased, even when participants' performance returned to normal. These results indicate that robotic training can modulate, with lasting effects, the subjective experience of training.

The second experiment focused on hand motor rehabilitation after spinal cord injury in a rat model. We modulated the difficulty of a pulling task by controlling the force level required to achieve success. Rats trained either with constant, low forces, or with an adaptive algorithm that controlled the success rate to be 50%. We found that animals in the low-force group attempted more pulls and were more successful at achieving the task than animals in the adaptive group. However, animals in the adaptive group recovered more grip pulling strength, as evidenced by higher pulling forces in the assessments conducted throughout the rehabilitation process. Thus, the benefits of training at an adaptively-controlled, high-challenge level exceeded the benefits of increased numbers of practice repetitions achieved at a lower challenge level.

The third experiment focused on hand motor rehabilitation after spinal cord injury in a non-human primate model. We developed a robotic device that provides in-cage, self-training exercises for animals with a spinal cord injury that affects their ability to use the right hand. The device uses training algorithms that accommodate animals with a wide range of capabilities to ensure they can engage in training even after suffering a severe injury. We found that animals were able to train with the device both before and after the lesion by setting the appropriate difficulty level.

These findings lead us to propose the basis for a framework to understand the effect of challenge on performance gains and motivation during unsupervised learning for robotic-based motor training. This framework proposes that in environments where the trainee chooses training amounts, total learning is determined by the product of

two component relations: 1) the challenge level and training frequency, and 2) the challenge level and learning-gain per trained movement. Since the challenge level has opposite effects on these component relations, this product yields a parabolic relation between the challenge level and the learning-gain per training frequency. Thus we can find a challenge level where total learning is maximum. The challenge level corresponding to this maximum represents the optimal challenge level for unsupervised training. Robotic training devices provide a means to both identify this optimal challenge point and control the challenge level so that training can be carried out around that point.

Chapter 1

Introduction

1.1 Conceptual Framework of the Dissertation

Movement drives our interaction with the environment. From kicking a ball to reaching for a glass, our bodies constantly plan the appropriate commands and send the corresponding signals that drive this interaction. These commands and signals, however, can vary greatly from one execution to the next, even when the goal of the movement is the same. In fact, they can vary so much that as a society we value greatly the few people who can perform specific movements with high accuracy and precision as in the case of surgeons or athletes.

The process by which we acquire and develop the skills necessary for the execution of a movement is called motor learning. In this process—critical in any occupation that requires skillful performance—neural connections are reshaped to improve the generation and transmission of signals between the central nervous system and those muscles involved in the movement. Although the specific details of how the neural circuitry is reshaped are not known, we do know that a great number of repetitions—

involving as many as 10,000 hours of deliberate motor training [31]—are needed before mastering a given motor skill.

The importance of a high-volume of repetitions in motor training means there must also be a high degree of motivation by the trainee that partakes in the training. An important factor that affects the motivation to participate in training, as well as the gains derived from this training, is the level of challenge experienced during training. Training programs in which tasks are too difficult can lead to frustration and diminished levels of self-efficacy and motivation. On the other hand, tasks that are too easy will not be engaging and lead to low adherence rates.

This dissertation focuses on the development and evaluation of algorithms that modulate the challenge level experience by a trainee in order to optimize training. We will explore both motor learning and rehabilitation paradigms in human and animal models.

1.2 Rehabilitation of the upper extremity

As of 2013, an estimated 273,000 people in the United States are alive today with spinal cord injury (SCI). Since 2010, more than 50% of the injuries have led to loss of control of the upper extremities due to partial (40.6%) or complete (10.6%) injury to the cervical region of the spinal cord (tetraplegia) [18]. For these individuals, recovery of hand function is the top priority when compared to restoration of sexual function, trunk stability, walking and other needs [6]. Other neurological injuries, such as stroke, and traumatic brain injuries may also have significant impacts in a person's ability to use his or her hands. In the United States alone, there are more than 7 million stroke survivors [95]. The quick onset of these injuries can have significant

effects on the quality of life of patients who—from one day to the next—are in some cases unable to perform basic everyday activities.

An injury to the motor system, such as a stroke or spinal cord injury, affects the neurological circuitry involved in the execution of movement. In the case of a stroke, the injury can take place where these signals originate and therefore the signals are not properly generated, and the injury can also destroy the white matter tracts that transmit the signal to the muscles. In the case of a spinal cord injury, the signals are properly generated, but the transmission of the signal is compromised in the spinal cord and the quality of the signal is diminished, or in some cases completely blocked. In either case, following the injury, patients must re-learn how to execute movements relying only on the spared circuitry and transmission pathways.

Following an initial period after the injury in which unique plasticity mechanisms triggered by the injury contribute to neural reorganization (so called 'spontaneous recovery' [101]; [33]; [13]), the re-learning process required to recover motor function is similar to the process originally carried out in the acquisition of a motor skill [23]. To improve recovery, rehabilitation programs then require individuals to actively engage in high-volume training where they are asked to perform hundreds, or even thousands, of repetitions of a given movement using the impaired limb. Results from a randomized control trial on humans suggests that as much as 6 hours of rehabilitation training per day is needed to reach significant recovery [118]. Contrary to this need, however, patients with hemiparesis or hemiplegia (i.e. weakness or paralysis of one side of the body, respectively), will tend to favor—sometimes completely—their unimpaired hand. This response to the injury may at times even lead into a behavior known as learned non-use whereby a patient's impaired hand loses even more functionality due to a lack of use[107]. A critical component in the recovery process thus lies in a patient's willingness to use the impaired limbs.

1.3 Use of robots in rehabilitation and motor training

Robots provide significant advantages in the field of motor training over conventional training approaches. Two key advantages are: 1) increased intensity and volume of training, and 2) high degree of quantification during training.

In rehabilitation, trainees must go through intense and high-volume training in order to recover movement after a neurological injury. However, physical rehabilitation can be a very labor-intensive process, sometimes—as in the case of gait training for a person with a severe gait disability—requiring multiple therapists to administer a single session. With today's aging population and an increasing number of neurological injuries, there is an insufficient supply of therapists to appropriately address the therapy needs of patients. One of the major goals of using robots in physical therapy is to decrease the workload on therapists by creating training programs that minimize the supervision needed thus providing more patients with the intensity and volume of rehabilitation training needed for recovery.

An important component in any motor training program is the ability to accurately and consistently assess the improvements and overall progression of the trainee. Regarding accuracy, current assessments are, for the most part, behaviorally-based and subjective. These tests, such as the box and blocks in humans, or the BBB test in the rodents [14], provide high-level measures (e.g. number of blocks moved from one container to another) of a limb's functionality. These assessments, although appropriate at assessing overall functionality, may lack the resolution to appropriately measure the effects of a given therapy on a patient. This lack of resolution can lead to interventions that are incorrectly deemed ineffective. Regarding consistency, these types of assessments often need to be carried out by expert therapists or trainers in order to reduce the variability associated with the measurement. Robots, with their

built-in sensors, can serve as important tools to improve the accuracy and consistency in quantifying recovery [53]. They can provide measurements at higher resolutions (e.g. three-dimensional kinematic trajectories) and with lower variability between assessments. The use of robotics, coupled with other technologies such as neuroimaging and pharmaceutical interventions, will lead to a better understanding of the mechanisms involved in rehabilitation after a neurological injury [23].

Similar to rehabilitation, motor training of healthy individuals can be very labor-intensive, requiring a significant involvement by coaches and/or trainers to prepare people in fields such as surgery, athletics, or music to excel in their performance. In addition to this, the quality of the feedback given about performance is directly dependent on the quality of the coach or trainer. The use of robots as tools for motor training can provide advantages both in the quality and quantity of training. The ease-of-access to computers and the decrease in the production cost of sensors and actuators means that robots—both simple and complex—will be readily available to supply the demand for effective quantification of performance. This trend is already apparent in the consumer electronics market with the proliferation of activity trackers that measure parameters such as the number of steps we take in a day to the movements executed in a round of golf. And we are also seeing this trend from groups such as the Computational Interaction and Robotics Laboratory out of Johns Hopkins University who are working to improve and speed-up the training of surgeons using robotic-based approaches [88].

The first part of this work focuses on the development of novel robot-based training paradigms that enhance motor learning in humans. We now know that practice of a motor task drives adaptation of the neural networks involved in its performance [48]. Significant changes in cortical representation have been observed for stroke patients, for example, after constraint-induced therapy [58]. Furthermore, evidence

suggests that similar mechanisms are at play both during the initial learning of a motor skill and the re-learning process following neurological injury [23]. Understanding the mechanisms involved in the acquisition of motor skills will lead to training algorithms that improve motivation, performance, and retention following a robotic intervention.

1.4 Animal models and robotic rehabilitation

The study of animal models is of great importance in the field of robotic rehabilitation. These models allow studies with consistent injury types and interventions in controlled laboratory settings [23], [80] and allow invasive techniques to understand mechanisms of recovery; something not feasible with humans. Interventions can range from physical rehabilitation to pharmacological agents to regenerative treatments [81], [106] and are, for the most part, based on rodent and non-human primate models. These two models are used because they provide a simplified version of the human central nervous system while keeping important similarities with humans.

Potential treatments are first tested on rodent models. Those which prove successful are ideally, but not always, then tested on non-human primate models before going on to clinical trials with humans. It is important to go through the non-human primate model in order to gain insight into the dosage increases and potential side-effects before moving on to the human population [20]. For more complete insight into the importance of animal models, including the advantages and disadvantages, in studying neurological trauma, please refer to [15] and [56].

As with humans, robotic devices are now being used in the rehabilitation of animals following neurological injury. This is a fairly new field of research where most robotic devices have focused on the rehabilitation of gait in rodent models after spinal cord injury [89]; [34]; [79]. Robotic devices have now started to be used for training of the upper extremity following injury with animal models. For example, Spalletti recently reported on a robotic device to study rehabilitation following an induced ischemic lesion on a rodent model [104]. The advantages of using robots for rehabilitation with animal models are similar to those in humans. Namely, they allow for high dosages of training with high-resolution measures of recovery. This, complemented with the benefits of consistent lesions in highly controlled laboratory environments, presents great potential for the development of therapies for clinical trials.

1.5 Outline of this document

This dissertation focuses on understanding the relationship between the difficulty level of a training task and its effects on motor learning and motivation. These relationships were studied using three robotic-based approaches with models of motor learning and neurorehabilitation in humans and animal models.

1. The first experiment focused on motor learning for humans who trained in a virtual game of golf putting.
2. . The second experiment targeted the rehabilitation of grip strength for rats following injury to the spinal cord using a novel device called the Robotic Rehabilitator for the Rodent Upper Extremity (RUE).

3. The final experiment focused on the rehabilitation of hand function for monkeys following injury to the spinal cord using a novel device called the Bimanual Vending Machine (BVM).

Chapter 2 represents preliminary results for the first two experiments: 1) error-based training algorithms and their effects on motivation and performance for a virtual golf putting task, and 2) performance-based algorithms and their effects on motivation and performance when training grip strength in a rodent model after injury to the spinal cord. This work laid the foundation for the central theme of this dissertation: the Real-World Challenge Point Framework. This was presented in the IEEE International Conference on Rehabilitation Robotics 2013 (ICORR 2013) where it received the Best Student Paper award.

Chapter 3 presents the complete results of the virtual golf experiment. It provides a full description of the methodology used in the experiment, as well as additional results beyond those presented in Chapter 2. A key theme is how altering subjects' performance errors, either by reducing or amplifying them, impacts their performance, motor learning, and motivation while performing the task.

Chapter 4, presents the results of RUE as an assessment tool. It also provides details of a spinal cord injury's effect on performance at this novel task. Furthermore, it describes the advantages of robotic-based assessments for assessing the pulling strength of rats using self-initiated, volitional, movements. This chapter shows that this method provides the resolution necessary to assess the functional task of pulling both before and after a cervical lesion to the spinal cord.

Chapter 5 expands on the results presented on Chapter 2. Whereas chapter 2 was a preliminary analysis of the first 120 days of training following injury, this chapter presents the data for more than 200 days of training following injury. It further an-

alyzes the effects that the difficulty level of the task had on both the motivation and the recovery of the animals following injury. We present the basis for a framework to understand the effect of challenge during unsupervised learning, including the predicted level of difficulty that optimizes recovery for this rat model of SCI.

Finally, Chapter 6 discusses the Bimanual Vending Machine, a robotic device designed to provide in-cage, automatic therapy for non-human primates. This work is part of a collaboration with the UC primate consortium - a group of scientists from UC San Diego, UC San Francisco, UC Los Angeles, UC Davis, and UC Irvine whose work focuses on testing promising spinal cord regeneration techniques using a non-human primate model of spinal cord injury. The goal of this project is to provide intense rehabilitation to animals receiving regenerative treatments for recovery following a spinal cord injury while constantly monitoring and quantifying their performance and recovery. We present results showing how the device is effective for training naive animals on a pulling movement. These results also include successful cases of animals that have been trained both pre- and post-lesion.

Finally, Chapter 7 reviews the main contributions of this dissertation to the field of robotic rehabilitation.

Chapter 2

Effort, performance, and motivation: Insights from robot-assisted training of human golf putting and rat grip strength

Jaime E. Duarte, Berkenesh Gebrekristos, Sergi Perez, Justin B. Rowe, Kelli Sharp, David J. Reinkensmeyer

2.1 Abstract

Robotic devices can modulate success rates and required effort levels during motor training, but it is unclear how this affects performance gains and motivation. Here we present results from training unimpaired humans in a virtual golf-putting task, and training spinal cord injured (SCI) rats in a grip strength task using robotically modulated success rates and effort levels. Robotic assistance in golf practice

increased trainees feelings of competence, and, paradoxically, increased their sense effort, even though it had mixed effects on learning. Reducing effort during a grip strength training task led rats with SCI to practice the task more frequently. However, the more frequent practice of these rats did not cause them to exceed the strength gains achieved by rats that exercised less often at higher required effort levels. These results show that increasing success and decreasing effort with robots increases motivation, but has mixed effects on performance gains.

2.2 Introduction

Robotic devices that are designed for motor training and rehabilitation can assist their users in achieving desired tasks, such as when they implement assist-as-needed or patient-cooperative training strategies. They can also make tasks more difficult, such as when they implement error augmentation or challenge-as-needed strategies [110], [68], [76]. A complex picture is emerging as to how these strategies affect motor gains. In some cases, these strategies have been found to have no incremental benefit on motor learning or rehabilitation, or even to be detrimental, while in others they seem to aid it [93]. A little-studied aspect of robot-enhanced training is its effect on motivation. Patients sometimes remark that they are motivated by assistance [92], but this increased motivation has not been well quantified. Understanding how human-robot interaction affects motivation is important for understanding the mechanism of performance gains achieved during training, as motivation influences learning [77], [24]. It is also important for understanding how robotic devices might actually be used in the ‘real world’, in which users are less constrained with respect to how often they must practice with a robotic device compared to laboratory tests that carefully control practice amounts.

Here we report preliminary results from two experiments in which we robotically modulated success rates and effort levels and quantified the effect on motivation and performance gains. In the first experiment we studied how unimpaired trainees responded to error-reducing or error-enhancing force fields in a virtual golf-putting task, using questions from the Intrinsic Motivation Inventory to assess motivation and effort and putt variability to assess performance gains. In the second experiment, we studied how frequently rats with a SCI self-trained their grip function in a robotic strength training task, when the force required by the task was either large or small. We used the number of attempts at the task in a fixed period as a marker of motivation, and quantified performance gains in terms of the strength gained after training.

2.3 Methods

2.3.1 Virtual golf putting training for humans

Subjects

Thirty healthy subjects (age 20-30, 8 females, 1 left-handed) with no history of neurologic disorders participated in the experiment. Each participant provided written informed consent in accordance with a protocol approved by the University of California-Irvine's Institutional Review Board.

Experimental apparatus and robot-generated dynamic environments

Subjects interacted with a three degrees-of-freedom lightweight haptic robot (PHAN-ToM 3.0 Premium, Sensable Technologies, Inc) through a handle. The robot handle attached to the robot arm through a passive 3DOF gimbals. Subjects controlled a virtual golf club head by moving the handle with the right hand. Motion of the robot arm was constrained to one dimension (left-right with respect to the subject) via software. The robot was used to apply forces to the subjects hand and record the position and velocity of the hand at a sample rate of 1000Hz.

The golf game was designed so that the velocity at which the club crossed the starting position during the downswing (defined as the impact velocity) determined the distance traveled by the ball on the screen. Note that compared to actual putting this design removed the effects of variability in the putting surface and variability in the location and angle of the putter face at impact. The goal was to simplify putting dynamics so that impact velocity uniquely determined putt distance.

The robot was programmed to provide dynamic environments in which a subjects impact velocity errors could be haptically reduced or amplified, or used in its back-driveable mode. In the haptic error-reduction training (ER) condition, the robot decreased velocity errors proportional to the predicted error for each putt. In the haptic error-amplification (EA) training condition, the robot increased the velocity errors proportionally to the predicted error. Subjects in the control group (CTRL) experienced no forces from the robot during training. The force field was defined as follows:

$$F_x = \begin{cases} -B_{ER}\dot{x} & \text{error-reduction} \\ B_{EA}\dot{x} & \text{error-amplification} \end{cases} \quad (2.1)$$

The gains used, B_{ER} and B_{EA} , were constant for all subjects and equal to $3.3 \frac{Ns}{m}$ and $3.5 \frac{Ns}{m}$ for the short and long targets in the error-reducing condition, respectively, and $1.5 \frac{Ns}{m}$ and $1.6 \frac{Ns}{m}$ for the error-amplification condition. These gains were chosen after pilot testing with several subjects so that the resulting force field significantly decreased or increased impact velocity errors while being qualitatively unnoticeable to subjects. The goal was to produce a dynamic environment in which subjects did not create a model specific to the haptic robot but rather a model of their arm [51]. The swing for this task can be divided into three main parts: backswing, downswing, and follow-through. Forces were applied only during the downswing by decreasing or increasing velocity errors proportional to the predicted error during the downswing for each putt. The error during downswing was calculated with respect to a target trajectory in the phase space of the swing.

The effect of this algorithm was to define for each putt a target trajectory that began at the actual maximum backswing length of the subject (at which point the head velocity was zero), and then move to the location of the virtual ball with a head velocity equal to the target impact velocity that would cause the ball to move to the center of the selected target (i.e. the short or long target).

Experimental protocol

Subjects were instructed on how to perform a putting-like motion (i.e. an appropriate backswing followed by a smooth downswing and follow through) to play the virtual golf game. The objective of the game was to impact the ball so that it would reach the center of one of two target locations: short or long (requiring an impact velocity of $1.12 \frac{m}{s}$ and $1.65 \frac{m}{s}$ respectively). A trial consisted of first placing the cursor on a predefined starting position a blue rectangle shown on the screen and then performing the

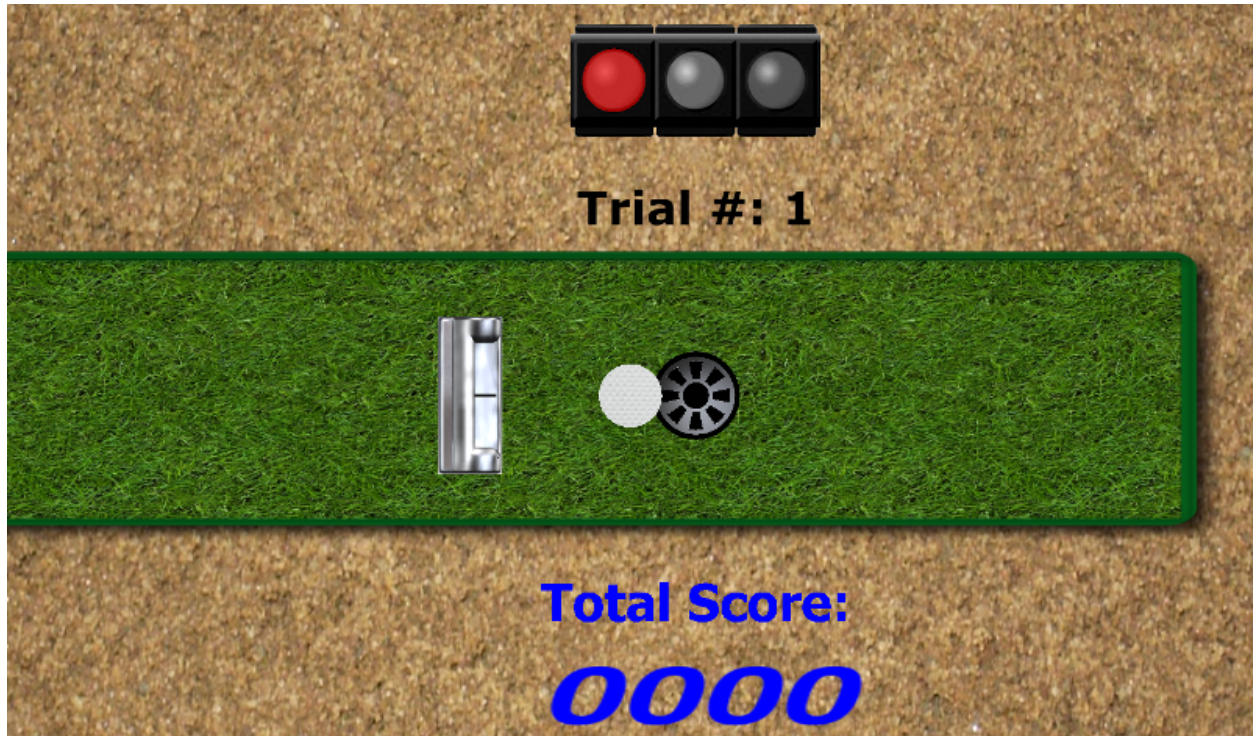


Figure 2.1: **Graphical interface of the virtual golf game** - Participants manipulated the head of a virtual golf putter by means of a 3DOF haptic robot. The objective of the game was for participants to hit the virtual golf ball to the center of the hole shown in the screen. The starting position for each swing was the same, however, the distance of the hole was set to either a short or long distance depending on the current phase of the experiment. A total score based on the distance error from the center of the hole and the number of consecutively made putts was also shown during game play.

putting-like motion. Once the club was held at this position for one second, a golf ball appeared on the screen directly in front of the cursor. The subject then performed the swing to impact the ball.

The experiment was conducted on two separate days for every subject. On Day 1, initial practice day, subjects were asked to perform a total of 100 putts, 50 to each target location. The target locations were randomized prior to the experiment. All subjects were presented with the same randomized order of targets. The purpose of the initial practice day was twofold: (1) familiarize subjects with the task in order to minimize practice effects, and (2) provide an initial putting skill measure that was then used to divide subjects into three training groups with matched average initial performance. This was achieved by ranking the 30 subjects based on their putting performance (defined as their average mean squared error of impact velocity) on Day 1, and then sequentially randomizing the ordered subjects into blocks of three into each training group.

Day 2, training day, was performed 2 to 3 weeks after day 1. It consisted of a total of 170 putts. Although subjects were not told, the 170 trials were divided into three phases: baseline assessment (40 trials), training (90 trials), and short-term retention (40 trials). The target location was randomized for the baseline and short-term retention phases. For the training phase, the same target location was presented in three consecutive trials to allow subjects to adjust their putts based on their performance. This pattern of three putts to the same distance was repeated 30 times during the 90 training trials. Throughout training, participants were asked questions taken from the Intrinsic Motivation Inventory (IMI). These questions aimed at assessing the participants perceived levels of effort and performance throughout the task [96]. During Day 2, subjects were asked to answer these questions once during baseline (after trial 20), twice during training (after trials 60 and 100), and twice during short-term

retention (after trial 140 and trial 170, the end of training). These trials were chosen so as to not interfere with the transitions from baseline to training and training to short-term retention while allowing participants enough time to experience each phase.

Data analysis

We were interested in the effects of training in a haptically enhanced environment on the variability of the impact velocity. We therefore quantified performance as the variance in the impact velocity of the virtual golf ball. Previous studies have shown that highly skilled putters are less variable in their impact velocity, even though mean velocities are similar for less and more highly skilled golfers. This variability also increases with target distance [57]. We defined the variability reduction due to training as the ratio of variability at short-term assessment on Day 2 to baseline variability on Day 2. ANOVA tests were conducted between groups on the different training phases with the significance level set to $\alpha = 0.05$. We were also interested in the effects that modulating participants success rates would have on their perceived levels of efforts and competence. This was quantified using questions from the Intrinsic Motivation Inventory. We used a relative scale in which we subtracted each participants response during training and short-term retention from his or her responses at baseline. The Kruskal-Wallis test was conducted between groups for each question with the significance level set at $\alpha = 0.05$.

2.3.2 Automatic Grip-Strength (autoGSM) training for rats

Subjects

Sixteen Sprague Dawley rats were used for this study. Rats were initially handled for about 3 weeks prior to the beginning of training in order to get them accustomed to human touch. Rats were placed on a food-restricted diet where they received 85% of the normal amount of food in order to motivate them to perform the training task.

Experimental apparatus

A robotic grip strength device was designed and implemented in order to measure and train the ability of rats to use their right forepaw in a pulling task. This device, known as the Automatic Grip Strength Meter (auto-GSM), is a 1 DOF robot consisting of a linear actuator and an automatic food dispenser. The rats interact with the robot by means of a metallic bar that holds a food reward on one of its ends. An acrylic glass box was designed to serve as the training ground for the rat as it allows for easy monitoring of the rat behavior with minimal interference on its behavior. The linear actuator serves as a linear spring that the rats must pull towards themselves in order to reach the food reward. When the spring is at rest the food reward sits behind the acrylic box out of reach from the animal. The device simulates a commonly used test to assess grip strength on rats, the Grip Strength Meter (GSM). This experimental setup allows for testing a volitional task where the animal is motivated to pull the bar until the food is within reach. For more details on the GSM and the robotic device see [85].

The autoGSM robot was programmed to work as a linear spring governed by the equation $F = k\Delta x$. Rats interacted with the robot by means of a metallic bar placed

at the front of the acrylic box. In its rest state ($\Delta x = 0$), the bar came into the box just enough to allow the rats to hold on to it. On the other end of the bar a food tray was placed that housed chocolate food pellets. The rats were trained to pull the bar with their forelimbs until the food pellet was within reach ($\Delta x = \Delta x_{desired}$). Once the bar was pulled far enough, the linear actuator locked the bar in place to allow the animals enough time to retrieve the food reward. If the rat was unable to pull the bar far enough to reach $\Delta x_{desired}$ the linear actuator snapped back into its resting position. A single trial consisted of the rat approaching the metallic bar, pulling it and either reaching $\Delta x_{desired}$ or not. A successful trial was defined as being able to reach the desired pulling length. Trials where the rat started to pull but was not able to reach the desired pulling length were considered unsuccessful.

Rats were placed into one of two training groups: control or autoGSM. In the control group, the stiffness of the spring was set to be as low as possible. This value was determined to be the minimum force needed for the metallic bar to pull away from the animal if the animal did not pull on it. In the autoGSM group, an adaptive algorithm was used to determine the stiffness of the spring. This algorithm, developed by Spencer [105], increased the stiffness value by a set amount δ when a successful pull was achieved and decreased the stiffness value by a value $\delta \times \alpha$ when the trial was unsuccessful. This algorithm seeks to adapt the spring force in order to have the animal pull at its maximum force by the end of each training session.

Rats were surgically intervened to have a unilateral contusion on the fifth cervical vertebra (C5). A contusion of $100kdynes$ was delivered using an Infinite Horizons Impactor (Precision Systems & Instrumentation, Lexington, KY). This type of injury is one of the most clinically relevant models as it simulates a hit to the spinal cord similar to those experienced in car accidents and sporting injuries. Animals were hit ipsilateral

to their dominant paw. All surgical procedures were conducted in accordance with IACUC recommendations.

Experimental protocol

Rats were trained twice a week according to their training group condition. A training session involved placing the rat in the acrylic box and allowing it to pull 5 times with no resistance in the bar prior to training with any forces from the robotic device. This was done in order to remind the rat that pulling the bar led to a food reward. After these initial 5 trials the spring force was activated and the rat began training. A training session was deemed completed if either the animal reached a total of 30 pulls or if 3 minutes had elapsed. Previous experiments from the group had shown these to be appropriate stopping criteria for healthy animals. Once a week, on a day different than the training days, the rats maximum force was tested. Similarly to the training days, rats were allowed to pull 5 times with no resistance before testing. After these 5 pulls testing begun. Testing was done by increasing the stiffness of the spring to a very high value, one with which the animals could not realistically complete the pull. This allowed us to efficiently assess the rats maximum volitional pulling strength. A testing session was deemed complete after three pulling attempts. The maximum force for a given testing session was defined as the maximum value achieved in the three attempts.

Data analysis

We were interested in the effects that modulating the required effort level would have on the rats ability and willingness to pull following injury to the spinal cord. We quantified this by measuring both the number of pulls attempted and the number

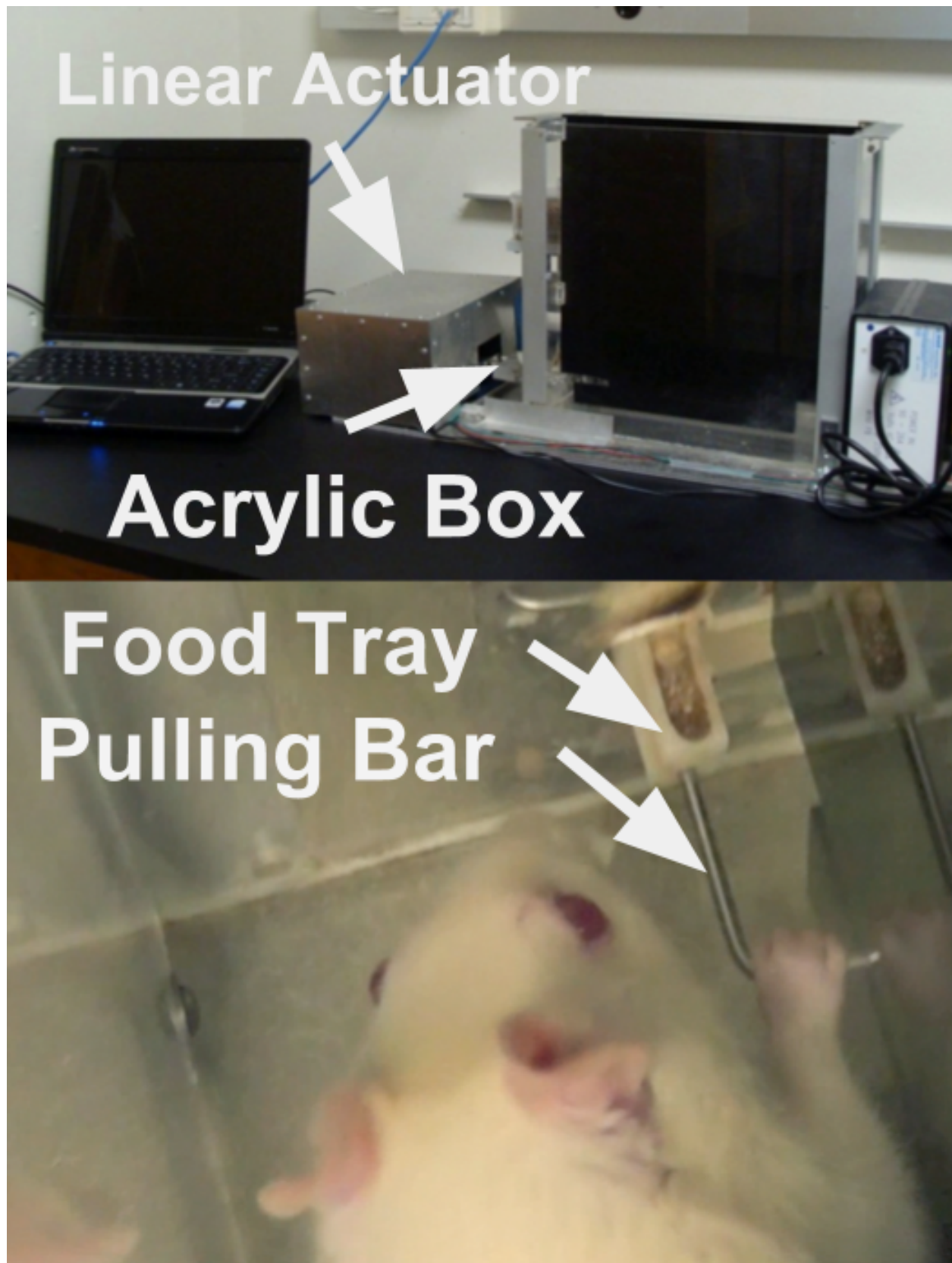


Figure 2.2: **Robotic training setup for the rats** - [Top] Computer, linear actuator, food dispenser, and acrylic glass box that comprise the full setup. [Bottom] View from the top of the acrylic glass box. This picture shows the required movement from the rat as well as the placement of the food tray on the pulling bar. In its retracted state, the food tray is out of the reach of the rat. The rat is then required to pull the bar to bring the food pellets within reach. Note the geometry of the bar used to ensure that

of successful pulls in a single training session. ANOVA tests were conducted on data from single training sessions at a significance level of $\alpha = 0 : 05$. We were also interested in the effects that training with higher force values would have on the rats volitional maximum grip strength following injury. We quantified this during testing days as previously described. ANOVA tests were conducted on data from single testing sessions at a significance level of $\alpha = 0 : 05$.

2.4 Results

We studied the effects of robotically modulating participants success rates and required effort levels on their motivation and performance gains. In humans for the virtual golf putting task, we found that decreasing the difficulty of the task by reducing execution errors led to higher feelings of satisfaction and effort, but with mixed effects on actual performance gains. In rats, we found that decreasing the difficulty of the task by reducing the required effort level led the animals to perform the task much more frequently, but this more frequent training did not increase their strength gains.

2.4.1 Human virtual golf putting

We compared how the responses of participants to specific questions from the Intrinsic Motivation Inventory changed as they went through the different phases of game play: baseline, training, and short-term retention (Figure 2.3). We asked participants to rate, on a scale from 1 to 7, with 7 being the highest, the statement: ‘I am satisfied with my performance at this task’. Relative to their baseline responses, participants feeling of satisfaction were significantly different once the force field was turned on

(Break 2: Kruskal-Wallis, $\chi^2(2, 27) = 11.1, p = 0.004$) and through training (Break 3: Kruskal-Wallis, $\chi^2(2, 27) = 11.9, p = 0.003$) and the beginning of short-term retention (Break 4: Kruskal-Wallis, $\chi^2(2, 27) = 15, p < 0.001$). At the end of the short-term retention phase the difference was close to being significant (Break 5: Kruskal-Wallis, $\chi^2(2, 27) = 5.2, p = 0.076$). Those in the error-reduction group showed the highest levels of satisfaction with their performance while those in the error-amplification group showed the lowest. Additionally, we asked participants to assess their perceived level of effort by scoring, from 1 to 7, with 7 being the highest, the statement: 'I put a lot of effort into this'. Relative to their baseline scores, participants perceived levels of effort were close to being significantly different towards the end of training (Break 3: Kruskal-Wallis, $\chi^2(2, 27) = 5.1, p = 0.08$) and they become significantly different at the beginning of the short-term retention phase (Break 4: Kruskal-Wallis, $\chi^2(2, 27) = 5.7, p = 0.05$). Those in the error-reduction group consistently showed higher perceived levels of effort than the other two groups.

During training, variability in the impact velocity was significantly different between training groups for both the short (See figure 2.4, ANOVA, $F(2, 27) = 30.1, p < 0.001$), and long (ANOVA, $F(2, 27) = 46.7, p < 0.001$) target locations, confirming that the robotic force fields either substantially decreased or increased putting errors depending on the type of force field experienced. To assess performance gains in the putting game, we compared participants impact velocity variability following training in the force fields, using a 10-sample moving average of the variance in order to gain a better understanding of the temporal patterns of the variability across training groups. For the short target, subjects in the error-reduction and error-amplification groups performed significantly better (ANOVA, $p < 0.05$) than the control group during the beginning and middle portion of the short-term retention phase. For the long target, all groups performed at the same level during the beginning and middle portion of the short-term retention phase with some differentiation apparent towards the end

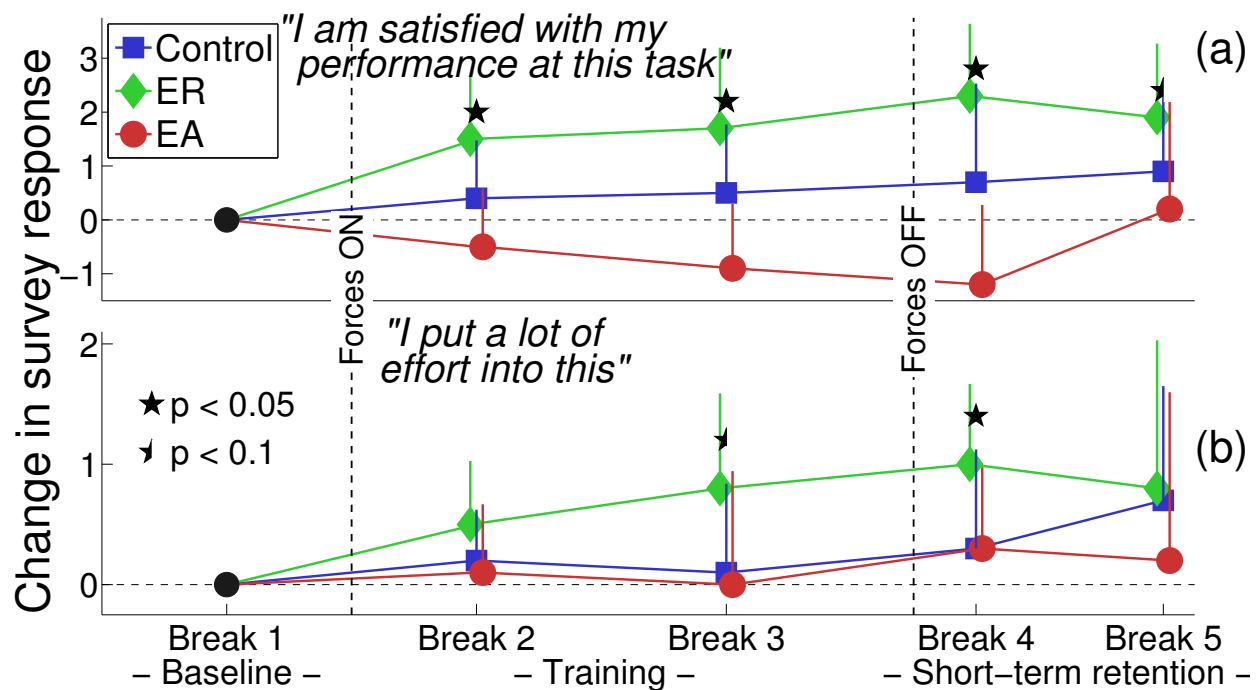


Figure 2.3: **Response to two of the questions in the Intrinsic Motivation Inventory (IMI)** - Responses were gathered as the golf participants went from training with no forces (baseline), training with forces (training), and finally training with no forces again (short-term retention). (a) To the question 'I am satisfied with my performance at this task' participants in the error-reduction (ER) group show a significantly higher level of self-efficacy compared to those who trained with no robotic intervention (Control) or error-amplifying (EA) forces both during training as well as after training where their performance is not as good. (b) To the question 'I put a lot of effort into this' participants in the ER group present higher levels of perceived effort even though during training the robot was significantly lowering the level of difficulty of the task.

of the assessment when the error-reduction group performed worse than the other groups.

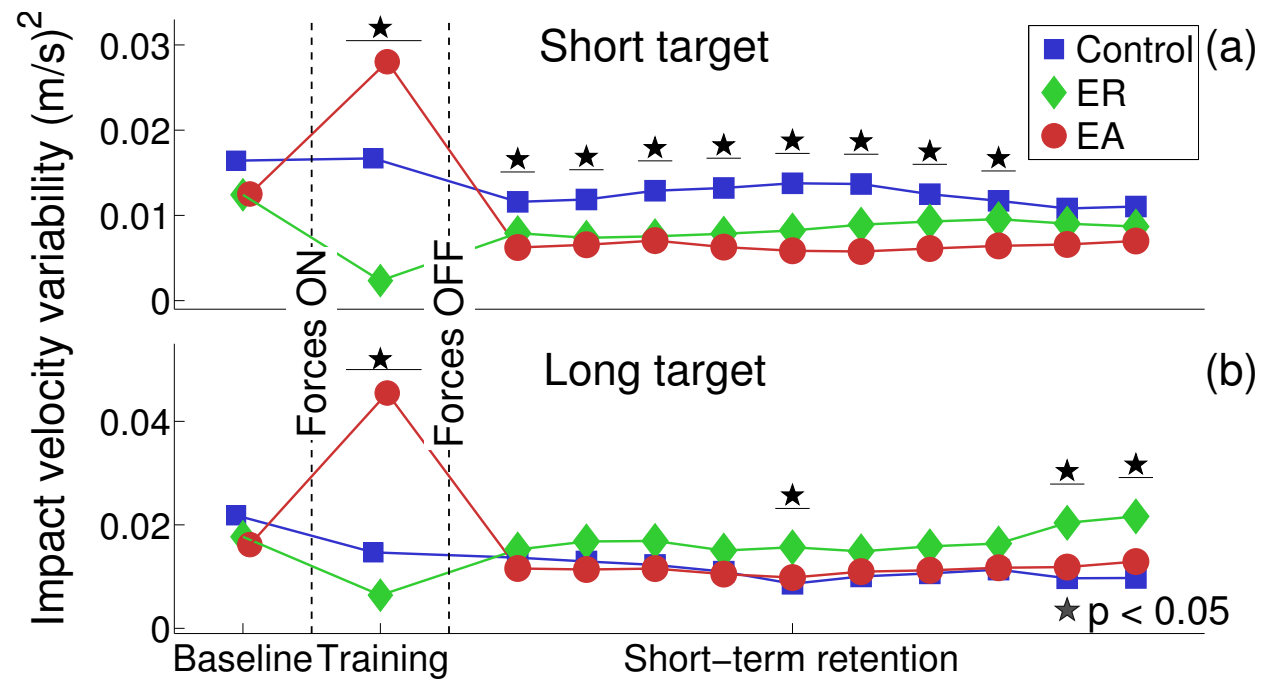


Figure 2.4: **Variability in impact velocity in the virtual golf task.** - This figure shows the average variability of the last 10 trials at baseline, the average variability across all trials during training, and a moving average of the variability during short-term retention. During baseline the three groups performed at similar levels. Once the robotic forces were turned on, those in the EA group experienced haptically-increased errors which led to significantly higher variability for both target locations. Those in the ER group experienced haptically-reduced errors which led to significantly lower variability for both target locations. Those in the control group show improvements due to regular training. Following the removal of the force field, those in the EA and ER groups performed significantly better than the Control group at the short target (a), but this difference was gone by the end of the short-term retention. For the long target (b) all three groups initially performed at comparable levels once the force field was removed. However, those in the ER group tended to perform slightly worse with the difference becoming significant towards the end of the short-term retention assessment.

2.4.2 Rat grip-strength training

We compared rats willingness to pull the bar before spinal cord injury, following SCI and before and after separating them into two training groups one that trained at higher levels of force (the autoGSM group), and one at lower levels of force (the control group). Willingness to pull was measured as the number of pulls in a one minute test period. Prior to being divided into the control and autoGSM groups both groups pulled at comparable frequencies and with similar success (Figure 2.5). Following injury, both groups significantly decreased by a comparable amount in their willingness to pull the bar. Once the rats were divided into the two training groups, those allowed to pull with lower forces (the control group) had a significantly higher number of pulls and successful pulls than those training with higher forces (autoGSM) (Figure 2.5) (ANOVA, $p < 0.05$). Regarding the strength training of the rats forelimbs, the group that trained with the higher forces consistently showed higher maximum force output, but these differences were not significant for any particular day of testing (Figure 2.5c).

2.5 Discussion

For the virtual golf task, we used a robotic device to either substantially reduce or increase putting errors. There was a clear effect of these robotic interventions on the subjects satisfaction with their performance: robotically decreasing putting errors improved satisfaction, while robotically increasing putting errors decreased satisfaction. Paradoxically, subjects who experienced robotically increased success also reported an increased sense of effort at the task. In terms of actual performance gains, training with error reduction marginally improved short-term retention for short putts, but

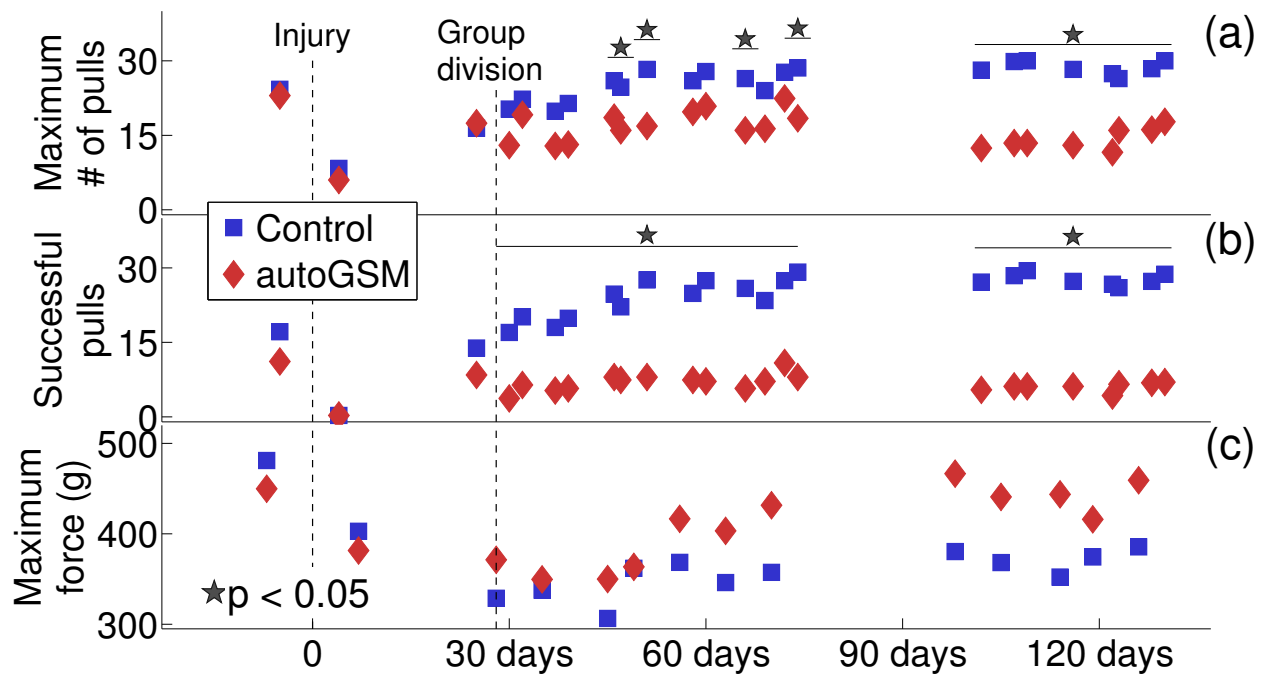


Figure 2.5: **Pulling and maximum forces data for the rats** - The rats had been trained on the pulling task for more than 70 days prior to the injury. After the injury the number of pulls tried was significantly lower (a) and the number of successful pulls goes to zero for all animals. The rats were trained for a few weeks until pulling became somewhat consistent again. At this time, they were separated into two groups: Control and autoGSM. Animals in the Control group trained at substantially lower force levels than those in the autoGSM group. Once the animals were separated, those in the Control group were willing to pull more often (a) and achieved significantly higher success at pulling (b) than those in the autoGSM. However, even after many weeks of training at different force levels, the maximum force generated by the two groups (c) was not significantly different in a single testing day.

degraded it for long putts, even though trainees were more satisfied with their performance. Training with error augmentation produced better performance for both short and long putts, even though trainees were less satisfied with their performance.

For the rat grip strength training task, injury of the spinal cord dramatically decreased the rats motivation to perform the task. Rats who were then permitted to train at the task with lower forces performed the task significantly more frequently, compared to rats who were required to pull forces near their maximum capability. Their increased frequency of training was not enough, however, to overtake the performance gains achieved by the rats pulling with more force but fewer times. A recent study by van der Brand et al. [111] showed that a training paradigm that encouraged rat participation (high motivation) triggered higher levels of plasticity and recovery of voluntary control compared to automated training (low motivation) for locomotion in rats with a spinal cord injury.

These were disparate experiments, but they produced compatible results, suggesting they may relate to a general principle of robot-assisted motor training. Enhancing motor performance with robots by using them to decrease task errors (as in the golf task) or to decrease the effort required to do the task (as in the grip training task) can increase motivation. On the other hand, practicing with robot assistance has variable effects on the performance gains experienced with training. Robots may thus serve a key role in motivating practice in the real world, although care must be given so that they do not impair performance gains.

Chapter 3

Effects of robotically modulating kinematic variability on motor skill learning and motivation

Jaime E. Duarte and David J. Reinkensmeyer

3.1 Abstract

It is unclear how the variability of kinematic errors experienced during training affects motor skill retention and motivation for training. We randomized 30 healthy adults into three groups and modulated their kinematic variability during practice of a virtual simulation of golf putting using a haptic robot. We used either haptic error reduction (ER), haptic error augmentation (EA), or practice without haptic input (control training) as participants putted to a short and a long target at a baseline session, a training session when the robotic manipulation was applied, and a long-term re-

tention session on three separate days. We quantified motor skill as the variability in impact velocity, and motivation using a self-reported, standardized scale. For the short target, both error manipulation strategies improved short-term performance, while only ER training improved long-term performance. For the long target, ER training degraded short term performance, but joined EA training in promoting long-term performance because the ER group exhibited substantially greater off-line learning. In terms of motivation, ER training improved self-reports of competence and satisfaction, while EA training worsened these self-reports, as well as enjoyment. The EA motivational effects persisted 1-3 days after training despite the similarity of the skill of this group to the ER group. In summary, either reducing or augmenting variability during training mostly positively affected putting skill learning by a small amount. Reducing variability transiently enhanced motivation, while augmenting variability persistently decreased motivation.

3.2 Introduction

The effective integration of robotic systems in motor skill training and neurorehabilitation requires an improved understanding of the learning mechanisms used by the human motor system when it interacts with these systems. These learning mechanisms involve both motor performance aspects and the psychological experience of the training; these two factors likely interact. Two prominent strategies for robotic-assisted training have emerged, both based on the manipulation of kinematic errors: error reduction (ER; also known as haptic guidance), and error augmentation (EA) (see review, [69]). However, the conditions under which these strategies work best, and the learning and motivation mechanisms they stimulate, are at present unclear.

Haptic guidance reduces a person's kinematic errors during training to improve motor learning. Different forms of haptic guidance have been developed ([59]; [16]; [110]; [62], [63]; [70]), but most of them share the goal of teaching task-related proprioceptive and/or visual cues by allowing individuals to experience the ideal feel and look of a task. Experiments testing the efficacy of haptic guidance in improving motor performance have produced mixed results. Although there have been studies verifying that haptic guidance can improve the learning of both spatial and temporal motor tasks ([16]; [68]; [76]; [62]; [70]), other studies have shown that haptic guidance provides no significant benefits when compared to either visual demonstration or unassisted training ([114];[110]; [32]; [59]).

The Guidance Hypothesis provides one possible theoretical framework for understanding why haptic guidance might in some cases inhibit the motor learning process. This hypothesis states that providing too much information during movement training causes the motor system to depend on the information; once the information is removed, then, the motor system will not have learned how to solve the problem independently ([98]). Consistent with this framework, recent models describing how the motor system adapts to account for novel dynamic environments suggest that the process is driven by a minimization of task error and control effort with a larger emphasis being placed on the minimization of error for short term changes ([29]; [57]). Reducing or eliminating task errors with haptic guidance could inhibit one of the primary teaching signals driving the adaptive learning process.

Despite the uncertainty about how haptic guidance can best be applied, commercial machines have been developed to show people how their movements should 'feel'. For example, in the sport of golf, the Top Swing golf robot (SwingAssist Worldwide) was designed to create for trainees a physical example of their ideal golf swing. Part of the marketing strategy for the device includes the idea that: 'If a picture is worth

100 words then a sensation is worth 10,000!'. Another example, the RoboPutt (Robo Innovations, Inc) has been created as a 'vending machine for putting lessons'; this device is also based on the premise that haptically guiding someone through an ideal swing will improve his or her putt swing. A simpler example is the Putting Guide, a device that restricts the motion of the putter head into a channel. It is unclear however if the haptic guidance provided by such devices is appropriate for improving a golf swing.

In contrast to ER strategies, EA training is based on the idea that motor learning is an error-driven process rather than a correct-feedback driven process. Thus, increasing kinematic errors during the execution of a motor task should enhance the motor learning process by causing the motor system to respond more strongly or faster ([84]; [30]). Increased error could also enhance attentional mechanisms, or invoke adaptive impedance control mechanisms for reducing kinematic error ([36]). Training with EA has been found to improve trajectory straightness in reaching ([19]), as well as the timing of a pinball task for more highly skilled trainees ([76]). One study that examined training of balance on a beam, however, found no benefits from EA training in improving short-term learning ([25]).

Important, but less-well studied, aspects of robot-assisted motor training are the effect of the intervention on motivation and retention. Stroke patients who received robot-assisted therapy using an ER strategy reported that such therapy was motivating ([43]), in part because of the improved self-efficacy accomplished with physical assistance ([92]). Sport psychology studies have found that positive feedback increases participants' intrinsic motivation and feelings of self-efficacy for a given training program, and can improve motor learning ([10]; [97]; [113]). The experience of success can also improve consolidation in motor learning ([109]).

For this study we chose an engaging and well-known task—golf putting—to study the relative merits of ER and EA training as compared to normal practice. We were specifically interested in how these training strategies affected learning and motivation when trainees were relatively well practiced at the task i.e. after the initial familiarization/learning curve had plateaued. Training approaches that enhanced motor learning in this stage would be useful. In this situation, we hypothesized that any benefits of ER training for learning ‘the feel’ of the task would be minimal since the trainees had already acquired the feel of the task, limiting the effectiveness of ER training, while EA training would still be beneficial. Specifically, we hypothesized that haptically reducing impact velocity errors would in this scenario hinder motor learning because it would prevent subjects from making and thus learning from those errors. On the other hand, we hypothesized that error-augmentation would be a beneficial training technique for teaching trainees to reduce variability in golf putting because it would provoke the motor system to learn to deal more effectively with errors.

We examined the role of ER and EA on the participants’ perception of training using a self-reported motivation scale. We hypothesized that training with ER would increase their feelings of competence and self-efficacy, but would lead them to feel less engaged and to perceive that they exerted less effort while training. Conversely, we hypothesized that training with EA would decrease their feelings of competence and self-efficacy, but would lead them to feel more engaged and to perceive that they exerted more effort during training. Additionally, we quantified any possible motivational ‘carry-over’ effect at a long-term retention test, 1-3 days later, when no robotic forces were applied during performance. We hypothesized that any motivational effects from training with the force fields would wash out by the end of the last day of the experiment, for the final session during which participants performed the

putting task with no forces, instead reflecting actual performance experiences during that day. Portions of this work were reported previously in a conference paper ([26]).

3.3 Methods

3.3.1 Participants

Thirty healthy participants (ages 20-30; 8 females) with no history of neurologic disorders completed the experiment. One participant was left-hand dominant. Each participant provided written informed consent in accordance with a protocol approved by the University of California-Irvine's Institutional Review Board.

3.3.2 Experimental apparatus and robot-generated dynamic environments

Participants were instructed how to play a game of virtual golf using a three degrees-of-freedom lightweight haptic robot (PHANToM 3.0 Premium, Sensable Technologies, Inc). The robot handle attached to the robot arm through a passive 3 DOF gimbals (Figure 3.1 (left)). To play the game, seated participants controlled the head of a virtual golf club using their dominant hand to putt a virtual ball to either a short or long target. The haptic robot was used to record the position, velocity, and forces and to apply the prescribed forces during game play at 1000 Hz.

To decrease variability in putting style, motion of the robot was constrained, via software, to one dimension – a straight line in the x-axis parallel to the participant's shoulders just above waist height. The use of a virtual environment allowed us to also re-

move the variability due to the putting surface (a constant friction force was the only force acting on the virtual ball after impact), the quality of the impact (we assumed no energy loss during impact), and the angle of impact (the impact angle was always in a straight line to the hole). In this controlled environment, impact velocity alone determined the distance traveled by the ball. Speed control is an important parameter in many sporting activities, but has only been studied in one experiment in the context of robotic training to our knowledge ([70]).

A putt can be divided into three parts: backswing, downswing, and follow through (see Figure 3.1 (right)). Impact velocity was defined as the velocity at which the virtual club crossed the starting position (i.e. at the end of the downswing). A small and constant impulse, opposite to the direction of motion, was applied at impact to simulate the impact with the ball. The force fields used for training, described below, were active only during the downswing portion of the putt.

The robot was programmed to provide a dynamic environment in which participants' impact velocity errors were haptically reduced (ER), augmented (EA), or unaltered (control). In ER training, the robot decreased velocity errors proportional to the predicted error for each putt. In the EA condition, the robot increased velocity errors proportional to the predicted error. And in the control condition, the robot did not manipulate velocity errors during training. The force fields for the ER and EA training conditions were defined as:

$$F_x = \begin{cases} -B_{ER}\dot{x} & \text{error-reduction} \\ B_{EA}\dot{x} & \text{error-amplification} \end{cases} \quad (3.1)$$

The gains, B_{ER} and B_{EA} , were kept constant across all participants (ER: $shorttarget = 0.0035(\frac{kg*m}{s})$, $longtarget = 0.003(\frac{kg*m}{s})$; EA: $shorttarget = -0.0016(\frac{kg*m}{s})$, $longtarget = -0.0015(\frac{kg*m}{s})$). These gains were chosen after pilot testing with several participants to find a force field that significantly decreased impact velocity errors while being qualitatively unnoticeable to participants. Throughout all phases of the experiment no instruction was given to the participants regarding their training condition. We wanted to produce an environment in which the participant attributed errors to their own performance and not the robot ([51]). Although we would have liked to assess participants' awareness of the training condition, questioning them at the end of training of Day 2 could have affected their performance on Day 3 and as such we refrained from doing this. The gains were set higher for the short target because the velocities required to perform the task were lower. Putting to the center of the hole required an impact velocity of $1.12\frac{m}{s}$ and $1.65\frac{m}{s}$, respectively, for the short and long targets. The long target location was, by design, inherently a more difficult task because it required a higher impact velocity than the shorter target.

To compute the velocity error for a given swing we developed an algorithm that generated a target trajectory in the phase space of the swing (Figure 3.1 (right)). The target trajectory was calculated as follows: (1) an ideal trajectory was defined using data from successful putts performed by several experienced participants in pilot testing; (2) the ideal trajectory was stored in a look-up table as x_{ideal} , $\dot{x}_{ideal}$ pairs for the downswing; (3) a morphing factor m was defined to decrease linearly from 1 to 0 as a function of the position of the putter head during the downswing, with the value 1 defined at the peak of the backswing (i.e. start of the downswing), and the value 0 defined at the ball impact location. The target trajectory was then calculated using

the following algorithm at the moment the putter reached its maximum backswing length x_{bsMax} :

```

forall the  $\dot{x}_{ideal}$  in the ideal trajectory table do
    | Access the  $x_{ideal}$  corresponding to  $\dot{x}_{ideal}$ ;
    | compute the target putter position  $x_{target}$  for this  $\dot{x}_{ideal}$  as
    |  $x_{target} = x_{ideal} - m(x_{bsIdeal} - x_{bsMax})$ 
end

```

where $x_{bsIdeal}$ is the location of the putter head at the start of the ideal downswing trajectory, which is the first entry in the look-up table. The effect of the algorithm was to define, for each putt, a target trajectory that began at the onset of the downswing (right after the end of the backswing), at which point the head velocity was zero, and ended at the location of the virtual ball with the velocity equaling the desired impact velocity. This desired impact velocity was the velocity that would cause the ball to travel from its initial position to the center of the target. A scoring mechanism was used to further engage participants in the experiment. Participants were presented, on the same screen as the game (see 3.1 (left)), with the error in the last putt - defined as the percentage error from the ideal impact velocity - the mean error of the last 5 putts, and the mean error of all putts completed. They also saw their current streak counter defined as the number of consecutive putts that were within a 10% error from the center of the hole (i.e. 'sunk putts'), as well as the maximum streak they had achieved during that experimental session. A 'sunk putt' was also rewarded by playing the sound of a golf ball dropping inside of the hole. Although we defined a 'sunk putt' to be within a window of 10% error, participants were told to try to putt to the center of the hole.

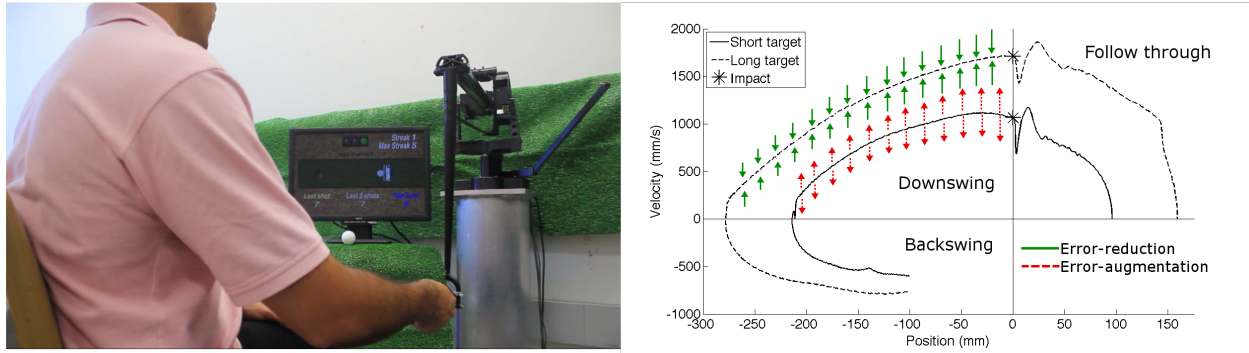


Figure 3.1: **Experimental setup and force schematics** - Left: Experimental setup for a participant playing the virtual putting game. Participants controlled the head of a virtual putter by using a 3DOF haptic robot. The computer screen provided participants with visual feedback about their performance which included a scoring system and a streak counter. Right: Two sample trajectories - one for the short target, and one for the long target - in the velocity vs. position (state-space) domain. The subcomponents of the swing are labeled as backswing, downswing, and follow-through. The arrows around the long target represent the ER force field, while the arrows around the short target represent the EA force field. The force fields were only active during the downswing.

3.3.3 Experimental protocol

Participants were instructed verbally and by demonstration how to perform the desired putting motion: shoulder abduction, followed by shoulder adduction across the body while keeping the wrist straight and elbow bent (see figure 3.1). They were told that the objective of the game was to impact the ball so that it would reach the center of the current target location: short or long. Participants first addressed the ball by placing the virtual club at a target displayed behind the pending location of the ball. Once the participant held the club at this position for one second, a golf ball appeared directly in front of the club. Participants then putted the ball. They were also shown a line across the path of their backswing that marked the minimum distance for the backswing, which was a point that experienced participants always passed when practicing. We displayed this line because some participants attempted to putt with a very short backswing followed by a jerky, forced, downward motion dissimilar

to skilled putting motion. To prevent this aberrant style of putting, and the possibility of a switch in style during training, we programmed the ball so that it would not move at impact unless the backswing passed the minimum length criterion.

Each participant putted on three separate days. On Day 1, the initial practice day, they performed a total of 100 putts, 50 to each target location. The target locations were randomized prior to the experiment and all participants were presented with the same randomized order of target locations. The purpose of the initial practice day was twofold: (1) familiarize participants with the task, removing any learning effects due to the initial interaction with the robot and experience of the task (i.e. we wanted participants to be relatively competent at the task prior to exposure to the force fields), and (2) extract an initial putting skill measure that was then used to divide participants into training groups with matched average initial skill. Skill matching was achieved by ranking the 30 participants based on their average mean squared error of impact velocity during the second half of the session on Day 1, taking sequential blocks of three participants from this ranking list, and randomizing each block of three participants into the three training conditions.

Day 2, the training day, was performed 2 to 3 weeks after Day 1. It consisted of a total of 170 putts. The trials were divided into three phases: baseline assessment (40 trials), training (90 trials), and short-term retention (40 trials) with participants unaware of this breakdown. The target location was randomized for the baseline and short-term retention phases with 20 trials to each target. For the training phase, the same target location was presented in sets of three consecutive trials. The goal was to resemble a training session in which a trainee adjusts his or her execution across several attempts based on previous errors at the same target. This pattern of three putts to the same distance was repeated 30 times during the 90 training trials with a total of 45 trials to each target.

On Day 3, which occurred 1 to 3 days after Day 2, long-term retention was evaluated by asking participants to repeat the same 100 trials as on Day 1. No robotic force fields were applied for any group on Day 3.

3.3.4 Assessment of competence and motivation

Breaks of at least one minute were periodically scheduled during all sessions to minimize fatigue and to query participants' feelings of competence and motivation. During these breaks participants responded, using the 7-point Likert-type scale (1 = strongly disagree and 7 = strongly agree), to a subset of four questions (marked with an * on the list below) extracted from the Intrinsic Motivation Inventory (IMI) ([96]). Additionally, at the end of each day, participants responded to a larger subset of thirteen questions, which also included the subset of four. The questions are shown in table 3.1.

Table 3.1: IMI table

<i>Question Number</i>	<i>Question statement</i>
1	I enjoyed doing this activity very much
2	I felt very tense while doing this activity
3	I would describe this activity as very interesting
4	This activity did not hold my attention at all *
5	I was anxious while working on this task
6	After working at this task for a while, I felt pretty competent *
7	I put a lot of effort into this *
8	I think that doing this activity was very useful
9	I am satisfied with my performance at this task *
10	This activity was fun to do
11	I think this is an important activity
12	I tried very hard on this activity
13	I thought this activity was quite enjoyable

The schedule of breaks was as follows: Days 1 and 3 trials 33 and 66, and Day 2 trials 30, 60, 90, 120, 150. Note that the first break on Day 2 was scheduled before

the force fields were applied; this provided a baseline measurement of the responses that was then used to compare the changes in responses due to the changes in the training environment. Other breaks on Day 2 were scheduled at least 10 trials before or after changing the force fields. This was done by design because we did not want the breaks to interfere with the transitions from training with or without the force fields.

3.3.5 Data analysis

We defined motor skill as the variability in impact velocity. Previous studies have shown that the main differentiator between highly skilled and lowly skilled putters lies in the variability in their impact velocity; this is in spite of their average impact velocities being comparable ([57]). This variability also increases with target distance. To calculate variability, we first removed trials where the impact velocity was 3 standard deviations away from the mean for each participant at each experimental phase of the experiment. Variability was then calculated for each participant using a ‘running variance’ approach, i.e. as the variance across a moving window which included the current trial and the 9 next trials for a given target location. Note that all statistical analyses involving the moving window of the variance were also tested at a size of 9 and 11; no differences were found in terms of significance when compared to the window size of 10. We performed initial post-processing of the data, including analyses of variance, using Matlab (Mathworks; v7.8); we used the R-package (v3.0.1) to perform the follow-up linear mixed model analyses described below.

We used linear mixed-models to analyze the performance of participants at the short- and long-term retention assessments. We used the logarithmic scale on the variability in impact performance as the response variable as it provided improved linearity

for the models. The models included the 3 training conditions and time as fixed effects, and the effect of repeated measures on the same participants as random effects. We used the control condition as the reference condition to compare performance for both the ER and EA groups. Separate models were used for the short and long target locations and the short- and long-term retention phases of the experiment. Different structures of the random effects were tested to include random intercepts or a combination of intercepts and slopes. Models were compared using an analysis of variance approach. No significant differences were found between models with random slopes as compared to random intercepts; as such, all models include only a random intercepts structure. Following fitting of the models, residuals were inspected by looking at the residuals as a function of fitted values and the distribution of the residuals was visually inspected for normality using Q-Q plots.

One-way ANOVAs were used to analyze the change between training groups from one point in time to another. Specifically, we tested for differences at two points: (1) the change between the end of the baseline assessment on Day 2 and the start of training on Day 2, and (2) the end of the short-term assessment (end of Day 2) and the start of the long-term assessment (start of Day 3). The goal was to evaluate the effects of turning on the force fields (1), and to evaluate the level of retention, or lack thereof (2). Significance level for these tests was set at a p-value of $\alpha = 0.05$. If the ANOVA was significant, multiple comparisons were done using Tukey's range test. As an additional tool for diagnostics we tested for differences between training conditions at each window of the moving variance. We used a one-way analysis of variance (ANOVA) with training condition as the main factor. Significance level for these tests was set at a p-value of $\alpha = 0.05$; p-values below 0.1 are also reported.

Changes in responses to the IMI during training Day 2 were computed relative to the response given during the first break on Day 2. To examine changes in IMI re-

sponse across days, changes in responses to the subset of 13 questions - given at the end of each day - were computed by subtracting the responses from the end of Day 1. We compared the changes in responses at each break, or day, using the non-parametric Kruskal-Wallis one-way ANOVA with training condition as the main factor. Significance was set at a p-value below $\alpha = 0.05$; p-values below 0.1 are also reported. Tukey's range test was used on pair-wise comparisons if the ANOVA was significant.

3.4 Results

3.4.1 Impact velocity variability

After Day 1, participants were relatively well practiced at the task. Their initial learning curves reached a plateau in Day 1 that continued into Day 2 for the short putt, or appeared to plateau by the end of the Day 2 baseline phase for the long putt. All groups had comparable performance at the end of baseline on Day 2 for both the short (Figure 3.2 , baseline) and long target locations (Figure 3.3, baseline). We used a paired-sample t-test to compare the change in impact velocity variability from the end of the baseline phase to the start of the training phase on Day 2. We found that the EA field significantly increased participants' impact velocity variability at both target locations (short, $p = 0.02$; long, $p = 0.03$), while the ER field decreased impact velocity variability for both target locations (short, $p = 0.002$; long, $p = 0.004$); thus the fields did what they were intended to do. There was a decrease in the variability of participants in the control condition at the short target location which was close to significant ($p = 0.07$); this was most likely due to the change in the presentation of the target location where it remained constant for sets of 3 shots at a time during training. Note however, that for the long target location the change was not significant ($p = 0.27$).

At the short target location, there was improved performance at the short-term retention assessment for participants in both the ER and EA groups when compared to the control group (Fig. 2, linear mixed model, main effects: ER, $p = 0.04$, EA $p = 0.06$; time-ER interaction $p = 0.03$). At the long-term retention assessment (Day 3) there was a significant time effect ($p < 0.001$) for improvements in performance across training groups; participants in the ER group performed significantly better than participants in the control group (main effects: ER, $p = 0.003$; time-ER interaction $p < 0.001$). No significant differences were found between the EA group and regular training.

For the long target location, performance at the beginning of the short-term retention assessment was similar between all three training conditions. However, a time-ER interaction effect ($p = 0.02$) showed that performance of the ER group worsened with respect to the others as the assessment elapsed. No significant differences were found in performance between the EA and control groups for the short-term retention assessment. For the long-term assessment, there was a significant trend for improvement in performance for both the ER and EA groups as compared with the control group (time-ER $p < 0.001$; time-EA $p < 0.001$). Performance for the EA group was significantly worse than the control group at the start of the assessment ($p = 0.049$).

We quantified consolidation (i.e. offline learning) as the change in performance from the end of Day 2 to the beginning of Day 3 (Figures 3.4 and 3.5). Consolidation, or lack thereof, was significantly different between groups (ANOVA, $F(2, 27)$, $p = 0.03$) for the long target but not the short target. On average, only participants in the ER training group showed offline learning. Follow-up multiple comparisons revealed significant differences in consolidation between the ER and EA groups (Tukey test, $p < 0.05$).

During the training phase, participants were allowed to putt three times in a row to each target. We checked whether they improved their performance during the sequence of three putts as would be the case if there was some form of error-based

learning (Figure 3.6). Participants in the EA group significantly reduced errors from the first putt to the second and third putts (ANOVA, $F(2,)$, $p < 0.001$). For the control group at the long target, participants' errors were significantly reduced by the third putt (ANOVA, $F(2,)$, $p = 0.037$) and approached significance at the short target (ANOVA, $F(2,)$, $p = 0.68$).

3.4.2 Ratings of Motivation

Training condition had a significant effect on how participants experienced training on Day 2 (Fig. 5). Participants in the ER group reported higher feelings of competence while participants in the EA group reported the opposite (Q6; Fig. 5A; Kruskal-Wallis test, Breaks 2 to 5: $p < 0.05$). Regarding the amount of effort put into the task, Q7, participants in the ER had a tendency to report higher effort levels while the error-reducing force field was active; however, this difference failed to reach significance (Fig. 5B; Kruskal-Wallis test, Break 3: $p = 0.08$; Break 4: $p = 0.06$). In terms of the reported levels of satisfaction, Q9, a similar behavior to competence was found. Participants in the ER group reported higher levels of satisfaction while those in the EA reported the opposite; note that this difference becomes less significant after the forces are turned off (Fig. 5C; Kruskal-Wallis test, Breaks 2 to 4: $p < 0.05$ and Break 5: $p = 0.07$). Finally, the use of the force fields did not have a significant effect on the reported levels of attention to the task between training conditions (Q10, Fig. 5D).

Looking at the responses across training days (Fig. 6), participants in the EA group reported higher negative feelings towards the task. Regarding the reported importance of the task, Q 11, the EA group reported significantly lower scores both after training with the force fields (Fig. 6A, Kruskal-Wallis test, $p = 0.02$), and after the long-term assessment, 1-3 days after having experienced the force fields (Fig. 6A, Kruskal-Wallis

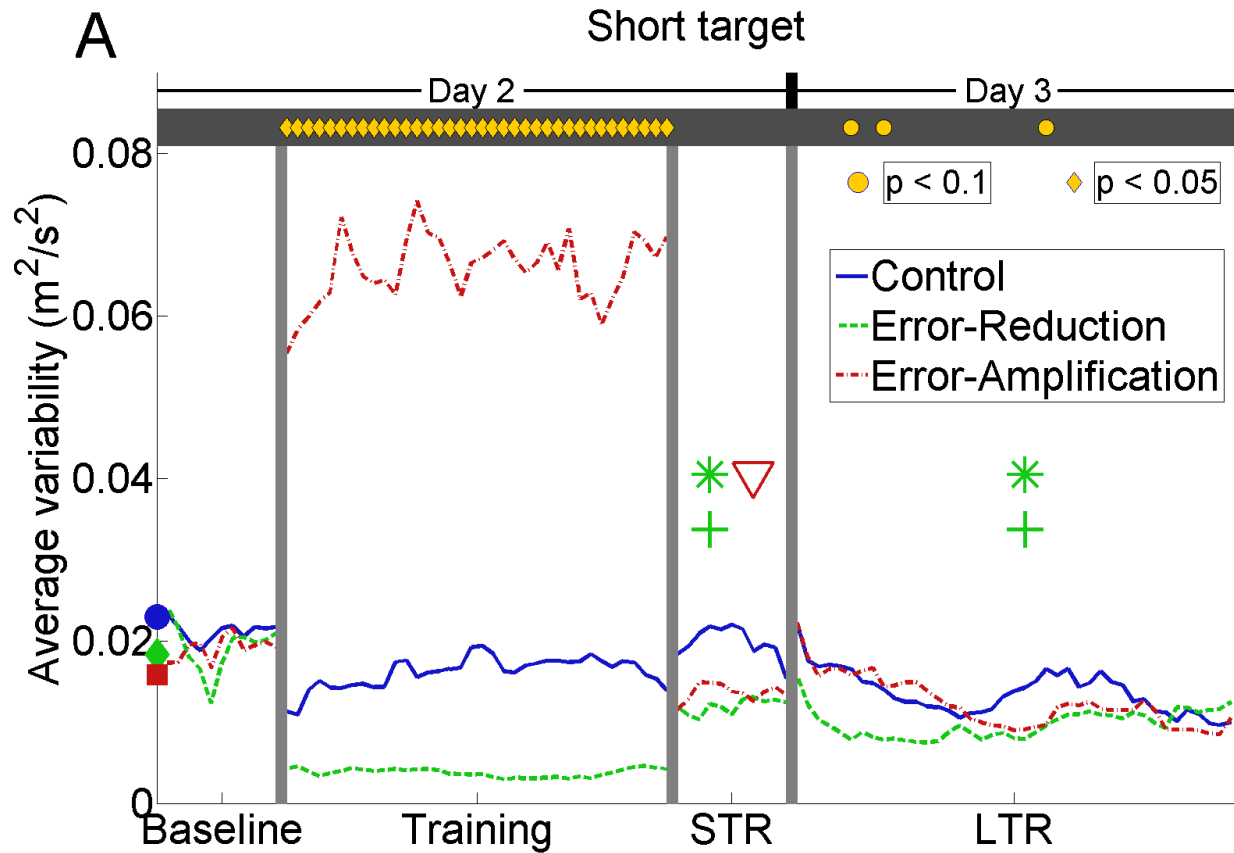


Figure 3.2: **Temporal evolution of the variability in impact velocity - Short target** - Variability was calculated as the variance across a moving window of 10 trials for each subject, then averaged across all subjects in each training condition for the short target. The plots show performance during Day 2 (Baseline, Training, and Short-term retention) and Day 3 (Long-term retention, which occurred 1-3 days after Day 2). The ER and EA force fields were active only during the training phase. Markers on the y-axis show the performance of the last 10 putts in Day 1 for the control (●), error-reduction (◊), and error-amplification (◻). Diamond markers (◊) on the top bar indicate a significant difference between training groups for a given moving window as determined by a one-way ANOVA. Asterisks (*) and triangles (▽) indicate significant main effects for the linear mixed model for ER and EA, respectively. Plus (+) and x (x) indicate significant time-condition interactions for the ER and EA conditions, respectively.

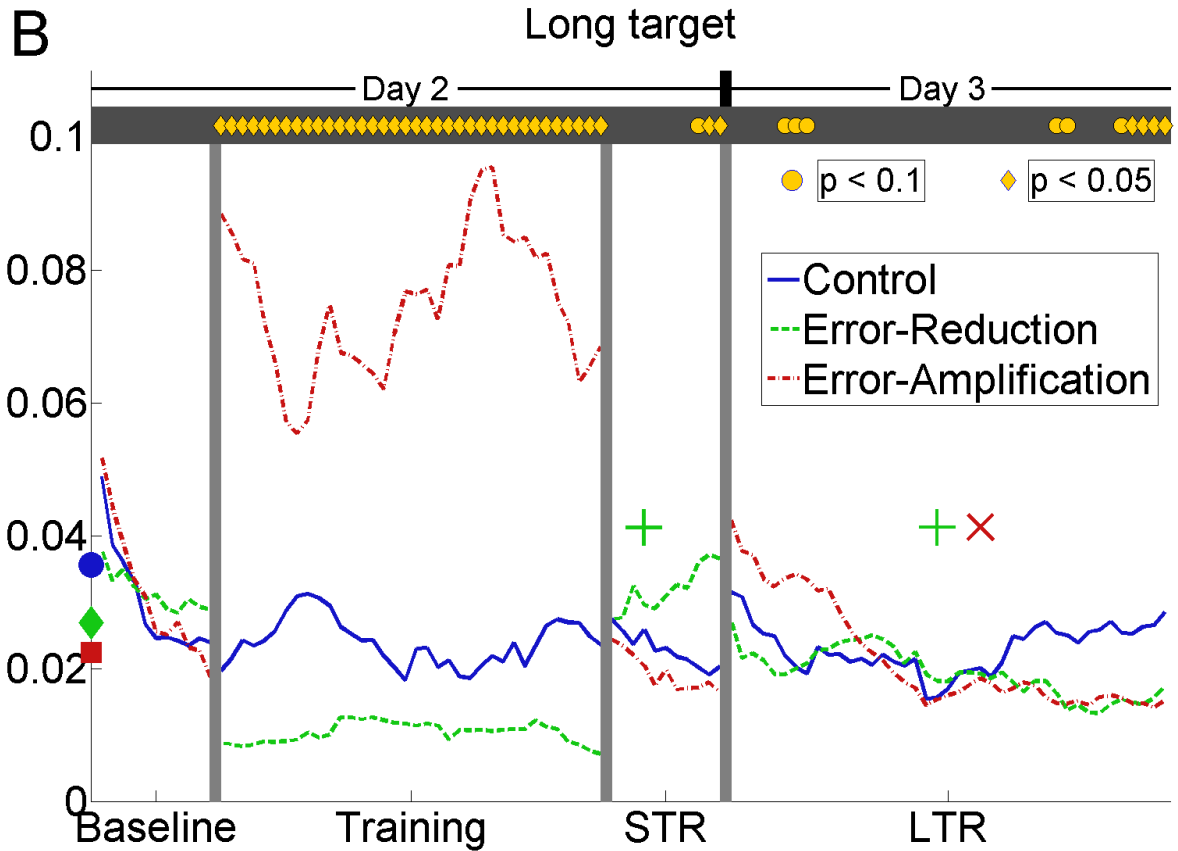


Figure 3.3: **Temporal evolution of the variability in impact velocity** - Variability was calculated as the variance across a moving window of 10 trials for each subject, then averaged across all subjects in each training condition for the long target. The plots show performance during Day 2 (Baseline, Training, and Short-term retention (STR)) and Day 3 (Long-term retention (LTR), which occurred 1-3 days after Day 2). The ER and EA force fields were active only during the training phase. Markers on the y-axis show the performance of the last 10 putts in Day 1 for the control (●), error-reduction (◇), and error-amplification (□). Diamond markers (◇) on the top bar indicate a significant difference between training groups for a given moving window as determined by a one-way ANOVA. Asterisks (*) and triangles (▽) indicate significant main effects for the linear mixed model for ER and EA, respectively. Plus (+) and x (x) indicate significant time-condition interactions for the ER and EA conditions, respectively.

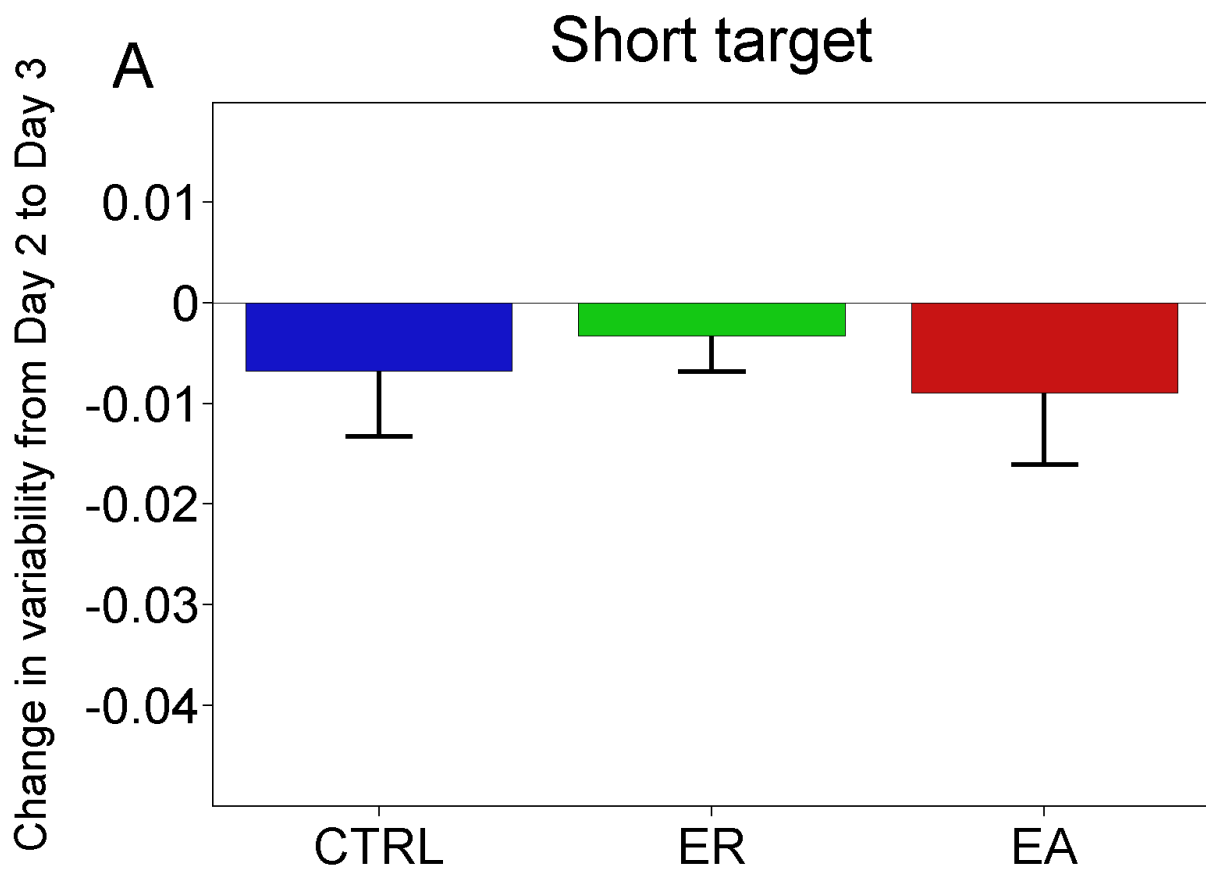


Figure 3.4: **Consolidation (offline learning)** - Consolidation across training groups for the short (left) and long (right) target location. There was a significant difference between training groups in the amount of retention from the end of Day 2 to the beginning of Day 3 for the long target (ANOVA $p = 0.03$, * = follow-up Tukey test indicated pairwise difference between ER and EA, $p = 0.??$). Error bars represent the standard error.

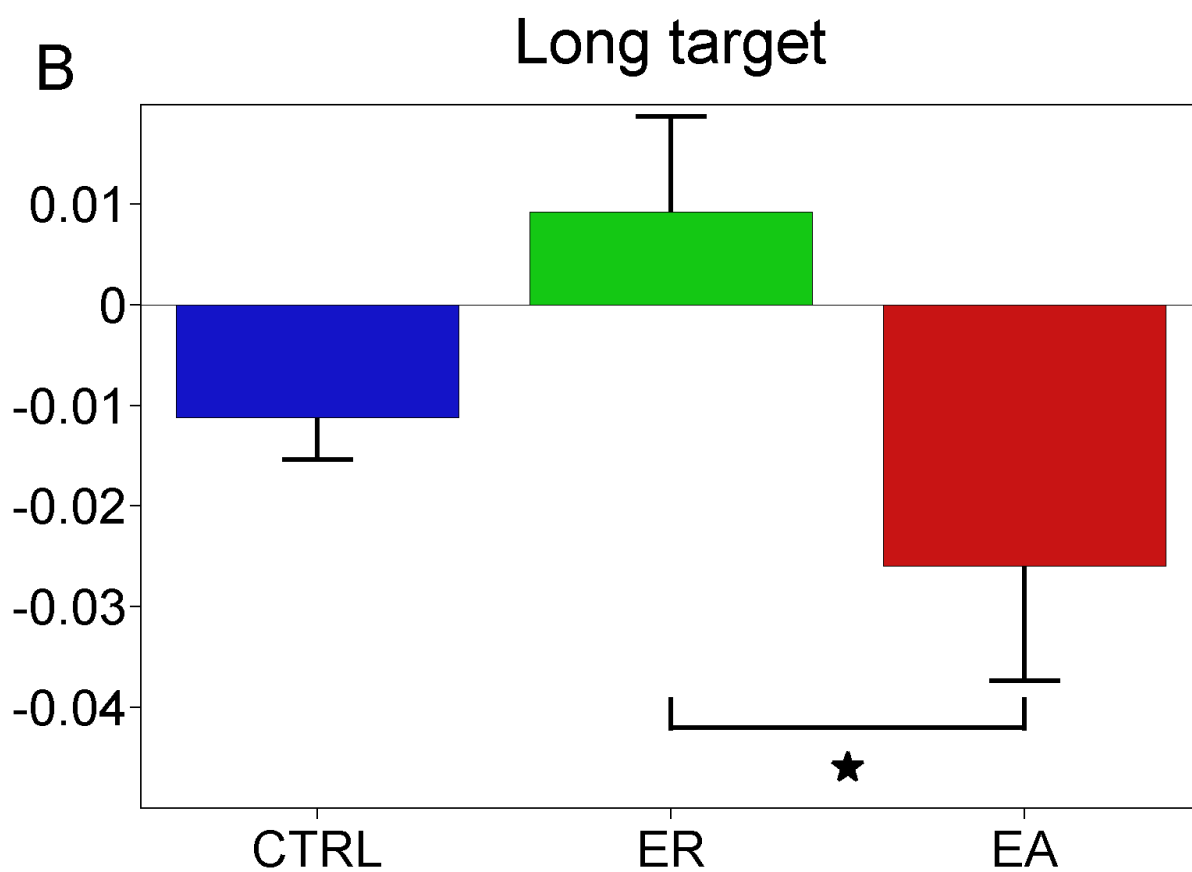


Figure 3.5: **Consolidation (offline learning)** - Consolidation across training groups for the short (left) and long (right) target location. There was a significant difference between training groups in the amount of retention from the end of Day 2 to the beginning of Day 3 for the long target (ANOVA $p = 0.03$, * = follow-up Tukey test indicated pairwise difference between ER and EA, $p = 0.??$). Error bars represent the standard error.

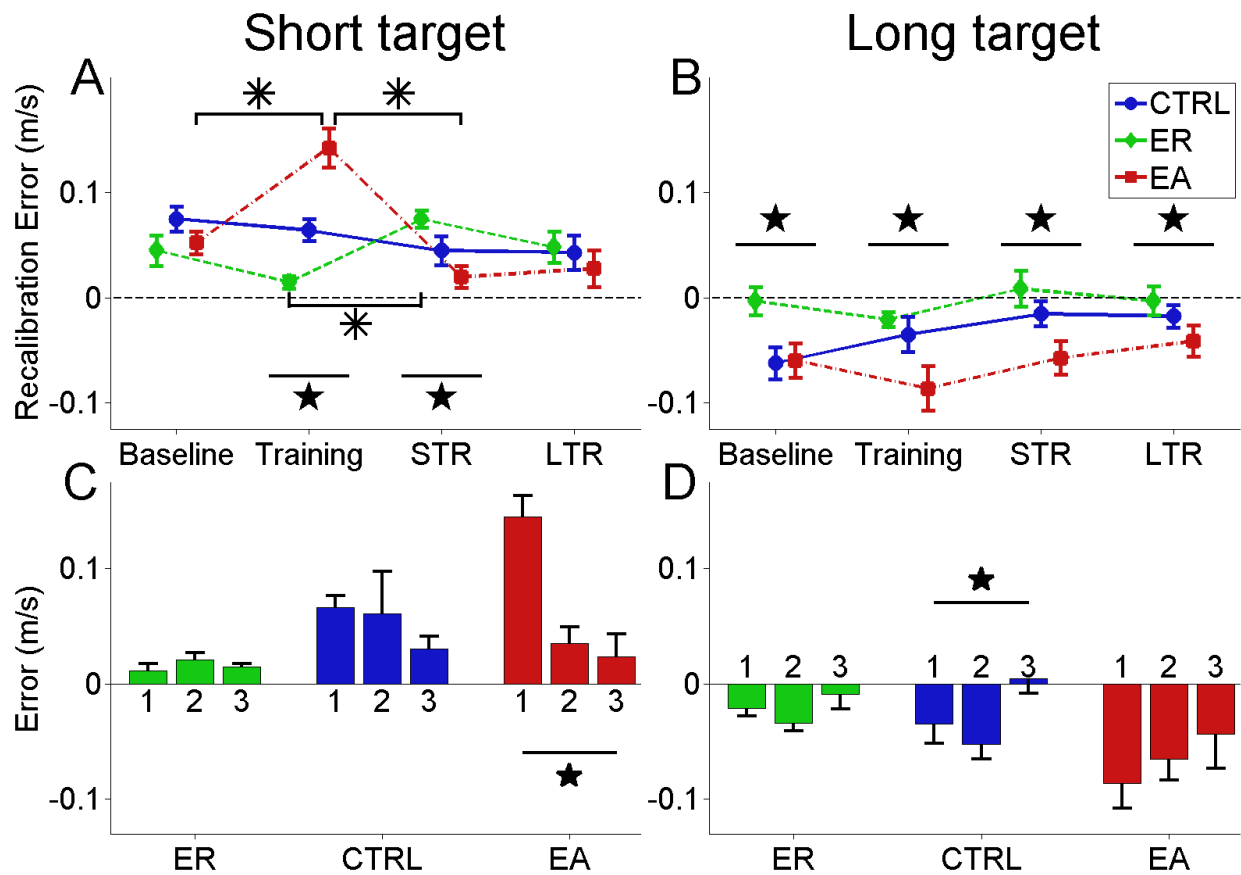


Figure 3.6: **Error-based learning across training conditions** - Plots A and B show the signed recalibration error (i.e. the error incurred after there is a change in target location) for the short (A) and long (B) target locations. There is a clear trend for the recalibration error to be in the direction of the previous putt; in other words, participants had a tendency to overshoot the short target and undershoot the long target following a change in the target location. Plots B and C show the signed errors incurred during the training phase of the experiment. For error-based learning, we expected errors to decrease for consecutive putts to the same target location. This was clear in the EA training condition at the short target (ANOVA, $p < 0.001$) and in the CTRL condition at the long target (ANOVA, $p = 0.037$). The asterisks show significant differences between experimental phases for a given training conditions, and the stars show significant differences between training conditions for a given experimental phase (A and B) or set of putts (C and D). Error bars represent the standard error.

test, $p = 0.001$). This same behavior was seen in relation to the reported levels of enjoyment of the task (Q13; Fig. 6B; Kruskal-Wallis test, Day 2: $p = 0.003$; Day 3: $p = 0.02$). Additional questions were also evident of a more negative perception of the task following training with the error-amplifying force fields but did not reach statistical significance (Q7,9,4; Fig. 6D-F). Responses to the other 7 questions were not significantly different between training conditions.

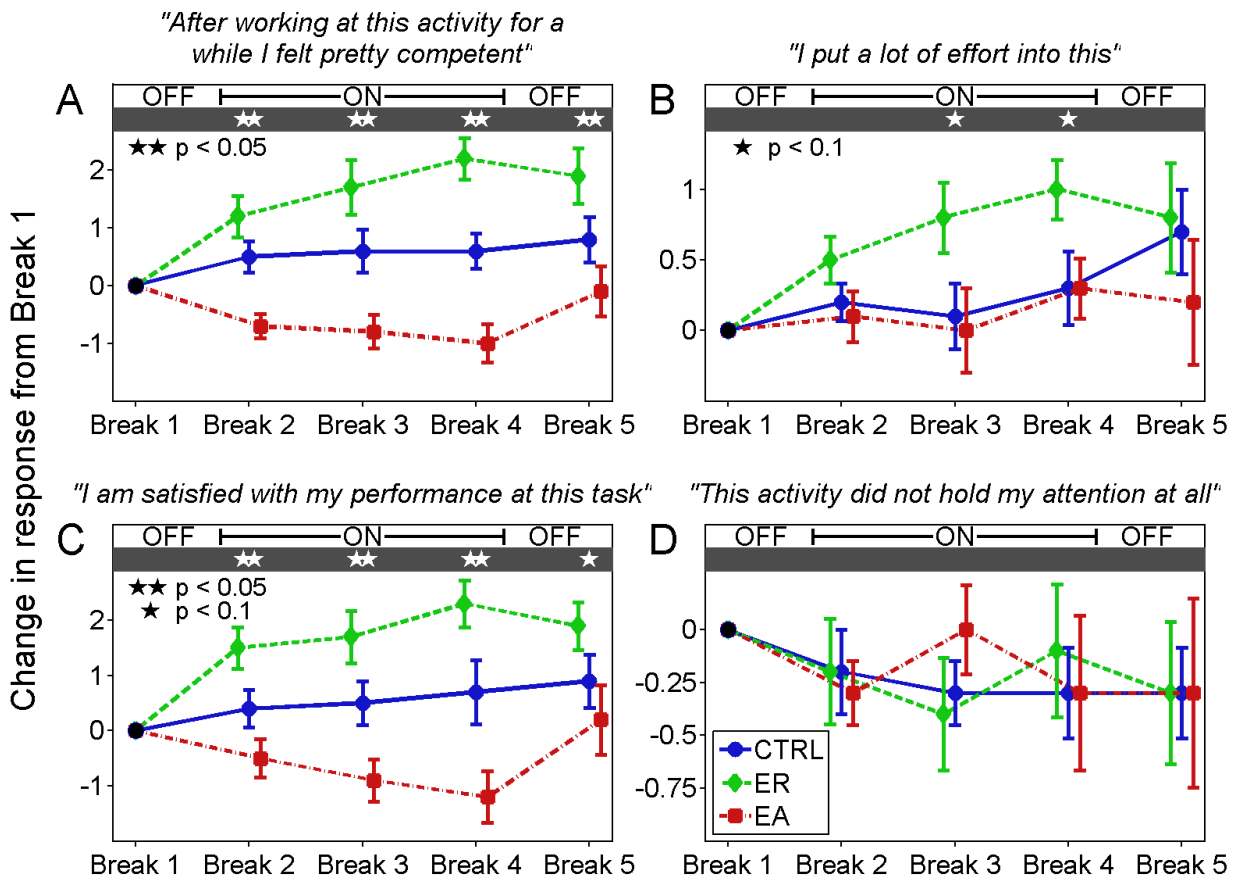


Figure 3.7: **Responses to a subset of 4 questions from the IMI during training on Day 2** - The top bar of each plot shows when the force field was active (i.e. during breaks 2, 3, and 4). Stars denote significant differences by Kruskal-Wallis ANOVA. For perceived effort levels (B), the ER group reported higher effort levels when the force fields were active, a trend that approached significance ($p = 0.09$ break 3; $p = .06$ break 4). Error bars represent the standard error.

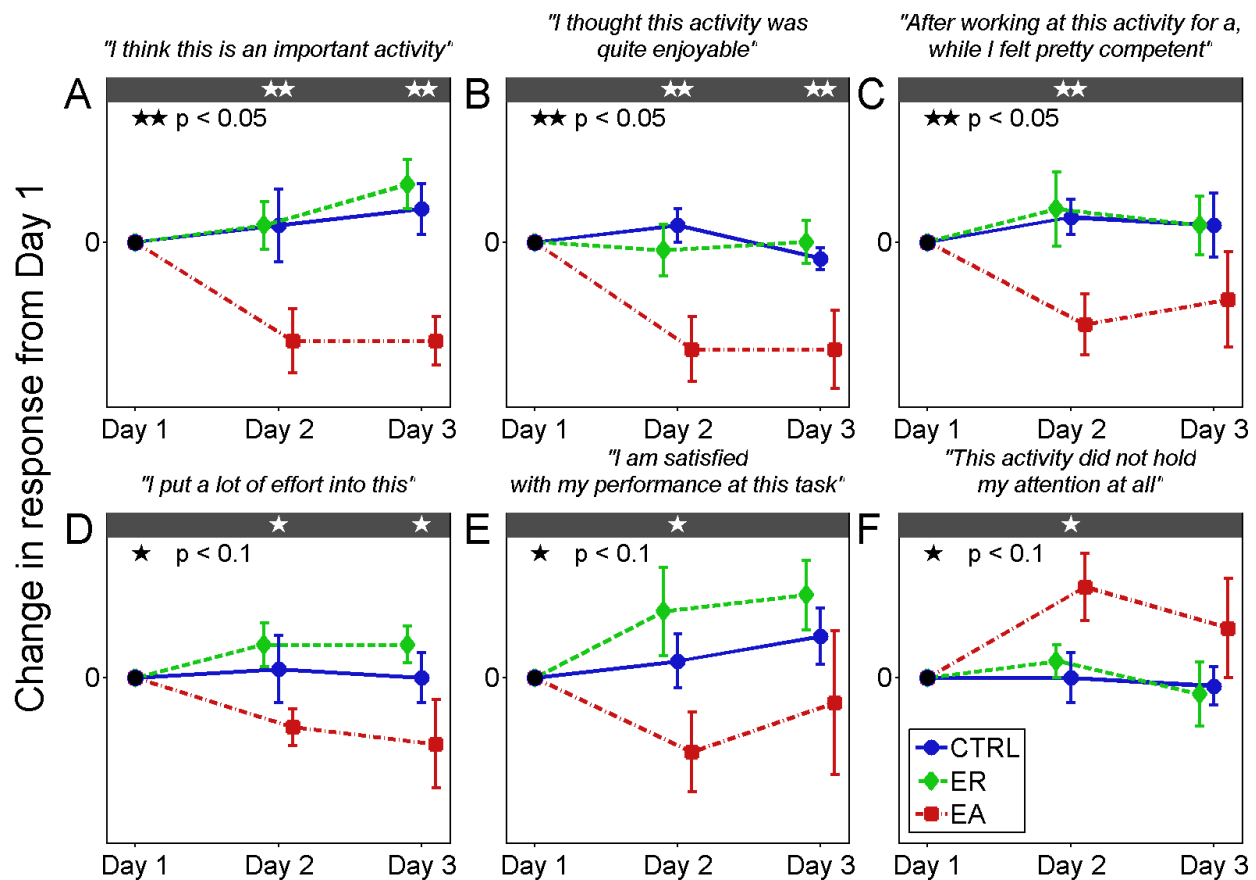


Figure 3.8: **Responses to a subset of 13 questions from the IMI asked at the end of each training day** - Only those questions with significant or near significant differences between training groups are shown. There was a significant trend for participants in the EA group to report more negative feelings towards the training at the end of Day 2 (A, B, and C). Some of these feelings persisted at the end of Day 3 (A and B) even though the force fields were not active during Day 3. Error bars represent the standard error.

3.5 Discussion

We assessed the effects of robotically modulating kinematic errors on motor learning and motivation for a virtual game of golf putting for participants who were well-practiced at the task. We manipulated velocity errors in the direction of the putting motion by reducing them (ER training), amplifying them (EA training), or leaving them unchanged (control training). Contrary to our expectations, haptically reducing kinematic errors during putting practice aided skill at the long term assessment for both short and long putts, and at the short term assessment for short putts. It however had a negative effect at the short-term assessment for the more challenging, long putt. The fact that it degraded performance at the short-term assessment for the long putt, but aided it in the long-term, was attributable to a significantly greater amount of off-line learning for this putt length following ER training. EA training had no negative effects on skill development, and produced slightly better performance of the short putt at the short-term assessment as well as for the long putt by the end of the long-term assessment.

Modulating kinematic errors during training also significantly affected participants' motivation with respect to the task. In accordance with our working hypotheses, training with ER led to higher feelings of competence and satisfaction, while training with EA caused participants to feel less competent and less satisfied. However, we were surprised that this latter effect persisted even days after participants had experienced the EA field. Also in disagreement with one of our working hypotheses was the finding that the EA group did not report higher effort levels during training even though we expected them to 'fight' with the robot. In contrast, participants in the EA group tended to report exerting an increased amount of effort, even though the robot 'helped' these participants perform the putting task. We first discuss the

positive and negative effects of ER and EA training, and then discuss implications for robot-aided motor training and rehabilitation.

3.5.1 Positive effects of ER training

ER training improved performance at the long term retention test for both the short and long putt. Positive effects of ER (or haptic guidance) have been reported previously for learning to drive a wheelchair ([68]), make spatiotemporal trajectories ([32]; [62]), and simulated tennis ([70]). For these tasks, it was suggested that ER aids in the development of the sense of timing for the task. Given that participants were relatively well practiced at the task we tested here, it is unlikely that the improved performance was due to ER training better teaching the ‘feel’ of the task i.e. the participants likely had already learned the ‘feel’ of the task. In addition, the putting task studied here is a velocity control task i.e. the trainee must achieve a target velocity of the putter hand at the impact location, rather than control the timing of movement.

Besides its effect on timing learning, previous studies suggest ER may affect whether the motor system uses explicit or implicit learning mechanisms. Reducing error has been shown to previously lead to implicit learning ([72]; [47]; [38]). Explicit and implicit learning consolidate differently [94]. In a golf putting task, practicing short before long putts was suggested to cause implicit learning and enhance transfer ([87]). However, in the present study, trainees experienced a substantial amount of putting practice before the ER field was turned on, likely already activating explicit learning mechanisms [72].

Instead of timing or implicit learning related mechanisms, we tentatively suggest that the positive effect of ER in the current study may be attributable to the motivational effects we also observed; i.e. ER trainees reported higher feelings of competence and

satisfaction, and a trend toward higher effort levels. Previous studies have found that providing positive feedback during training promotes retention ([97]). For example, participants who experienced higher success rates in a visuomotor rotation adaptation test during training, by virtue of relaxing the criterion for counting a successful trial, performed better at a 24-hr retention test than participants who experienced less success by virtue of a stricter success criterion ([109]). Also consistent with this concept is the observation that training with ER improved retention between Day 2 and Day 3 for the long putt. A possible mechanism that account for better learning with more experience of success is error-related negativity, which is the reduced release of dopamine during motor learning when failure is common ([42]). ER prevents performance failure and thus may in some training situations cause a greater release of dopamine, better sealing motor memory ([109]).

3.5.2 Negative effects of ER training

The decreased short-term learning following training with ER for the long target was the only finding consistent with the Guidance Hypothesis. The long putt was more difficult to master, as evidenced by the higher errors and longer initial learning curve. Perhaps removing the experience of large errors during ER training reduced the ability of the motor system to find solutions to this more challenging problem. In addition, studies suggest that the gradual introduction of errors improves retention ([45]; [49]); while the form of ER used here reduced error size, it also effectively eliminated error instead of gradually allowing it. We note here also that there was somewhat of an irony in the responses given by the ER group to the questions on satisfaction and competence after removal of the force field in that they were still more positive than the other groups even when their performance on the long putts was worsening; they were however doing better on the short putts.

3.5.3 Positive effects of EA training

Training with error augmentation improved short-term putting skill relative to the control group for the short putt, another example of a benefit of EA training ([30]; [84]; [44]; [1]). We anticipated EA might improve short-term learning through three possible mechanisms: increasing attention to the task, enhancing error-based learning, or impedance control. Self-reports of attention were not different during training for the three groups. With respect to error-based learning, participants in the EA showed evidence of error-based learning at the short target location; this was especially evident in the change in error size from the first putt to the second and third putts. Additionally, there was a trend for errors to decrease when putting at the long target location; however, these differences were not significant. Regarding the possibility of impedance control, we did not see a decrease in variability across the practice period when EA was on as might have been expected if the motor system was iteratively increasing impedance ([36]). The mechanism of short-term positive effects of EA needs further research; a useful future direction would be to measure mechanical impedance during the putting task.

Participants who trained with EA also eventually outperformed control subjects by the end of the long term retention test. The reason for the different time dynamics of performance of EA trainees on Day 3 with respect to control trainees is unclear.

3.5.4 Negative effects of EA training

Participants who trained with EA reported lower levels of competence and enjoyment during training, and, surprisingly, on Day 3, when no force fields were applied and their performance was as good as or better than the control group, they continued

these reports. Evidently the experience of an inexplicably, large, sudden increase in error and corresponding decline in success in sinking putts persistently impaired motivation in a way that was out-of-step with actual performance. Two factors that have been shown to correlate with motivation in exercise training are perception of success, which refers to how successful trainees feel they were in improving their ability through training, and self-efficacy, which refers to how confident a trainee is that they could achieve a target performance level if tested again ([73]). EA almost certainly had a negative effect on perception of success because trainees experienced a long period of time in which they rarely sank putts. The fact that EA suddenly and inexplicably caused trainees' errors to become large, and that trainees were not able to adapt to the EA field while it was on, likely also diminished self-efficacy.

The approximate tripling of error via EA had a long-term persisting effect on task perception that was not consistent with the participant's actual performance, which was not worse. In contrast, halving error via ER had only a temporary effect on task perception. The perceptual effect of ER was also inconsistent with performance, at least in the short-term retention test for the long putt which the ER-trained subjects performed worse. Perception can clearly be decoupled from performance.

There may be an asymmetry of motivational response such that error augmentation causes longer-lasting perceptual effects than error reduction. An interesting follow-up experiment would be to apply the force fields from the start of training. In this case, the EA subjects would experience only a change from poor to good performance when the field was removed, although their average performance would still be worse, while the ER subjects would experience only a change from good to poor performance when the field was removed, while their average performance would be better. How would the overall level of performance, the slope of the change in performance, and the trainees' perception of self-efficacy affect motivation? ER and EA

techniques provide a way to address such questions, and should be further explored to determine how the size of errors and pattern of change of errors affects motivation, perception of success, and self-efficacy immediately following training and later, which are pragmatic issues for effectively translating robot training to real-world applications.

3.5.5 Implications for robot-assisted motor skill training and neurorehabilitation

Self-efficacy is an important concept in both sports and neurorehabilitation training because it leads to higher motivation and persistence when faced with difficulties in performing the task ([11]). A possible approach is to use ER fields early on in motor training to generate an expectation of behavior that leads trainees to make use of their impaired body in settings other than the lab. Bandura [11] argued that a person's 'expectations of personal mastery affect both initiation and persistence of coping behavior'. Therapies that positively affect people's expectations of their motor capabilities may lead them to be more persistent at using their bodies. One plausible scenario is one in which people's capabilities are reinforced during training by using devices that through assistive approaches such as ER improve people's motivation and perceived self-efficacy. Such may be a valid rationale for the ER based commercial golf swing trainers mentioned in the introduction. For neurorehabilitation, similar motivational and motor learning mechanisms are also likely operating. Subjective reports from stroke patients who have undergone robotic therapy suggest they find it more motivating in part because it allows them to accomplish tasks they normally could not achieve ([92]). Schweighofer and Winstein [102] have provided evidence for a threshold-based dynamic in achieved rehabilitation dosage after stroke

where patients who achieve a threshold level of movement ability engage in spontaneous use of the hand outside of therapy, further increasing the dose of therapy and improving their outcomes. The evidence presented in this paper for the ability of error reduction to improve a participants perception of training provides a possible explanation as to why robot-assisted rehabilitation therapies have shown increased retention levels when compared to conventional training ([60], [43]).

Chapter 4

Robotic Rehabilitator of the Rodent Upper Extremity (RUE): A system for assessing and training forelimb motor function

In collaboration with Kelli Sharp, Sergi Perez, Berkey Gebrekristos, Ardi Guanawan

4.1 Abstract

Recovery of hand function is a high priority for individuals with cervical spinal cord injury (cSCI). An important factor in this recovery process is the recovery of grip strength. In rodent models of cSCI a well-established method for assessing grip strength is the Grip Strength Meter (GSM). The GSM measures the force at which an animal releases its grip from a bar as an experimenter pulls its body away from it. This method as-

sumes that the force at release reflects the grip strength of the animal, which may not be the case since the pull is initiated by the experimenter rather than the animal. It also requires pulls achieved by use of a spastic paw to be discounted. To address these issues, we developed a novel robotic device, the Robotic Rehabilitator of the Rodent Upper Extremity (RUE), to measure and train the forelimb strength of rodents. RUE is similar to the GSM in that it uses a bar pulling paradigm, but it differs from the GSM because it 1) requires the animal to voluntarily reach for and pull the bar and 2) motivates the animals using a food reward in which the proximity of the food reward to the mouth is controlled by the force exerted and 3) can temporarily block the motion of the bar to elicit higher effort from the animal. We trained 16 animals to interact with RUE for 23 weeks before and 38 weeks after a mild (100 kdyn) unilateral contusion at the C5 vertebrae. We measured their forelimb strength once per week using both RUE's 'blocked pull' paradigm and the GSM method. Before the lesion, peak pulling force measured with RUE was $446.65g \pm 17.73gSEM$ on average, 2.6 times higher than with the GSM which was $168.41g \pm 3.13gSEM$. Measurements with RUE were significantly more variable ($p < 0.001$) than with the GSM. The two measurement methods were uncorrelated ($R < 0.001$, $p = 0.99$). After the lesion, RUE measured a significant loss in peak pulling force of, on average, $30.01\% \pm 2.89\%SEM$. The loss in pulling force correlated with a reduction in white matter area, when compared to the uninjured side ($R = 0.59$, $p = 0.04$), but not gray matter. Only one rat met the active paw placement criteria required for GSM-based strength measurement after injury. These results indicate that the GSM does not measure peak forelimb strength, likely because it does not sufficiently motivate the animal to engage in the task. In contrast, RUE can measure volitional forelimb strength both before and after cSCI, a useful feature for quantifying the effects of rehabilitation and other treatment approaches.

4.2 Introduction

There are an estimated 273,000 people in the US who have sustained an injury to the spinal cord. More than 50% of these injuries are at the cervical level and thus lead to loss of voluntary control of the upper extremity [18]. For people with tetraplegia, regaining function of their upper extremities and hands ranks atop their priorities, even above functions such as bowel/bladder control, and sexual functions [103]. A key outcome measure of hand function is grip strength. In humans, the standard way of measuring grip strength involves asking patients to squeeze a dynamometer as hard as they can for three repetitions. The three values are then averaged and this is defined as their maximum grip strength [27].

In rodents, there is no standard tool to measure grip strength. Instead, a battery of tests are used, usually in conjunction with one another, to assess the level of function of the forelimb. Some of these tests include: the grip strength meter (GSM) ([71]; [8]; [5]; [9]; [3]; [119]), the food pellet reaching task ([74]), the sticker removal task [100], and the pasta matrix reaching task [2], among others (for a thorough list of forelimb assessments for rat models see [50]). Of particular interest for us is the use of the GSM as a tool to assess grip strength.

The GSM was developed more than 25 years ago to test the effects of environmental and psychopharmacological agents on motor function of the forelimb [75]. Although its name implies a measure of grip strength, the GSM does not measure grip strength in the same way it is measured in humans (i.e. by measuring squeezing force). Instead, this test measures the force at which an animal releases its grip from a bar as an experimenter pulls its body away from it. This test has good reliability and has been used in a variety of environmental and pharmacological studies [78]. However, it is unclear whether the GSM measures maximum voluntary grip strength.

The GSM has also been used to measure forelimb function after cSCI ([8]; [5]; [9]; [3]; [119];), and has good reliability and sensitivity to the injury. However, in applications involving cSCI, the criteria for validity of a GSM measurement is stricter. This is because cSCI can lead to spastic muscles that leave the hand in a clawed position and measurements with the GSM would not reflect voluntary control of the animal's grip in this case. Thus in GSM applied to cSCI, experimenters perform a visual inspection of the hand after it releases the bar; if the fingers remain in a clawed position then the measurement is registered as a 0 (see [5]). This strict criterion of an appropriate grip in order to obtain a valid GSM measurement after cSCI may cause subtle motor improvements to be unaccounted. Studies have often not obtained valid GSM strength measurements because of this issue from a majority of rodents specially right after SCI ([8]; [3]).

To address and study these issues, we designed a robotic system that uses a reward-based approach to train and assess motor function of the rodent upper extremity. In this device, the Robotic Rehabilitator of the Rodent Upper Extremity (RUE), animals are placed inside a box where they must volitionally reach for and pull on a bar to bring a food reward within reach for eating. This bar is connected to a robotic interface by which the force required to complete the pulling task can be modified.

This chapter is part of a set of two articles describing the use of RUE as a tool for the assessment (this chapter) and rehabilitation (accompanying chapter – Chapter 5) of motor function in a rodent model of SCI. Specifically, we focused on a model of unilateral contusion to the C5 vertebrae of the rat spinal cord. In this chapter we compare the method for assessing forelimb function via RUE to the well-known and widely-used grip strength meter (GSM). We hypothesized that the reward-based approach used with RUE would lead to increased motivation for the animals to engage in the task and therefore higher forces measured during the assessment than the

GSM. We further hypothesized that by focusing on the functional abilities of the animal to perform the task of reaching and pulling-and not on the paw placement of the animal-we would be able to measure the effect of the injury as well as the subsequent rehabilitation process on voluntary limb function more robustly.

4.3 Methods

4.3.1 Animals

Experimental animals were female Sprague-Dawley rats (Harlan, Inc., San Diego, CA) that were 210-240 grams ($222.68 \pm 2.16g$) at the beginning of the experiment and between 3 and 4 months of age. A total of sixteen rats were utilized for this experiment. The Institutional Animal Care and Use Committee (IACUC) at the University of California, Irvine, approved all experimental protocols utilized in this experiment.

Animals were handled for three weeks prior to device acclimation. The animals were maintained on a food-restricted diet in which they received 85% of a normal daily intake. Animals were food restricted as a means to incentivize them to participate during training sessions. The animals were weighed weekly to ensure overall health.

All procedures described were carried out with a set of 4 animals prior to the 16 animals we report here [85]. Testing with these 4 animals helped us refine the procedures used with RUE.

4.3.2 Robotic Rehabilitator of the Rodent Upper Extremity (RUE)

We designed a robotic-based system, RUE, for assessing and training rats in a self-initiated forelimb task consisting of reaching for and pulling on a bar to retrieve a food reward. The system is comprised of a one degree-of-freedom resistance-based trainer, an automated food reward mechanism, and an acrylic box to house the animals during training (Figure 4.1A). The acrylic box is 6" wide by 12" long and 12" high. The width of the box was divided into two halves by means of an opaque acrylic divider to force the animal to pull the bar with a specific forelimb. All assessments in this study were carried out with the right paw.

Animals interacted with the trainer by means of a custom-made metal bar (Figure 4.1B) coupled to a voice coil actuator (VCS10-023-BS-01-MH; H2W Technologies Inc., Santa Clarita, CA) that generated the prescribed forces during the assessments. A linear potentiometer (LCP12A-25-10K; ETI Systems, Carlsbad, CA) was coupled to the voice coil actuator to measure its position. The resistance-based trainer was programmed to behave as a linear spring.

Successful trials were rewarded with 20mg chocolate-flavored food pellets (Bio Serv, Frenchtown,NJ). They were delivered by a custom-made food tray placed on the opposite end of the metal bar (Figure 4.1C) using an automatic food pellet dispenser (ENV-2030-20, Med Associates Inc, St. Albans, VT). In it's resting state, the bar was retracted so that the food tray remained behind the front acrylic panel, out of reach of the animals. The goal for the animals was to bring the food tray within reach by pulling on the bar (Figure 4.1D) far enough forward to retrieve the food pellet with the mouth (Figure 4.1E).

The robotic system was controlled and data recorded at a sampling rate of 1000Hz using a USB Data Acquisition board (NI-6009; National Instruments, Austin, TX) inter-

faced with Matlab (The MathWorks Inc, Natick, MA). A custom-made user interface was created in Matlab for the animal trainers to setup and run the assessments.

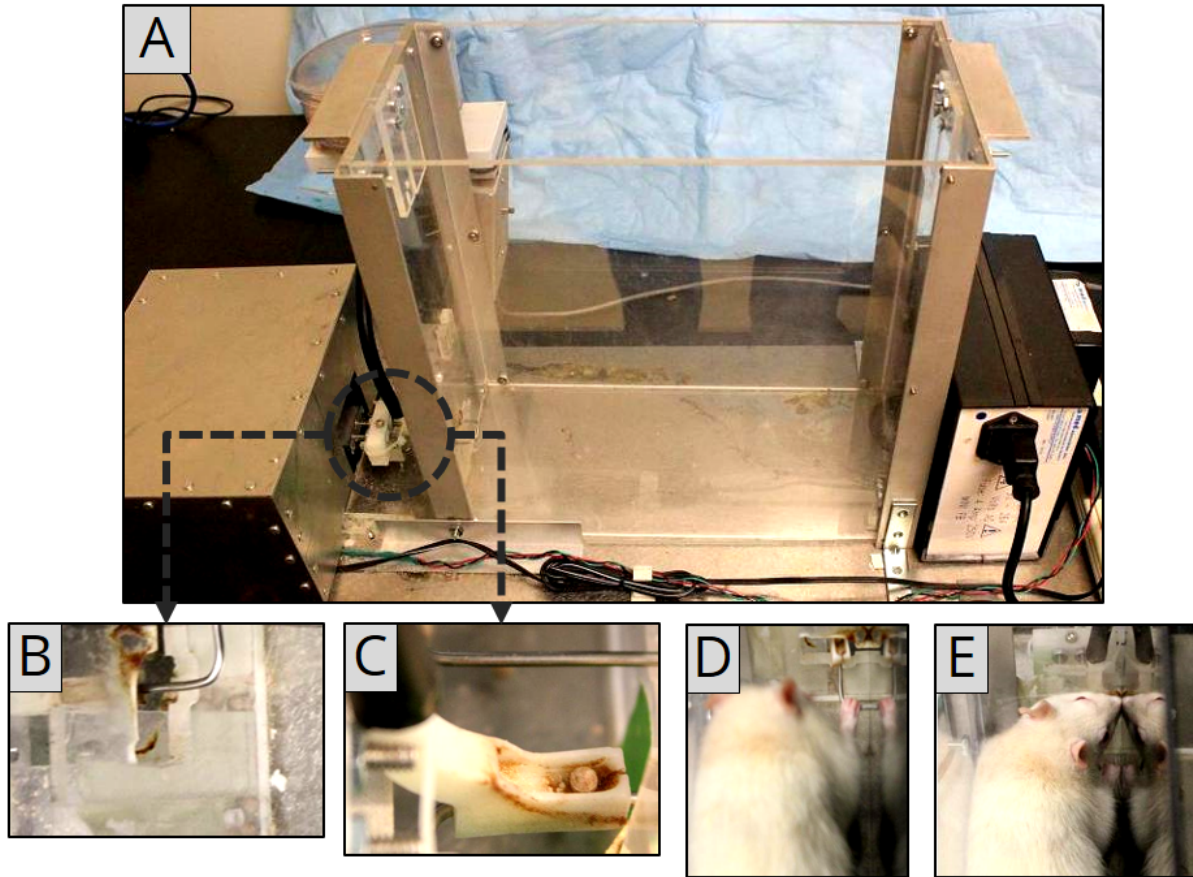


Figure 4.1: **Robotic Rehabilitator of the Rodent Upper Extremity (RUE)** - AutoGSM device. (A) The device was composed of a linear actuator, automated food dispenser, and an acrylic box to house the animal during training. (B) Animals pulled on a metallic, coupled to a linear actuator, in order to retrieve a food reward placed in the food tray (C). (D) Sample image of an animal pulling the metallic bar to retrieve the food pellets. (E) Once the food was within reach, the animal could retrieve it with the mouth.

4.3.3 Measuring grip strength

Grip strength meter

In this experiment, we followed the procedure previously developed for use with the grip strength meter and SCI models [8]. Briefly, the first week was used to acclimate the animals to being handled. This was followed by 10 training session where the animals were assessed using the GSM. To this end, they were held around the midsection with one forearm restrained by the experimenter and the unrestrained forepaw brought in contact with the grip strength meter (GSM, designed by TSE Systems and distributed by Sci Pro, Inc.). The animal was held in place until it grasped the bar and then gently pulled away from the bar by the experimenter. The grip strength was defined as the maximal force recorded by the GSM before the animal released the bar. This maximal force was recorded for four attempts and its average computed in each assessment.

RUE

Robotic-based assessments of strength with the RUE were carried once per week. On two other days each week, the animals trained with RUE for 3 minutes. For a complete description of the training protocol please refer to Chapter 5. Briefly, animals trained with either constant force-set at a value much lower than their maximum strength-or with an adaptive algorithm that sought to train them close to their maximum strength. Before conducting any robotic assessments, 45 training sessions were conducted over a span of 87 days. Following this initial training period, 11 pre-lesion and then 28 post-lesion assessments were performed with the RUE.

The procedure for strength assessment was as follows. First, the animal pulled for 4 to 5 times without resistance on the bar in order to reinforce the task-reward pairing. The bar was then 'blocked' by increasing its stiffness coefficient of the robot to a value above the animal's pulling capability. The animal then pulled for 3 to 5 repetitions. By unexpectedly blocking the bar, we expected the animal to pull at its highest force capacity in order to retrieve the food reward. We recorded the maximum pulling force exerted during the blocked trials as the animal's maximum forelimb strength.

Unlike the GSM, RUE measures the pulling strength of self-initiated movements motivated by a food reward. We did not remove trials where the forelimb force might have involved reliance on the spastic contracture of the paw to hold it to the bar—a behavior rejected in the GSM measurements.

4.3.4 Lesion of the spinal cord

For surgery, rats were anesthetized with 1.5 – 3.0% isoflurane (Western medical Supply, Inc., Arcadia, CA). Hair overlaying the cervical vertebra was removed by shaving with clippers, the skin was treated with betadine and incised, and the multiple muscle layers overlaying the cervical vertebral column were bluntly dissected. A dorsal laminectomy at C5 was performed with ronguers. The animal was placed in the stabilizing platform with Addison forceps providing stability rostral and caudal to the laminectomy. The impactor probe (2.5mm probe) was centered over the exposed spinal cord to the right of the dorsal vein. Unilateral mild lesions with 100 kD of force were created using the Infinite Horizons (IH) Impactor (Precision Systems & Instrumentation, Lexington, KY). After generating the lesions, the muscle was sutured in layers with 5 – 0 chromic gut (Henry Schein, Melville, NY) and the skin was closed with 9mm staples (Fisher Scientific, Pittsburg, PA).

Following surgery, rats were immediately placed on a water circulating heating pad until they recovered from the anesthetic. Post-surgical care included delivery of lactated ringers ($5\text{ml}/100\text{g}$, subcutaneously) for hydration for 3 days and Baytril (Enrofloxacin $2.5\text{ml}/\text{kg}$, subcutaneously, Western Medical Supplies, Arcadia, CA) for 7 days for prophylaxis against urinary tract infections (UTIs). The analgesic Buprenex (Buprenorphine, $0.01\text{ mg}/\text{kg}$, Western Medical Supplies, Arcadia, CA) was given for 3 days for pain management. Staples were removed at 14 days post injury. Rats were housed 3-4 per cage and were monitored twice daily for general health, coat quality (indicative of normal grooming activity) and mobility within the cage. Rats with cervical contusion injuries typically resume these activities the day following injury. In addition, signs of paralysis were monitored, including lack of hind limb movement, tail flaccidity, and unstable/uncoordinated movement. Rats were also monitored for skin lesions on the paralyzed limbs or autophagia of the toes.

4.3.5 Histology

At the end of the testing period (approximately 321 days post injury), rats were killed with an overdose of Euthasol® (Delmarva Laboratories, Inc., Richmond, VA) and perfused with 4% paraformaldehyde. Dissected spinal cords were post-fixed in 4% paraformaldehyde in 0.1M buffered phosphate at 4°C . Whole spinal cords were cryoprotected in 27% sucrose prior to embedding in OCT Tissue-Tek and flash freezing. A 7mm segment of the spinal cord centered around the lesion epicenter was collected. Twenty μm cross sections were taken and thaw mounted onto microscope slides. Sets of 3 slides were made such that sections on each slide were $200\mu\text{m}$ apart and the full 7mm length of the spinal cord was represented on each slide.

4.3.6 Staining

One set of slides was stained with Ehrlich's Hematoxylin and Eosin (H&E). Sections were washed in PBS, dehydrated through graded ethanols, and de-fatted in Xylenes. Slides were hydrated through graded ethanols to water, stained in Ehrlich's Hematoxylin, washed in water, differentiated in 1% hydrochloric acid in 70% ethanol, washed again in water, blued in 10% ammonium hydroxide, washed again in water, then equilibrated in 95% ethanol before staining in Eosin. Excess Eosin was removed in 95% ethanol, the slides completely dehydrated in 100% ethanol, cleared in Xylenes, and coverslipped with DPX.

Sets of sections were immunostained for GFAP to identify reactive astrocytes. Sections were washed in PBS, blocked in PBS with 5% normal donkey serum and 0.1% Triton X-100, then incubated in diluted primary antibody GFAP 1:1500 (Sigma) overnight. Sections were washed in PBS, incubated in 1:250 Alexafluor- 488 conjugated secondary antibodies 1–2 hours, then washed in PBS. Sections were coverslipped with Kiaser.

4.3.7 Data analysis

Lesion measurements

We used ImageJ software (NIH, Bethesda, MD) to measure the areas of healthy and injured gray and white matter. We focused on those sections at or near the lesion epicenter. Values were expressed as a percentage of the ratio between injured to non-injured halves.

The reduction in size was calculated as the ratio between the injured to the uninjured side. We computed this for the overall hemisphere, gray matter alone, and white matter alone. The reduction in force capability was measured by linearly fitting, for each animal, the force measured with the RUE for pre- and post-lesion data separately. The linear regressions were then used to predict the forces at $DPI = -1$ and $DPI = 1$. The reduction in force capability was thus defined as the change in force between these two instances in time.

Statistical analysis

The pre-lesion measurements using both the GSM and RUE were matched in pairs for each animal and at each testing day in order to measure the correlation between the measurements.

To measure whether there was a significant difference in the measurements immediately before and immediately after the induced lesion, we used a two-sample t-test.

Histological measurements were matched to the corresponding change in force due to the injury and correlations measured.

All statistical analyses were done using Matlab (The MathWorks Inc, Natick, MA). All measurements reported as significant fall below a significance level of $\alpha = 0.05$.

4.4 Results

4.4.1 Exclusion of animals from the analysis

Four animals were excluded from the post-lesion data analysis. Two of the animals were removed after histologically reviewing their lesion and determining that no injury had been sustained. The other two animals were removed because they did not engage in the pulling task following the injury. All four animals were included in the pre-lesion analyses as these exclusion criteria were inapplicable then.

4.4.2 Measurements of forelimb function

Pre-lesion, both methods successfully measured strength for all animals. These measurements were, on average, 2.6 times higher with the RUE than the GSM (Figure 4.2A). Post-lesion, the RUE recorded strength measurements for 10 out of 12 animals while the GSM recorded strength measurements for 1 out of 12 animals (Figure 4.2B) because of a failure to meet the paw-placing criterion.

Strength as measured with the RUE decreased after the cSCI by an average of $121.29g \pm 14.25gSEM$ on the first assessment taken post-lesion (day 10); a significant decrease (t-test, $p = 0.03$).

The GSM and RUE strength measurements prior to injury were uncorrelated (Fig. 4.3, $R < 0.001$, $p = 0.89$). Additionally, the variability in measurements between animals was, on average, 5.8 times more variable with the RUE than with the GSM (Fig. 4.2, t-test, $p < 0.001$).

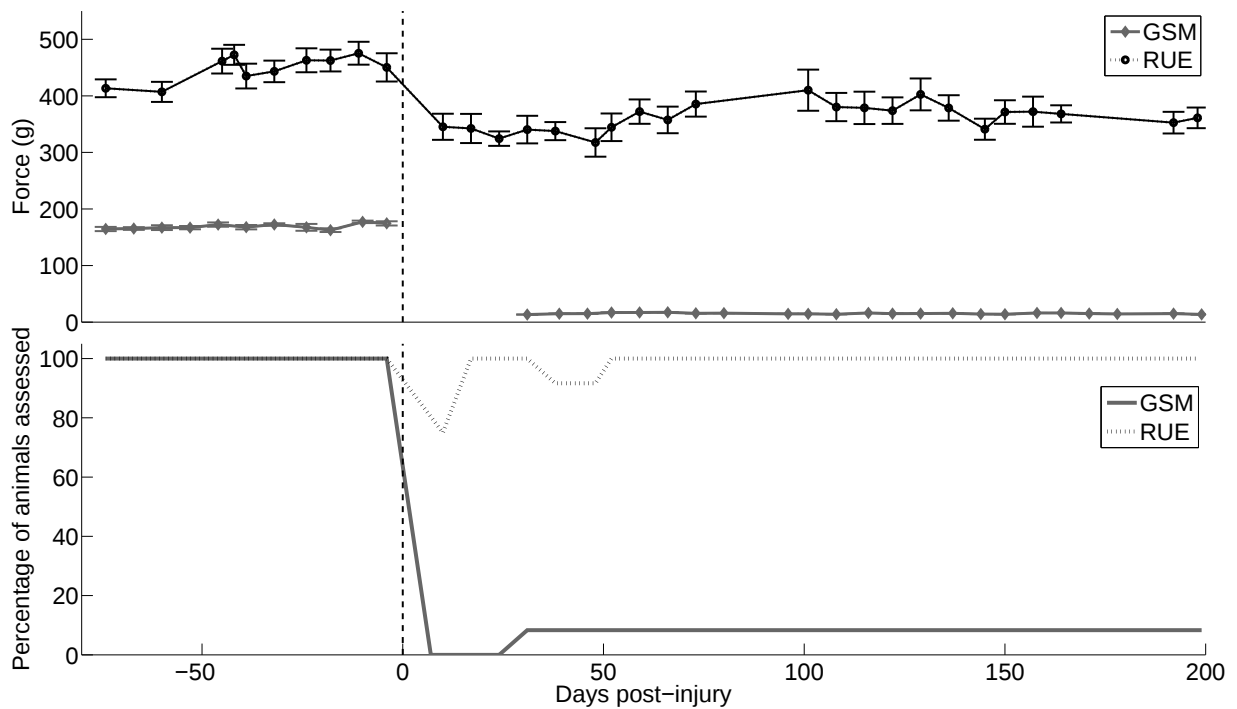


Figure 4.2: **Assessment of forelimb function** - [A] Pre-lesion measurements of forelimb strength were 2.6 times higher with RUE than with the GSM. Errorbars represent the standard error of the mean. Variability in the measurements is higher for RUE than GSM. [B] Post-lesion, RUE consistently recorded forelimb strength for all animals while the GSM only had 1 recording which met the spasticity criterion.

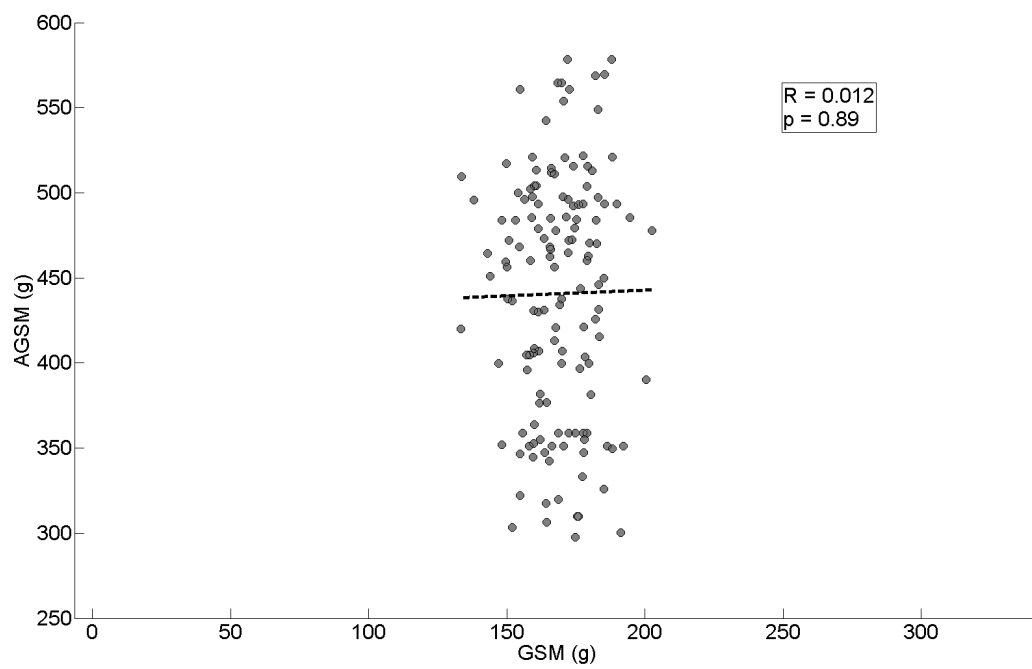


Figure 4.3: **Correlation between GSM and RUE measurements** - There was no correlation between the two measurements ($R < 0.001$, $p = 0.89$). This figure also shows the significant difference in variability between the two assessment methods.

4.4.3 Histology analysis

We quantified the effect of the injury anatomy on the performance with RUE by comparing the reduction in size of the injured side to the reduction in force capability pre- to post-injury. Reduction in white matter was significantly correlated with reduction in strength (Figure 4.4C, $R = 0.59$, $p = 0.04$). Total hemisphere size and gray matter were not significantly correlated with the loss in strength (Figures 4.4A and 4.4B, respectively).

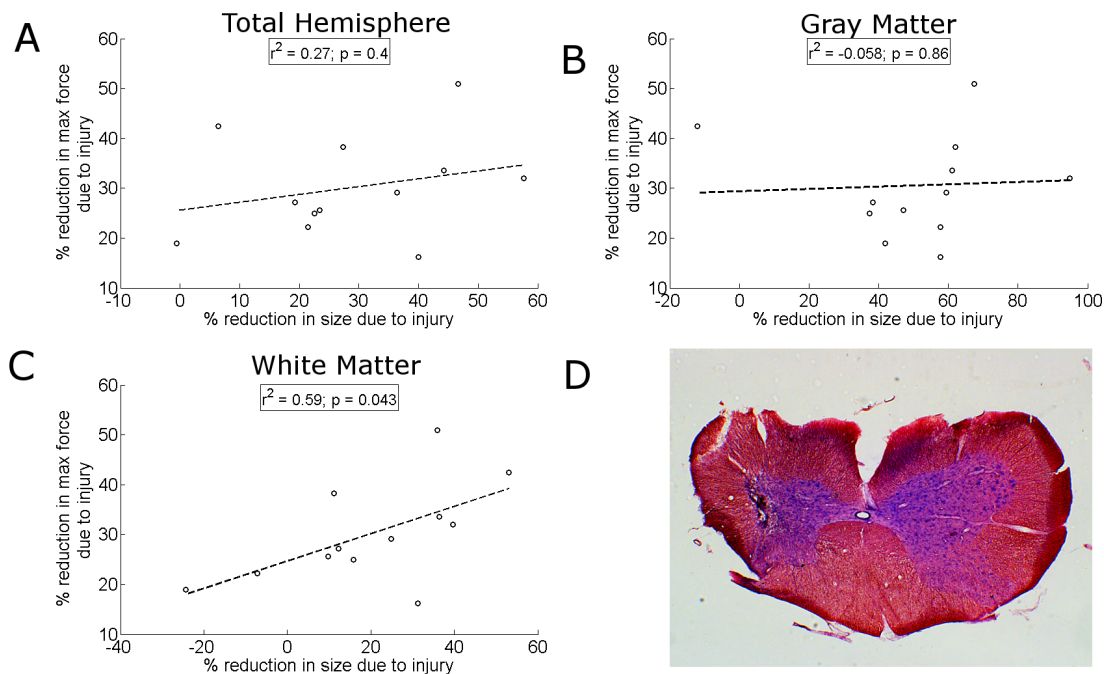


Figure 4.4: **Analysis of injury size and its effect on performance** - The reduction in white matter area (C) from the lesion was significantly correlated with the loss of strength due to the lesion ($R = 0.59$, $p = 0.04$). Neither the reduction in gray matter (B), nor the overall reduction in area of the injured hemisphere (A) were correlated with the loss of strength. (D) is a sample image of a lesioned spinal cord. The left side of the image is where the injury was applied.

4.5 Discussion

We created a device, the Robotic Rehabilitator of the Rodent Upper Extremity (RUE), and used it to assess forelimb strength of rats before and after a unilateral cSCI. RUE peak pulling force was sensitive to a moderate, lateral cSCI contusion, and was correlated with the amount of white matter sparing determined by histological analysis. As we argue next, RUE has several potential advantages over the GSM method of measuring forelimb strength, and could provide a useful new tool for studying cSCI.

4.5.1 Comparison with GSM

The RUE measures forelimb strength based on the forces exerted during a food-motivated, self-initiated, pull. These forces were on average 2.6 times larger than those measured with the GSM. Thus the RUE method is closer to measuring peak pulling force than the GSM method. However, it is still unclear if the RUE is measuring maximum pulling force, since there is no guarantee that the animal pulls with a maximum effort. Rather, RUE makes the assumption that an animal that is frustrated when it cannot obtain the food reward it is used to retrieving will pull as hard as possible to retrieve it. Indeed, the pulling force on the blocked trials was at least 1.9 times greater than the peak force on the training trials. Thus, RUE seems to measure something that corresponds more closely with the parameter of 'volitional strength', given the higher forces that animals achieve on blocked trials, as well as the higher forces it measures when compared to the GSM.

The fact that histological analysis revealed a significant correlation between the loss of strength of the forelimb and the reduction in white matter due to the injury is consistent with this concept. Previous work has emphasized that that weakness after

spinal cord injury and stroke can result from a decrease in the quantity of descending fibers transmitting motor signals to the motorneuronal pools of the spinal cord, resulting in decreased recruitment of those pools [91]. This finding is of important clinical relevance as it provides a functional outcome measure that may be sensitive to regeneration treatments targeting white matter tracts following SCI.

By requiring volitional performance of the pulling task, we argue that the RUE obviates concerns of paw spasticity corrupting the measure of peak force. With the GSM, the pulling force could arise because the paw spastically grips the bar, while the passive forelimb is pulled to the extreme of its passive range of motion by the experimenter. Thus, GSM protocols for cSCI require careful observation of paw placement, and omission of measurements thought to rely on a spastic grip. This can be the majority of measurements (all measurements post cSCI for 11 of 12 animals in the current study), causing a substantial data loss. With the RUE, the rat may grip the limb with a spastic paw, but the pulling force must be actively generated. Therefore, the RUE measures movements and forces generated by the animal, regardless of the influence of paw spasticity.

The RUE measurements were more variable than the GSM measurements. This is again consistent with the idea that the RUE measures volitional pulling force that depends on the motivation level of the animal, which might be expected to vary depending on hunger/time of day/pain etc. RUE measurements may also be more variable because the animal was allowed to grasp or hook the bar in any way it chose. Variations in grasping posture may affect the force with which an animal can pull.

On the other hand, compared to the GSM, RUE required a more complex and time consuming protocol to administer. To motivate the animals to participate in the training, they were placed on a food-restricted diet of 85% their normal food intake. The animals were then habituated and shaped to RUE over a couple of weeks prior to

any training. Once the animals were comfortable in the device, they were trained to associate pulling the bar with the food reward. Only when all the animals were successfully pulling the bar pre-lesion adaptive training started.

4.5.2 Future directions with RUE

RUE may be useful not only as an assessment tool, but also to retrain forelimb strength, thereby simulating the neurorehabilitation process in humans. Although the rehabilitation data presented in this chapter showed no change in peak force performance from the start to the end of the rehabilitation intervention, we show in the accompanying chapter that the percentage of strength recovery, relative to the pre-lesion abilities of each animal, is in fact significant. As explained in the next chapter, the rehabilitation program had animals train in either low- and high-force groups. We will show that those animals training with the higher forces show, on average, greater recovery than those training with lower forces. Thus, since RUE can achieve forelimb strength increases with an appropriate protocol design, it may be useful for enhancing neuroplasticity and neuroregeneration in rehabilitation treatments ([35]; [4]).

One of the current limitations of the RUE is a lack of understanding of how the animal uses its digits as it reaches and pulls on the bar. We plan to address this limitation in future studies by implementing video recording and computer vision capabilities that record the animal's paw movements as it interacts with the robot. Another limitation is that, much like in current rehabilitation practice for humans, rehabilitation training is only available to the animal for the short window of time it spends in the RUE enclosure compared to the amount of time it spends in its home cage. To address this, we are designing a version that will attach to the animal's home cage. By doing this we will provide the animal with a significantly longer exposure to the device

that allows the animal to engage in the strength-training task as often as it chooses, similar to how a running wheel may be left in a cage to encourage exercise [40].

Another limitation of RUE, similar to the GSM, is that it does not directly measure grip strength, defined in the usual way as the squeezing force of the paw. Future studies should compare grip strength—measured as a paw squeezing force—to forelimb strength—measured with RUE or a similar device. The food delivery paradigm used with RUE (i.e. the fact that the food proximity to the mouth was made to depend on the force exerted), as well as the ‘blocked trial’ paradigm, could potentially be used with a device that measures squeezing force to motivate effort by the animal.

Chapter 5

Effects of adaptive challenge on strength recovery and the motivation to train in rats with a unilateral cervical contusion: Toward optimal challenge for unsupervised motor rehabilitation

In collaboration with Kelli Sharp, Sergi Perez, Berkey Gebrekristos

5.1 Abstract

It is currently unclear how manipulating the challenge level of training exercises after spinal cord injury simultaneously affects motivation and recovery of the trainee. We used a robotic device, RUE, to manipulate the challenge of a forelimb strength-training task in rats with a cervical spinal cord injury (SCI). 16 rats trained both before and after the injury to pull on a bar in order to retrieve a food reward. Following the injury, the animals trained for 38 weeks with either low force (low challenge) or high force (adaptive challenge) twice per week for three minutes. The challenge level for the high force group was set using an adaptive algorithm that adjusted the resistance from pull-to-pull based on the success or failure of the previous pull. We found that animals in the low-force group attempted twice as many pulls and were twice as successful at retrieving the food reward as the adaptive group. However, even though the adaptive group performed significantly fewer pulls, they showed greater recovery in weekly strength assessments. We use these findings to propose a framework for understanding the effect of challenge during unsupervised motor training. This framework proposes that there exists a challenge level that optimizes recovery for unsupervised training programs during which the trainee is given freedom to practice as frequently as desired. Thus, fewer repetitions at higher challenge levels will lead to greater recovery in some cases, while in other cases more repetitions at lower challenge levels will be more beneficial. An iterative experimental approach can be used to estimate the optimal challenge level for different rehabilitation tasks and trainee populations.

5.2 Introduction

Neurological injuries such as stroke or spinal cord injury (SCI) can lead to weakness or paralysis of the upper extremity, making activities of daily living—such as bathing, cooking, or eating—difficult to perform. One of the major goals in physical rehabilitation is to increase the use of the impaired limbs in activities of daily living, in order to improve independence. Physical rehabilitation usually begins at the hospital where the injury was initially treated, then moves to a specialized physical rehabilitation clinic for outpatient treatment, and finally ends at the patient's home. While the first two portions of the treatment are often carried out under high levels of supervision by rehabilitation clinicians, the majority of later rehabilitation is largely unsupervised. In supervised motor training, motivation to engage in training is derived in part from the clinicians supervising the training, who typically set and monitor target amounts of training. Motivation for unsupervised motor training is more patient-driven, and training amounts are patient determined.

Rehabilitation training is currently one of the most successful treatments available for stroke and spinal cord injury, [35] but the training must be intense and high in volume in order to drive the necessary plasticity that promotes recovery [118]. For example, rat models of SCI rehabilitation of the forelimb have shown that rehabilitation training leads to increased plasticity and recovery of function, but only when that training is intensive enough ([39]; [52]; [83]).

In an unsupervised training program, the trainee must choose the correct exercises and appropriate exercise parameters, such as length of training and challenge level of the exercise. This is currently difficult because there is limited knowledge of how these parameters effect recovery. In the case of the challenge level, its simultaneous effect on recovery and motivation is in particular not well understood. Broadly, it is

known that choosing a challenge level that is too high can lead to frustration and low levels of self-efficacy [12]. On the other hand, choosing a challenge level that is too low can lead not only to boredom and a lack of engagement, but also may produce sub-optimal learning [41]. Ideally, these factors would be well-characterized in order to maximize recovery.

One important parameter that can be affected by the challenge level of a task is self-efficacy. Self-efficacy refers to a person's belief that he or she can execute a given task [11]. This concept is critical in physical rehabilitation and has been found to play a key role in patients' adherence to an exercise regime[54]. A goal when designing therapy exercises for supervised and unsupervised training programs, therefore, is to promote patients' self-efficacy in order to maximize therapy adherence.

In this chapter we evaluate the use of RUE as a training tool for a rodent model of cervical spinal cord injury. The goal of this study was to evaluate how the challenge level of a motor training task affects the motivation to engage in the task and the gains derived from this training. We hypothesized that the motivation to participate in the task would be higher for animals training at low difficulty levels. However, we hypothesized that animals training at a higher difficulty level would receive a larger benefit from the training program.

5.3 Methods

5.3.1 Animals

16 Sprague-Dawley female rats were used in this study. To motivate engagement with the task, they were placed on a food-restricted diet set at 85% of the normal amount

of food intake. All experimental protocols were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of California, Irvine.

5.3.2 Experimental protocol

The experiment was divided into three experimental phases: 1) familiarization, 2) pre-lesion: adaptive vs. constant-force training, and 3) post-lesion: adaptive vs. constant-force training. Animals trained twice each week, usually on Wednesdays and Fridays, and a strength assessment was carried out once each week, usually on Mondays.

The first two phases of the experiment were designed to test the robotic devices capabilities as an assessment and training tool and were the focus of Chapter 4. The purpose of the third phase, and the focus of this chapter, was to understand the effects of two training methodologies: low-resistance training and adaptive training on the recovery of pulling strength of animals after a C5 unilateral contusion to the spinal cord.

Following the surgical procedure to administer the injury as described in Chapter 4, animals were given one week of rest from training. All animals then trained for two weeks with very low resistance on the bar (i.e. the minimal resistance needed to make the bar retract if it were pulled and then released; about 35g). These two weeks were used to ensure that the animals had recovered enough to perform the task. After these two weeks of low-resistance training, animals were randomly assigned to one of two training groups: Group 1 ($n = 7$), continued training with the same low-resistance as before and Group 2 ($n = 5$) trained using an adaptive training algorithm (described below). During this portion of the experiment, animals performed a total of 37 training sessions and 21 testing sessions spanning 201 days post-lesion. A training session was deemed complete when either the animal had attempted 30

pulls or 3 minutes of training had elapsed. There were two periods of time where the animals were not trained or assessed which correspond to periods of unavailability of the animal trainers.

5.3.3 Robotic device

We designed a robotic-based system, RUE, to assess and train rats in a volitional fore-limb reach-and-pull motor task. As described in more detail in Chapter 4, the system is composed of a one degree-of-freedom linear actuator, an automated food reward mechanism, and an acrylic box to house the animals during training. For this experiment, a *20mg* chocolate-flavored pellet (Bio Serv, Frenchtown,NJ) was placed in a plastic tray just outside of the acrylic box and out of reach for the animals. The plastic tray was mounted on a bar that was coupled to the linear actuator. The animals were trained to pull the bar in order to bring the food reward within reach.

5.3.4 Training and assessment conditions

The linear actuator was programmed to behave as a spring. Using a spring allows for the possibility of modulating the level of difficulty of the task in two ways: 1) by changing the range of motion required to complete the task, and/or 2) by changing the amount of force required to pull the spring. For this experiment, we kept the required range of motion constant and manipulated the amount of force required.

For a linear spring, the force is governed by the equation: $F = -K * \Delta x$, where K is the spring constant, and Δx is the distance that the spring has been moved from its rest position. Since the required range of motion was constant, we modulated the level of difficulty by changing a single parameter: the spring coefficient, K .

We will now describe how we changed the spring coefficient in order to train and assess the animals under different conditions.

Low-force strength training

In the low-force training condition the resistance of the bar was set constant by setting both Δx and K to constant values (i.e. $F = \text{constant}$). This led to a peak resistance force on the bar of $36.7g$, a value well below the maximum forces previously computed for each animal.

Adaptive strength training

In the adaptive training condition, we sought to train animals close to their maximum capabilities. To achieve this, we implemented an algorithm previously developed by our research group [105]. The algorithm was designed to set the steady-state success rate of a subject performing a motor task by modulating the difficulty level based on the subject's performance. Specifically, this algorithm increases the difficulty level by a step size, δ , following a successful trial and decreases the difficulty level by a value proportional to the step size, $\alpha\delta$, following an unsuccessful trial.

To implement the adaptive algorithm in this experiment, where the level of difficulty is directly proportional to the spring constant, we needed to specify three parameters: 1) the step size (ΔK), 2) the step ratio (α), and 3) the initial spring constant (K_0).

The step size, ΔK , determines the convergence rate and variability of the difficulty level. Choosing ΔK requires a trade-off. A high ΔK value means that each iteration will have a big change relative to its previous value; this is good in terms of convergence rate, but leads to a high variability in the difficulty level experienced by the

animal. On the other hand, a low ΔK value leads to a stable algorithm with low variability, but a much slower convergence rate. For this experiment we chose a ΔK value of $0.02N/m$.

The step ratio, α , is related to the success rate (SR) of a training session by the equation: $\alpha = \frac{SR}{(1-SR)}$. For this experiment, we chose a value of $\alpha = 0.4$. This means that the steady-state success rate of the animals for a given session should be around 30%.

The final parameter, the initial spring constant, K_0 , defines the starting level of difficulty for a given training session. Setting this value too far away from the value at convergence—either too high or too low—means that the animal would have spent most of the training session at an incorrect difficulty level. For the first session, this parameter was set at $0.1 \frac{N}{m}$. For the subsequent session, the initial spring constant was set to 80% of the maximum K value reached in the previous session. This was done to reduce the time to convergence of the difficulty level for each given session.

Strength assessment

To measure the maximum force that an animal could generate we unexpectedly ‘blocked’ the bar on some trials by setting K at a value 5 times above the animal’s maximum-recorded K value. Using this setup of a very stiff spring we assumed that the animal exerted its maximum pulling force, as the animal volitionally increased its force in response to the blocked bar that kept the food pellet out of reach.

The assessment was carried out by first allowing the animal to pull for a few times with very low resistance on the bar—to reinforce the association between pulling and food reward—and then unexpectedly increasing the value of K .

5.3.5 Unilateral cervical lesion to the spinal cord

Following training for 11 weeks with the robotic device, the animals were subject to a C5 unilateral contusion to the spinal cord. Injuries were delivered using an Infinite Horizon impactor (Precision Systems & Instrumentation, Lexington, KY) set to deliver an injury of $100kdynes$. For a full description of the surgery to administer the lesion and the post-operative care, please refer to Chapter 4.

5.3.6 Finding the optimal challenge for unsupervised motor training

We defined challenge level as: (Challenge Level = $1 - \text{Success Rate}$). Thus an animal with a high success rate had a low challenge level and one with a low success rate had a high challenge level. The challenge level, like the success rate, ranges in values between 0 and 1.

To find the optimal challenge we needed to compute, for each animal, 1) the repetitions performed in a session, and 2) an estimate the gains in strength from a single repetition. The repetitions were defined as the average number of successful trials in a given training session. To find the gains in strength from a single repetition we used a linear regression on the forces recorded during the force assessments with days post-lesion as the single regressor. We then used this regression line to compute the total gain as the change in gains from the first to the last assessment. The total gain was then divided by the number of repetitions obtained in step 1 to find the gain-per-repetition.

Using these two parameters, averaged across animals for each training condition, we defined the relations: 1) repetitions per session versus challenge level, and 2) gain

per repetition versus challenge level. We then used these relations and the measured challenge level of each animal to find the overall challenge level that would theoretically optimize recovery for this task.

5.3.7 Data analysis

We extracted the maximum forces exerted by each animal during each assessment and training session. The maximum force was defined as the single highest value of force recorded during a given session. For each training session we also extracted both the total number of pulls attempted and the total number of successful pulls. An attempted pull was defined as movement of the bar exceeding a 'start-distance threshold', defined as $3mm$. Successful pulls were those that in addition to the start-distance threshold also exceeded a 'successful-distance threshold', defined as $20mm$. Note that when the bar was pulled past the successful-distance threshold, the food pellet just passed through the window, allowing the animal to take it with its mouth. We programmed the robot to hold the bar at this position for 2 seconds before retracting to allow the animal to take the food.

In the post-lesion analysis of the testing forces we were interested in the change in force relative to the pre-lesion assessments. We therefore calculated the change in force (expressed as a percentage) relative to the average maximum forces exhibited in the last three assessments prior to injury. We did this calculation for each animal and each assessment post-lesion.

For each training session we also extracted both the total number of pulls attempted and the total number of successful pulls. An attempted pull was defined as movement of the bar exceeding the start-distance threshold. Successful pulls were those

that in addition to the start-distance threshold also exceeded the successful-distance threshold.

Statistical analysis

We used a linear mixed model to test the effects that training condition had on the forces exerted during testing and training, as well as on the total number and the percentage of successful repetitions in each training session. The training condition (adaptive vs. low-force) and number of days post-injury (DPI) were set as the fixed factors and animals as the random factor. We evaluated the main effects and their interaction at a significance level of $\alpha = 0.05$. All analyses with the linear mixed models were carried out for the data starting on the day that the animals were separated into their training groups.

For the average values obtained by each animal during each training or testing session we also conducted a t-test to identify if there was a significant effect of the training condition on each of the following outcome measures: 1) amount of strength recovery, 2) maximum training forces, 3) total number of pull attempts during training, and 4) percentage of successful attempts during training. We set the significance level for these comparisons at a significance level of $\alpha = 0.05$.

Post-processing and extraction of outcome measures was done using scripts built with Matlab (Mathworks; v7.8). Linear mixed model analyses were done using the R statistical package (R-package v3.0.1). Results are presented as the mean $\pm$ standard error of the mean (SEM).

5.4 Results

5.4.1 Exclusion of animals from the analysis

5.4.2 Adaptive strength training led to higher training forces

Prior to group separation ($DPI < 26$) both groups trained with low resistance. Once the groups were separated, the maximum forces experienced in training were higher for the adaptive group, as expected (Figure 5.1, linear mixed model main effect of training condition, $p < 0.001$). Following group separation, the maximum forces experienced across training sessions were, on average, 5.5 times higher for the adaptive group than for the low-force group. The average of the maximum forces across training sessions was $36.74g \pm 0g$ for the low-force group and $202.70g \pm 39.78g$ for the adaptive group. The training forces for the adaptive group increased through training (linear mixed model, significant interaction term of group and DPI, $p < 0.001$).

5.4.3 SCI decrease strength and adaptive strength training led to greater recovery in strength

The animals' maximum forces measured during blocked strength assessments decreased, on average, by 30% following the injury (Figure 5.2). Over the course of the next 200 days of training, the adaptive group exhibited greater recovery in strength, but the difference relative to the low-force group only approached significance (Figure 5.2, linear mixed model main effect of training condition, $p = 0.085$). The rate of recovery for all animals, defined as the gains in strength across DPI, was significantly

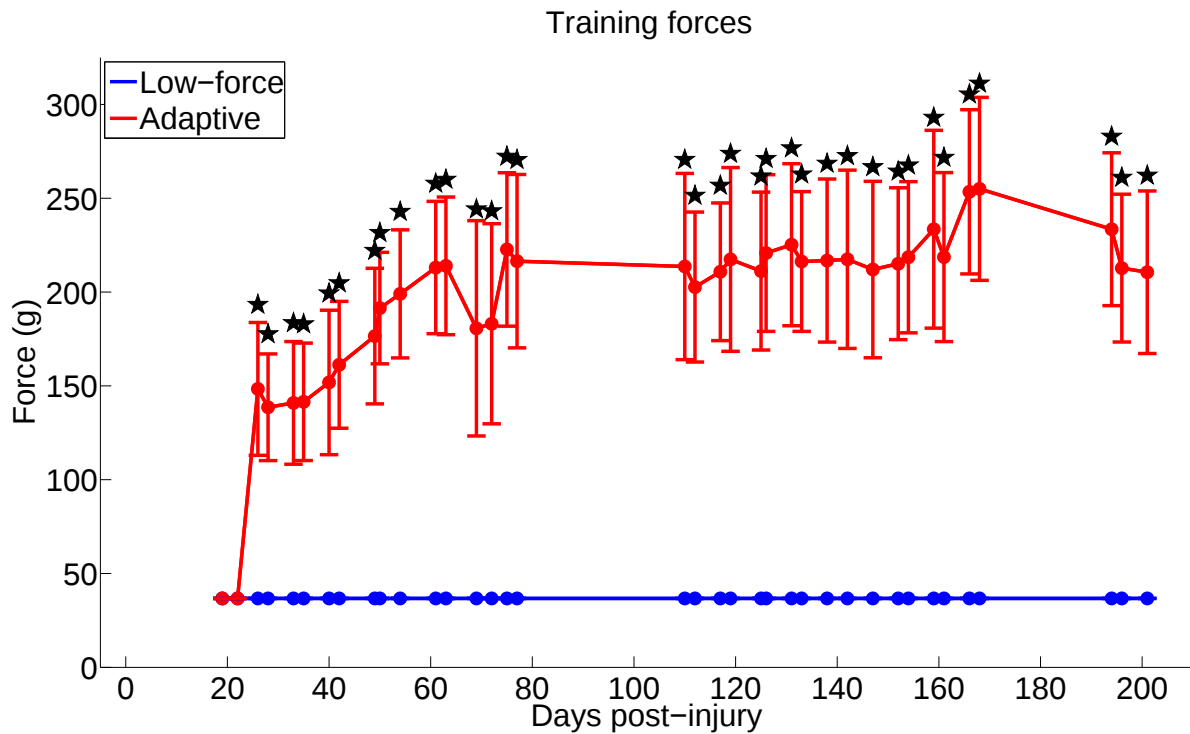


Figure 5.1: **Maximum forces during training sessions** - Animals in the low-force group trained in all sessions with a constant resistnace of $36.74g \pm 0g$. Animals in the adaptive group trained with significantly larger forces (linear mixed model, significant interaction term of group and DPI, $p < 0.001$) which were on average $202.70g \pm 39.78g$ throughout all training sessions. Stars mark a significant difference at a given training session as measured with a t-test. Errorbars represent the standard error of the mean.

different from 0 (linear mixed model, main effect of DPI $p = 0.0029$), but it was not different between the two groups (linear mixed model, interaction effect $p = 0.13$).

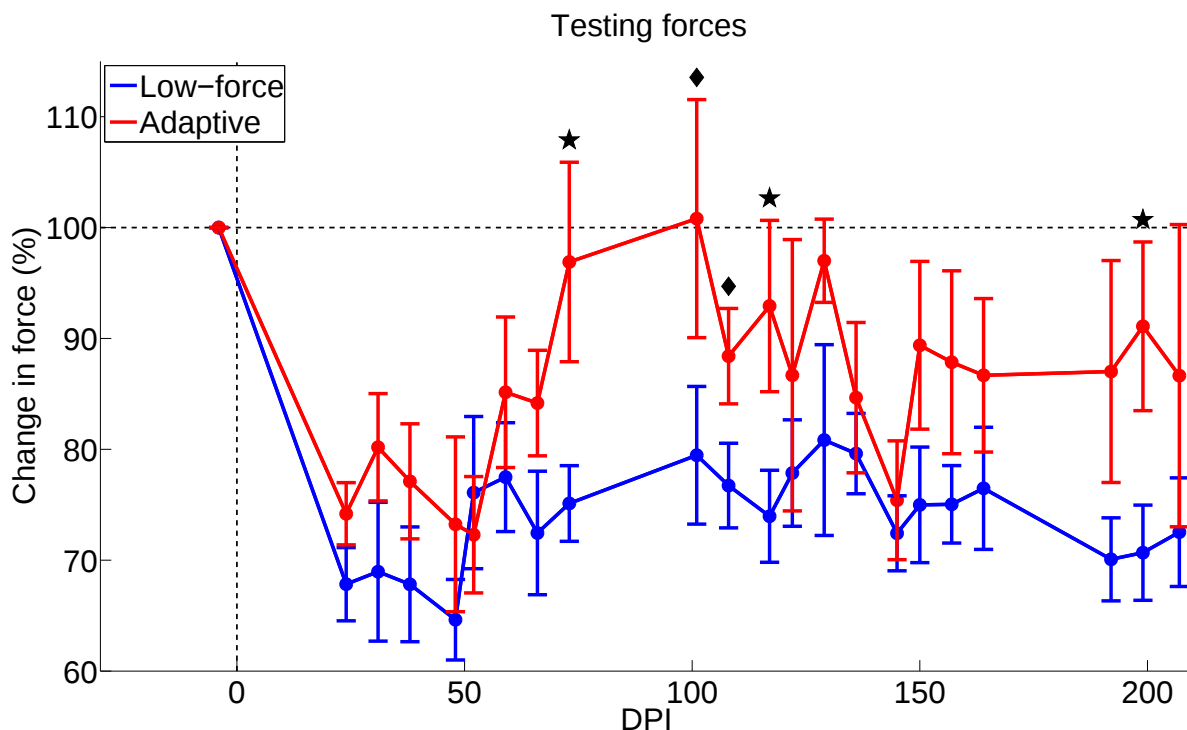


Figure 5.2: **Recovery of strength following the cervical spinal cord injury** - Animals in the adaptive group showed greater recovery than the low-force group, but this difference failed to reach significance (linear mixed model main effect of training condition, $p = 0.085$) The rate of recovery (i.e. recovery in force as a function of time) was significant for both groups (linear mixed model, main effect of DPI $p = 0.0029$), but it was not a significantly different between the groups (linear mixed model, interaction effect $p = 0.13$). Stars mark a significant difference at a given training session as measured with a t-test. Errorbars represent the standard error of the mean.

5.4.4 Blocking the pull bar led rats to pull harder

Animals in the adaptive group produced forces that were, on average, 1.9 times higher during the blocked assessments than the maximum forces recorded during the training sessions ($386.73g \pm 43.44g$ during assessments versus $202.70g \pm 39.78g$ during training).

5.4.5 Adaptive strength training led to a decreased engagement in the task

Animals in the adaptive group attempted a significantly lower number of pulls than animals in the low-force group (Figure 5.3, linear mixed model main effect of training condition, $p < 0.001$). On average, animals in the adaptive group attempted 15.7 ± 3.7 repetitions in each training system, while animals in the low-force group attempted 26.4 ± 2.5 repetitions in an average training session.

Following the injury, and prior to group separation, both groups attempted a similar number of repetitions (Figure 5.3, t-test, $p = 0.64$) during the low-resistance training provided in this period. Once the animals were separated into the training conditions, the average number of attempts between groups diverged significantly (Figure 5.3, linear mixed model interaction effect, $p < 0.001$).

5.4.6 Adaptive strength training led to a lower success rate during training

The success rate was significantly lower for animals in the adaptive group when compared to animals in the low-force group (Figure 4, linear mixed model main effect of training condition, $p < 0.001$). These rates diverged significantly from one another following group separation (Figure 4, linear mixed model interaction effect, $p = 0.001$).

The average success rate, across all training sessions, was $41.14\% \pm 8.41\%$ for the adaptive and $92.03\% \pm 6.54\%$ for the low-force group. For the adaptive group this success rate is higher than the target 30% success rate defined by the step ratio parameter of the adaptive algorithm.

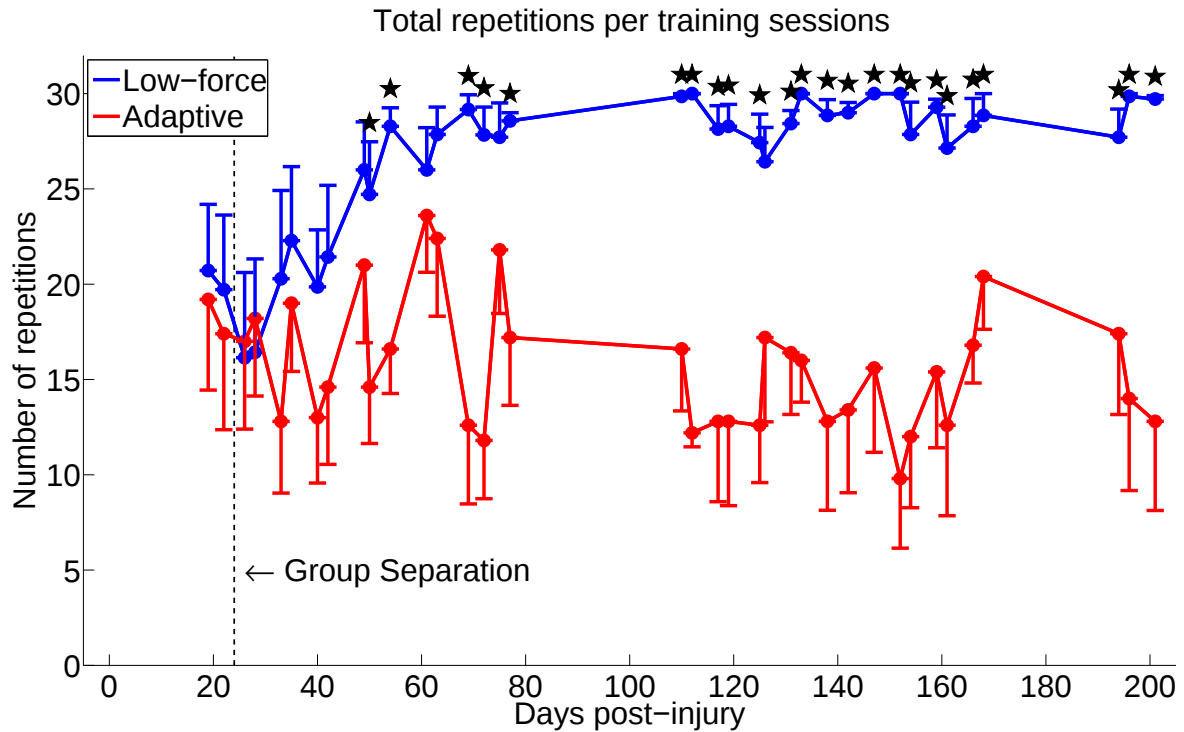


Figure 5.3: **Total pull attempts in a training session** - Animals in the low-force group attempted almost twice as many pulls as animals in the adaptive group. This difference was significant throughout the 200 days of training (linear mixed model main effect of training condition, $p < 0.001$). Average repetitions per training sessions were 26.4 ± 2.5 for the low-force group and 15.7 ± 3.7 for the adaptive group. Stars mark a significant difference at a given training session as measured with a t-test. Errorbars represent the standard error of the mean.

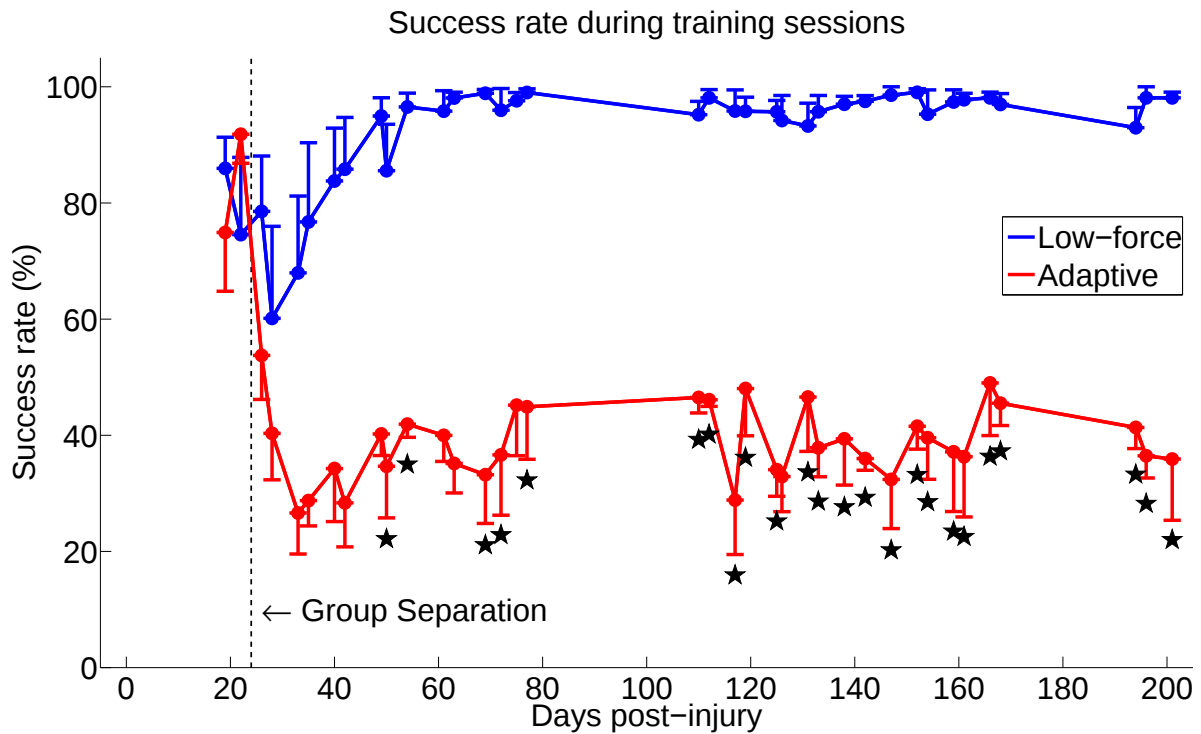


Figure 5.4: **Success rate in the pulling task** - Animals in the low-force group were significantly more successful at completing the task than animals in the adaptive group (linear mixed model main effect of training condition, $p < 0.001$). The average success rate was $92.03\% \pm 6.54\%$ for the low-force and $41.14\% \pm 8.41\%$ for the adaptive group. Stars mark a significant difference at a given training session as measured with a t-test. Errorbars represent the standard error of the mean.

5.4.7 The optimal challenge for unsupervised motor training framework

Taking these findings, we can estimate the optimal challenge for promoting recovery after SCI for this task under the following assumptions. First, we assume that there is a proportional relationship between the challenge level of the task and the gains obtained per repetition (Figure 5.5A). We also assume there is an inversely proportional relationship between the challenge level of the task and the number of successful repetitions an animal will complete in a training session (Figure 5.5B). Multiplying these two relationships leads to parabolic relationship with a single maximum for the expected gain per training sessions versus the challenge level presented in that session. From this model, we propose the optimal challenge framework for unsupervised motor training, which is that there exists a challenge level that optimizes motor recovery in unsupervised training programs where the trainee chooses how much to engage in training. For this experiment, we found the optimal challenge level to be 36.6%, or a success rate at the task of 63.4% (Figure 5.5C).

5.4.8 Training conditions did not affect the weights of the animals

We tracked the weight of the animals across the experiment in order to monitor their health. The change in weight from the onset of injury ($292.85g \pm 4.69g$) to the end of the rehabilitation program ($303.59g \pm 7.35g$) was not significant ($p = 0.23$). The weights of the animals in each training conditions were comparable at the end of training (t-test, $p = 0.64$).

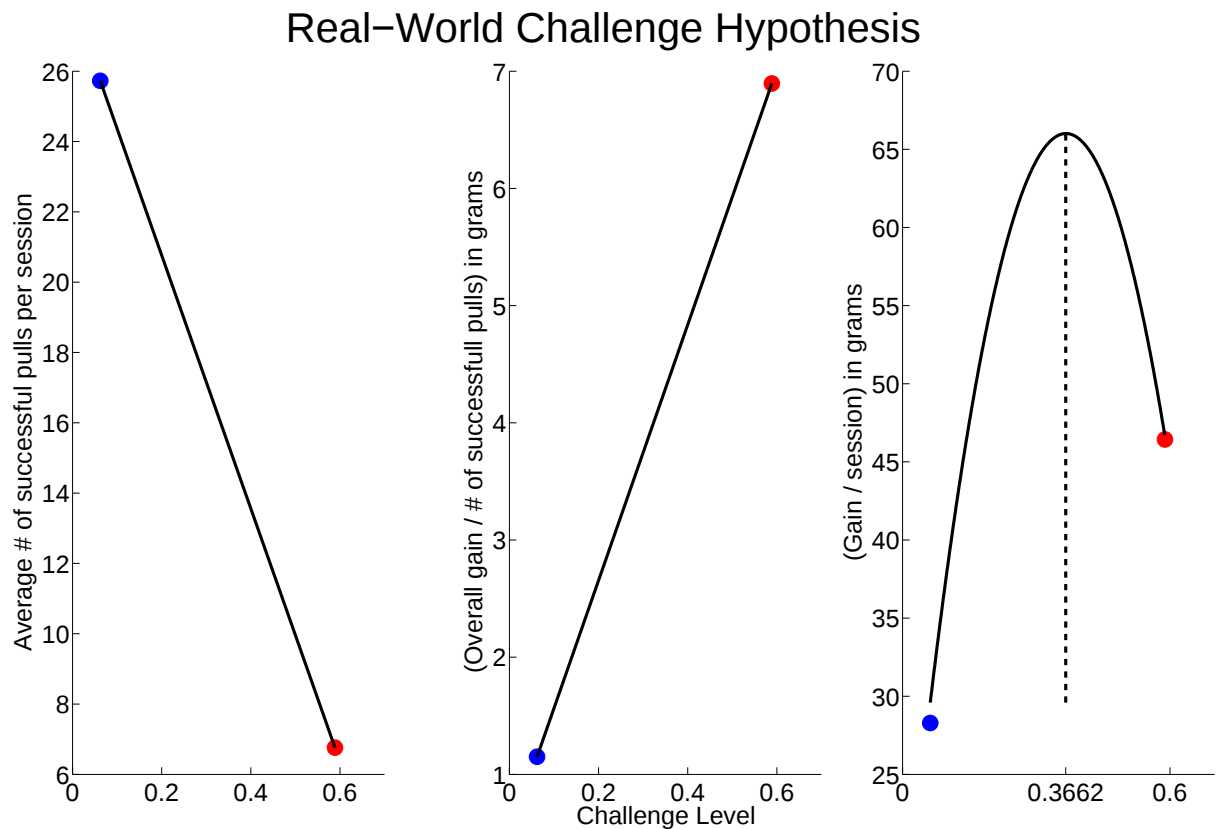


Figure 5.5: **Real-World Challenge Point Framework** - The Real-World Challenge Point Framework was derived using experimental data. For all diagrams, the x-axis represents the challenge level, which was defined as $1 - \text{Success Rate}$. This optimal point is derived from the product of the component relations between number of pulls and challenge level (left), and gains in strength and challenge level (middle). Because of the opposite slopes in these relations, the product yields a parabola (right) from which we can readily obtain the optimal challenge level. For this task, the optimal challenge of 0.36 means that animals should train with a success rate of 0.64, or 64%.

5.5 Discussion

This study examined the effects that manipulating the challenge level of a forelimb strength-training task had on the recovery of rats following a unilateral contusion to the C5 vertebrae. We specifically quantified how training with low forces versus training with an adaptive algorithm that required animals to train with higher forces affected the recovery in strength and the number of repetitions that the animals achieved during each training session.

5.5.1 Adaptive strength training led to larger strength recovery with a smaller therapy dosage

Animals that trained with the adaptive algorithm attempted less repetitions and were less successful at completing the task than animals in the low-force group. This suggests that these animals were less motivated to perform the task. However, they showed greater strength recovery than animals in the low-force group, thus implying that the benefits in strength recovery per repetition were higher when training with higher forces.

5.5.2 Both training groups were challenged at suboptimal levels

The shape of the curves for total repetitions and success rate of the low-force group is comparable to curves seen regularly for recovery or initial learning of a motor task. However, the fact that they reach a ceiling effect, as evidenced by a success rate close to 100%, indicates that these animals were challenged at a suboptimal level. On the other hand, following group separation, animals in the adaptive group quickly

lowered the total number of pull attempts suggesting a decreased level of motivation, or perhaps a diminished level of self-efficacy in their ability to perform the task.

5.5.3 Implications for unsupervised motor training in animal and human models

For rehabilitation treatments involving unsupervised motor training where the trainee is free to choose the amount and frequency of training, it is important to challenge the individual at a level that is close to, or at, their optimal level. This optimal challenge level is subject-specific and may change over time as the trainee's abilities and feelings of self-efficacy evolve.

Further analyses should be done where the animal is exposed to the training device for a longer period of time. This study was carried out with training sessions that were conducted twice a week and had a maximum length of 3 minutes. Another study of forelimb function rehabilitation had animals train 6 times a week for 10 minutes each day [39]. By re-designing RUE to allow for fully unsupervised training, we expect we can expose animals to training for multiple hours per day. This should lead to increased recovery, but most importantly, to an increased understanding of the animals' voluntary training frequency.

5.5.4 How to find the optimal challenge level for motor training

Much like the process taken in this study, we propose that finding the optimal challenge level for an individual in a particular motor task could use an iterative approach similar to the one used in a gradient ascent optimization algorithm. First an initial

challenge level must be chosen and training carried out at this level to assess both the participant's volitional training frequency and the gains in performance. Once this data point is obtained, a second challenge level, above or below the current challenge level should be tested. Again, the volitional training frequency and gains in performance must be computed at this challenge level. Using the data points from training at each of these challenge levels one can assess the appropriateness of the challenge levels and choose a third challenge level on which to train, as shown in the Results section.

We would argue that the search should start with challenge levels that are on the easier side in order to foster the participant's self-efficacy at the task. This is because self-efficacy at the beginning of an exercise regime has been shown to be a strong predictor of adherence to the training [82].

In conclusion, this study shows how the challenge level of a motor training task in a rat model of SCI can affect both the recovery and the intrinsic motivation to train. We suggest there is an optimal challenge level that maximizes recovery.

Chapter 6

The Bimanual Vending Machine: A robotic device for unsupervised hand movement training during neural repair of a cervical spinal cord injury in a primate model

In collaboration with Albert Sans and the University of California Spinal Cord Injury Consortium

6.1 Abstract

Successful neurorepair for sensory motor recovery following spinal cord injury (SCI) will likely require using intensive movement training to supplement cell- and drug-based treatments. Currently, intensive movement training for primate models of cer-

vical SCI is labor intensive, requiring one-on-one interaction with a human trainer. We developed a robotic device for providing in-cage movement training of the hand following unilateral injury to the cervical spinal cord. Such an injury leaves an animal with one functional hand and one impaired hand; therefore the animal rarely uses the impaired hand in a spontaneous way. The robotic device motivates in-cage exercises of the impaired upper extremity by requiring the animal to interact with a robotic manipulandum with the impaired hand in order to deliver a food reward to the other hand. This chapter presents a description of the device design and example usage data before and after a SCI. Animals readily learned to use the device to achieve repetitive and quantifiable, in-cage, self-training of the impaired hand. This provides a proof of concept that robotic training can induce animals who normally show little spontaneous use of the impaired hand to repeatedly exercise their impaired hand in their cage with minimum trainer interaction.

6.2 Introduction

Animal models are essential for developing neurorepair treatments for spinal cord injury (SCI). They provide a means to test and understand the mechanisms of such treatments, including drug therapies, regenerative treatments, physical rehabilitation, or combinations of the three, allowing them to be optimized for delivery to humans. Experiments with candidate treatments usually begin with rodent models. Subsequent testing in nonhuman primate models is rarer, and this may account for some difficulties that have been experienced during translation to humans, because some treatments were not optimized for primate anatomy and physiology. To address this problem, the University of California Spinal Cord Injury Consortium has developed a nonhuman primate model to test the potential of candidate neural re-

pair interventions for SCI recovery [80]. This model seeks to better understand the endogenous plasticity previously found in nonhuman primates and humans and to test the translation of potential treatments for human clinical trials in light of this plasticity.

One promising approach for SCI repair is neuroregeneration, such as with stem cell therapies, which are intended to create new circuitry that connect the brain and spinal cord [66]. This new circuitry is expected to involve the regeneration of injured axons or the sprouting of axons unharmed by the initial lesion. Several studies have found that axons can in fact be made to regenerate across the location of the injury and create synapses with neurons below the lesion ([65]; [21]). However, robust functional recovery has not been obtained and in some cases, regeneration has caused negative effects such as increased pain or spasticity ([64]; [37]; [46]).

The fact that functional recovery may not occur even after axons have been induced to successfully cross the lesion site and connect with circuitry below the lesion highlights the fact that new axons may not automatically replicate pre-lesion circuitry. One approach to addressing this issue is to use rehabilitation training to provide mechanical stimulation that enhances the tissue microenvironment, helping cells integrate in a functional way [4]. Research in both animal models and humans has shown that rehabilitation exercise enhances sensory motor recovery following SCI ([37]; [28]; [22]; [67]) as well as stroke ([58]; [55], [108]). Rehabilitation exercises could provide guidance clues or shape synaptic connectivity so that target circuitry learns to produce functional output patterns.

Recovery of hand function is a high priority for individuals with cervical SCI, or about 50% of people with SCI [7]. In the current experimental approach used by the UC Spinal Cord Injury Consortium, animals receive a cervical SCI via either a lateral hemisection or lateral contusion. This injury leaves the animal with one functional hand

as well as fairly robust use of the legs, reducing the suffering of the animal since the animal can ambulate, groom, and feed independently. However, because the animal has one functional hand and two functional legs, it rarely uses the hemiparetic hand, and thus does not spontaneously generate the motor activity that is thought to be needed to shape new circuitry.

Therefore, in the current experimental paradigm, monkeys are evaluated on a battery of hand training exercises to measure recovery and encourage use of the hand [81]. Execution of the battery requires that the animal be removed from its cage, sat in a chair, and assisted in performing the exercises. The labor-intensive nature of this approach currently limits the training of animals to a total of about 1.5 hours per week. It is unclear if this dosage is sufficient to drive the creation and strengthening of neural connections necessary for functional improvements. Studies in humans suggest that training duration of at least several hours per day are needed to optimally induce recovery after stroke [61].

Current options for providing unsupervised training to hemiparetic animals are limited and are mostly based on behavioral tasks. The UC Spinal Cord Injury Consortium has developed a series of exercises and assessments to monitor the functional recovery of the animal's upper extremity [81]. These tests include 4 tasks in a restraint chair where the sole focus is on hand training, treadmill training, and open-field training in which animals are placed in a larger cage and given specific tasks to retrieve food rewards. These tests are very time consuming and require extensive involvement by the animal trainers. Moreover, managing a large number of animals means that each animal only gets a few hours of hand-specific training per week. This is likely insufficient to drive the desired level of functional recovery.

We developed a robotic device, the Bimanual Vending Machine (BVM), to increase hand training dosage in this primate model of cervical SCI. The BVM provides a means

to administer unsupervised, in-cage, and self-initiated training of the hand. It requires animals to simultaneously use both hands in order to retrieve a food reward while at the same time recording the animal's interaction with the device. This chapter describes the design of the BVM and provides a proof-of-concept of the device using initial experimental testing.

6.3 Methods

6.3.1 Animals and injury model

All experimental protocols described in this chapter were carried out in the California National Primate Research Center at UC Davis with IACUC approval. To date, 14 non-human primates have interacted with the BVM. The animals were Rhesus macaque monkeys between 6 to 10 years old, who participated in other protocols that involved hand and locomotor training, including treadmill walking and open field exercises. Some of these animals received an injury to the right cervical spinal cord at the C7 level, either via lateral hemicontusion or lateral hemisection, impairing the right hand. For a complete description of the training activities and injuries see [81].

6.3.2 Robotic device

Overview

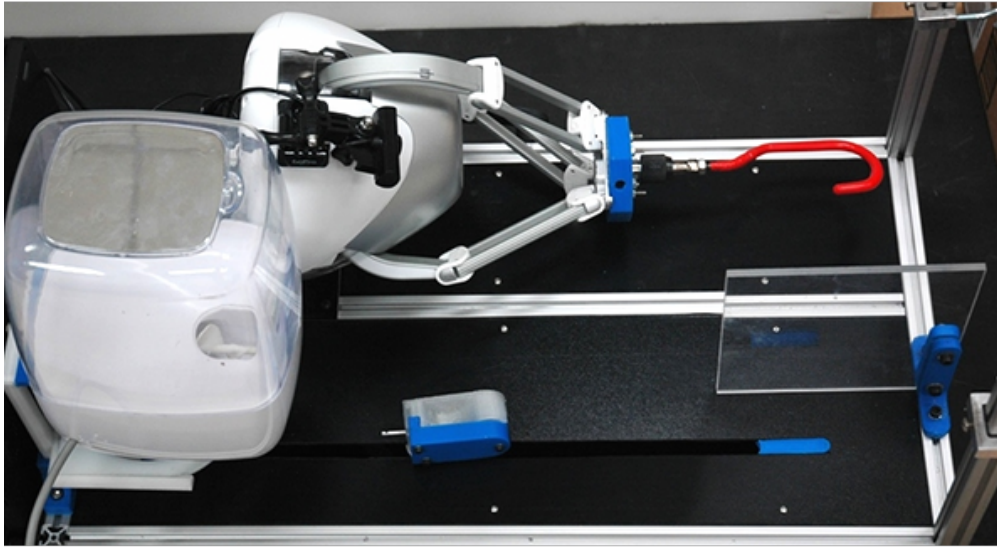
The Bimanual Vending Machine (BVM) consists of six main parts (Figure 6.1A): 1) a three degrees-of-freedom robotic manipulandum, consisting of a commercially available parallel, haptic robot for force feedback (Novint Falcon, Novint Technologies); 2)

a set of handles that can be attached to the robotic manipulandum (Figure 6.1B); 3) a custom-designed automatic food treat dispenser (the food treat we have used is an almond, but can be anything almond-sized); 4) a motorized food delivery cart that brings the dispensed food within range of the monkeys cage and can indicate its state using a colored LED; 5) a video camera that records the monkeys hand movements; and 6) a computer interface that allows the trainer to set the training parameters and records the sensor data from the training session (Figure 6.1C). Optical proximity sensors mounted on the food dispenser and the food cart detect dispensing of a food treat into the cart, as well as removal of the food treat. The data recorded by the computer interface includes the position, velocity, and forces of the manipulandum as well as the total number of successful repetitions, defined as movement of the food cart toward the animal followed by removal of the treat, and total training time for each session.

To facilitate training of the animal on how to use the device, the food reward tray is equipped with a color-based light system that provides cues about the state of the system. The system presents a different color to the animal when the food cart is: 1) empty (blue), 2) loaded with a reward (red), or 3) in the process of being loaded with a food reward (green).

The device was assembled atop a lightweight aluminum frame that can be hung on the cage front. The total weight was kept under *20lbs* for portability. In addition to the lightweight design, the system is battery-powered and is controlled by a simple graphical user interface implemented on a touch-based computer.

A



B



C

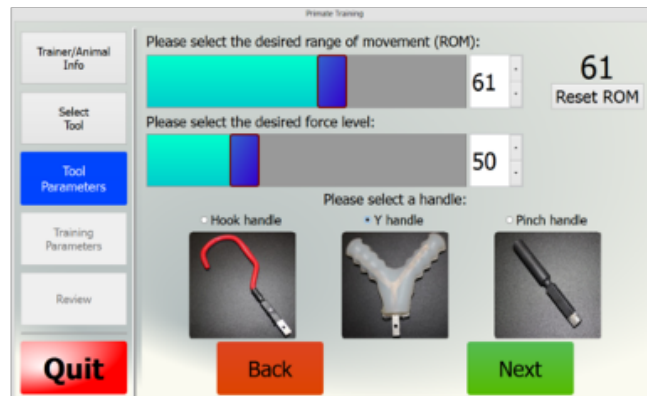


Figure 6.1: **The Bimanual Vending Machine** - **A.** Bimanual Vending Machine. The main components of the device are the haptic robot, reward system (i.e. food dispenser), and a central computer to control the device. **B.** Library of handles. Three handles have been designed to geometrically force specific grip types as the animal interacts with the device. **C.** User interface for setting up a training session. Animal trainers control the parameters of a training session by means of an easy-to-use graphic interface. This sample screen shows the selection of the required range of motion (ROM) and force levels required to complete a repetition.

Control strategy

The device requires the active participation of the animal to simultaneously use both hands to retrieve a food reward. Specifically, animals use their right (i.e. injured) hand to manipulate the handle attached to the haptic robot. As the animal performs the desired hand exercise with the handle, the robot measures performance of the exercise, characterizing it with a scalar 'score' that varies from 0 to 1. For example, in 'pull mode', the score is 0 at the rest position of the handle, and 1 when the monkey pulls the handle to the limit of its range of motion toward the cage (see below). The motorized cart containing a food reward is programmed to move toward the cage in proportion to the score. It moves within reach of the monkey's left hand for retrieval when the score enters the approximate range of 0.9 - 1. Because of this proportional-type control, if the animal releases the handle, the cart quickly retracts out of reach of the animal. This prevents the animal from cheating by using only one hand to both manipulate the haptic robot and retrieve the food reward.

The trainer can select the complexity and challenge level of the desired grasping movement by choosing how different range of motion or grasp-force targets map to the score. The trainer can also change the handle attached to the haptic robot to require different grasp types (Figure 6.1B).

Training modes

We have initially developed two training modes: pulling mode and bump mode. In pulling mode, the haptic robot is programmed to behave as a spring-damper system. The resting position of the spring is defined so that the handle retracts away from the animal when the animal releases it. Pulling the handle towards the cage causes

the food tray to move towards the cage in proportion to the score, defined as the relative distance from 0 to 1 that the handle is pulled in the x-axis (i.e. horizontally toward the cage), with respect to the range of motion of the robot in this direction. This corresponds to a pull distance of about 12 cm. Only movements in the x-axis increase the score. As soon as the animal releases the handle, the robot retracts the handle to its resting position and the food tray mimics this motion. As described above, this proportional strategy requires the animal to continuously hold the handle with one hand while he or she retrieves the food reward with the other hand. Trainers can modify the range of motion, the resistance force of the spring, or both in order to determine the challenge level of this exercise.

Bump mode is a simpler mode of training that we implemented to allow animals with more severe hand impairment to interact with the robot. In this mode, the manipulandum was again set as a spring with its resting position so as to pull the handle away from the cage when the handle is not touched. However, in bump mode, animals are rewarded for any interaction, in any direction, which moves the handle away from its rest position. That is, the score is the distance the handle moves from its rest position in any direction, rather than the distance in the positive horizontal direction. Again, to maintain the requirement of bimanual training, the food tray retracts quickly as soon as the animal releases it. In this mode, if an animal is unable to grasp the handle or generate enough force to pull the handle, simply bumping the handle away from its rest position will deliver a reward.

6.4 Results

To date, the BVM has trained 14 animals in pre- and post-lesion states in their home cage for more than 100 training sessions.

All animals trained with the device were able to use it, both pre- and post-lesion. Reports from the trainers indicate that the animals readily learned how to use the device following 1-3 short familiarization sessions. A typically familiarization session involved the trainer placing the BVM in front of the animals cage, then hand delivering a food reward when the animal interacted in any way with the handle. As the animal began interacting more frequently with the handle, the trainer transitioned to allowing the automatic food delivery system to deliver the food reward to the animal.

As an example, we describe use of the device by one animal that trained in both training modes and used all three handles (Table 1). This particular animal took part in 12 training sessions, 9 pre-lesion, and 3 post-lesion. In the pre-lesion sessions, it trained with the hook ($n = 4$), the round peg ($n = 3$) and the Y-handle ($n = 2$). Using the hook it trained for a total of 21.3 minutes, performing 96 successful repetitions for an average of 4.5 successful repetitions per minute. Using the round peg, it trained for a total of 2.4 minutes and performed 35 successful repetitions for an average of 14.5 successful repetitions per minute. Using the Y-handle, it trained for over 6 minutes without performing any successful repetitions. Comments from the trainers indicate that the animal was 'wary' of this handle. As expected, using different handles during training led the animal to use different grasping strategies (Figure 6.2).

Following the lateral hemisection injury to the animal, the ensuing weakness of the impaired (right) hand rendered the task of pulling the hook difficult for the animal. Thus, in pull mode, the animal adopted a strategy of first using its unimpaired (left) hand to bring the hook close to the cage (Figure 6.3A). It then grasped the hook with its impaired (right) hand (Figure 6.3B), and held it in place while it retrieved the food reward with its unimpaired hand (Figure 6.3C). Once it retrieved the food, it released its impaired hand from the handle by using its unimpaired hand to unwind the impaired fingers from the handle. In bump mode, the animal used a similar strategy

Table 6.1: Animal 37143 trained for 12 sessions with the BVM. It performed both the pulling and bump modes. It also trained with all 3 handles, although it was not willing to engage in training with the Y-handle.

37143							
		Pulling mode			Bump mode		
Total sessions	12	11			1		
		Hook	Round peg	Y-handle	Hook	Round peg	Y-handle
Pre-lesion							
Number of sessions	9	4	3	2	0	0	0
Total time (minutes)		21.29	2.42	6.26	0	0	0
Successful repetitions		96	35	0	0	0	0
Average $\frac{reps}{min}$		4.51	14.48	0	0	0	0
Post-lesion							
Number of sessions	3	2	0	0	1	0	0
Total time (minutes)		4.56	0	0	5.49	0	0
Successful repetitions		33	0	0	36	0	0
Average $\frac{reps}{min}$		7.23	0	0	6.56	0	0

of using the unimpaired hand to pull the handle close to the cage before grasping it with the impaired hand.

The robot acquired data regarding the movement of the haptic robot during training (Figure 6.4). The data recorded includes the position, velocity, and forces applied in the X, Y, and Z axes. This data provides insight into the quantity of the movements executed by the animal, and could potentially be used to gain insight into the quality of each movement performed.

6.5 Discussion

We developed the Bimanual Vending Machine (BVM) to provide self-initiated, in-cage, quantifiable hand training exercises to monkeys that have received a cervical SCI. Animals successfully used the BVM before and after a cervical-level injury to the spinal cord. Reports from the animal trainers indicate that animals were able to learn to



Figure 6.2: **Use of different grasps to complete the task.** - The use of the different handles successfully forced animals to perform different grasps in order to interact with the robot. This provides an additional means to modulate the difficulty of the task (i.e. some handles may be harder/easier to use than others).



Figure 6.3: **Pulling strategy following cervical lesion to the spinal cord** - Following the injury, the animal is unable to perform the pulling task with its impaired hand. The animal then finds a solution in which it pulls the handle within reach using its unimpaired hand (A), and then proceeds to curl the fingers of its impaired hand around the hook (B). Finally, once it feels it can hold on to the hook (remember that the hook is constantly pulling away from the animal) it reaches for the food with its impaired hand.

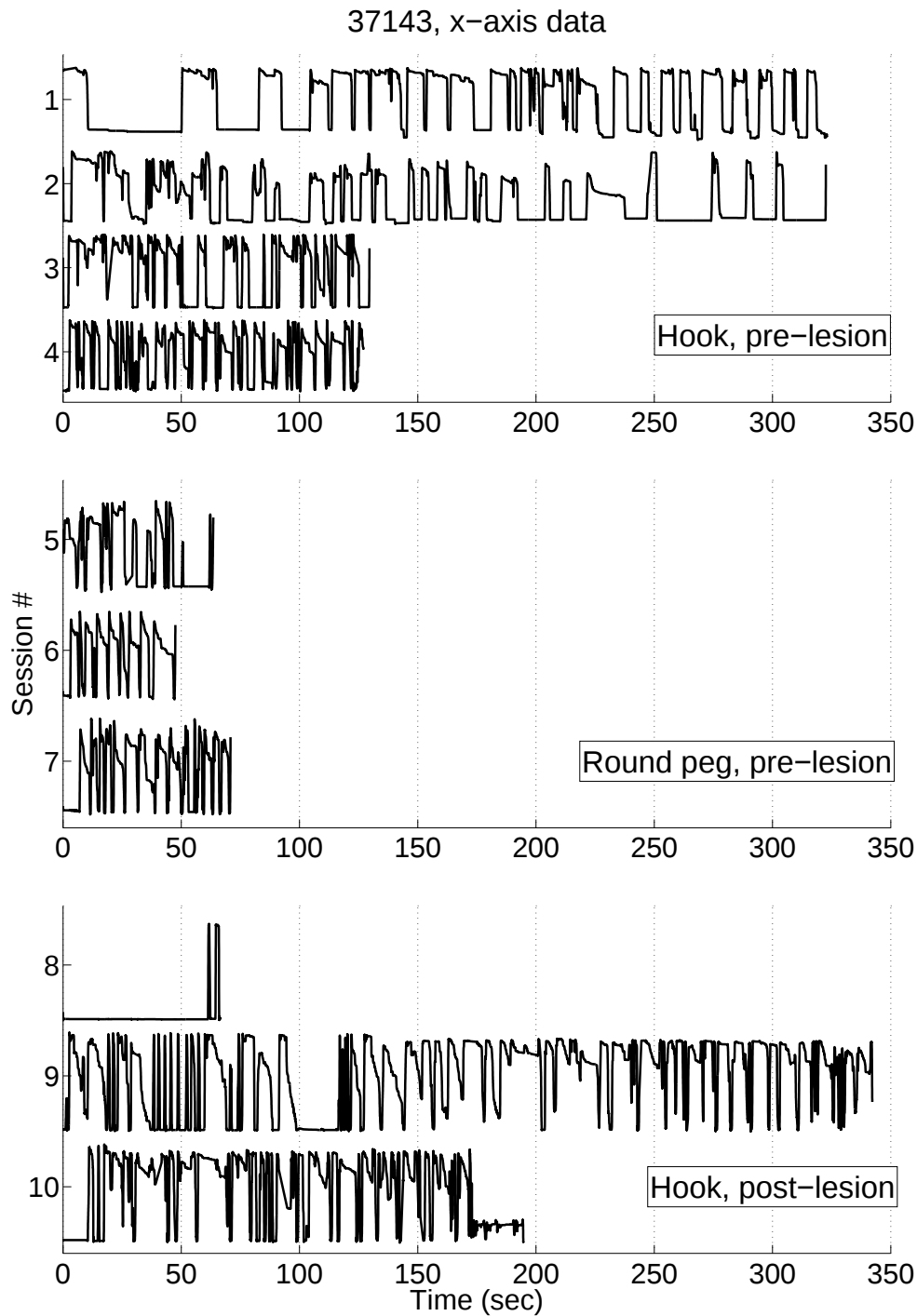


Figure 6.4: **Sample training data for animal 37143** - Sample set of data for 10 training sessions by animal 37143. The sessions are labeled on the y-axis in chronological order from 1 to 10. The first six sessions were performed prior to lesion while the last three occurred after. In the four pre-lesion sessions it used the hook to perform a total of 96 repetitions in 21.29 minutes. In the following three sessions it used the round peg and performed 35 repetitions in 2.42 minutes. In the last three sessions, it used the hook to train in both pulling (33 repetitions in 4.56 minutes) and bump mode (36 repetitions in 5.49 minutes).

perform the desired bimanual training within a few training sessions both when naïve to the BVM and following the injuries. These initial results are a proof of concept of the device's potential for providing the rehabilitation therapy of the hand required for these animals. Specifically, the animals 1) were willing to engage in the training task 2) used both hands during training, and 3) achieved in-cage and self-initiated training without constant monitoring by the trainers.

An important component of the BVM lies in the development of training algorithms that accommodate the animal's physical abilities. While the initial training was carried out using only the pulling mode, we quickly realized that this mode may not allow animals with diminished forelimb control after the lesion to obtain food reward if they cannot grasp the handle. As a result, we created the bump mode to allow minimal grasping effort by the animals while still requiring them to use both hands to retrieve the food rewards.

The use of a robotic device for rehabilitation therapy allows for interesting possibilities to automatically and progressively challenge an animal during training. For example, we recently developed an algorithm for the BVM for automatically shaping an animal to switch between different target exercises, such as moving from bump mode to pull mode [99]. The algorithm is designed to reward trainees with different physical capabilities at comparable rates during the transition, to avoid frustration, while still causing the trainee to shift its behavior to a target mode. We have tested this training algorithm with human subjects [99] and shown that it can achieve these goals for this primate population. One interesting result was that artificially increasing reward during training decreased the subjects' tendency to engage in exploration and therefore slowed learning, particularly when we changed the target movement. The BVM will provide a mechanism to study phenomena such as this, an understanding of which will allow optimization of rehabilitation therapy during neural repair attempts.

We have not yet shown that the device can help an animal achieve the number of repetitions that is currently thought to be needed to trigger plasticity after a neurologic injury, 300-400 per day [61]. In the present study, the animal's pull rate varied from 5-15 pulls per minute. Taking as an example 10 pulls per minute, it would require 30-40 minutes of interaction per day to achieve 300-400 repetitions. In the present study, animals typically trained with the device for only a few minutes before losing interest, likely because they became full from eating the food rewards. It may be possible to achieve 30-40 minutes per day by dispersing training through the day, or by making the robot available continuously to the animal. We may also be able to train the animal to perform multiple movements before obtaining a single food reward, for example by dispensing food only on the Nth successful pull.

A key goal in both regenerative medicine and rehabilitation training is to aid the body in using its innate healing potential to maximize function [4]. In the case of combination therapies, one might expect that this innate healing potential will interact in a complex way with the combined treatments [90]. For example, one interaction might be that of competition for restored neural resources. Following a SCI or regeneration of axons injured by a SCI, the motor system must relearn to control movement with a diminished availability of neural resources. Movement training in one task may cause a competition for those resources, leading to diminished performance in motor tasks that are not explicitly trained [17]. In terms of the device we have developed here, competition would imply that it is necessary to understand how the training modes chosen maximize recovery across tasks in a way that is most functionally beneficial to the trainee.

We hypothesize, that in accordance with a model developed from large clinical studies of stroke recovery [102], the gains in strength and dexterity derived from training with the BVM will translate into more frequent use of the hand in activities of daily

living. We hypothesize that this enhanced spontaneous hand use, as well as the training with the device, will provide the motor activity needed for regenerative therapy interventions to create functional recovery of the hand, thereby accelerating the discovery of treatments that can be applied to humans with a spinal cord injury. This will ultimately lead to the appropriate assessment of treatments and their possibilities for translation into human clinical trials. By automating intensive training, we hope to ensure that neural repair for the clinically important problem of hand function restoration after SCI does not fail to reach human clinical trials.

Chapter 7

Summary of the major contributions of this dissertation

The work presented in this dissertation sits at the intersection of the fields of robotics, neuroscience, and psychology. It focused on two main areas: 1) the effects of the challenge level of a motor task on the motivation and performance during and after training, and 2) the development of robotic devices to provide volitional training and rehabilitation of the upper extremity for rodents and nonhuman primate models of cervical spinal cord injury. In conclusion, we provide a summary of the major findings in these two focus areas and their relationship to key themes in psychology of motor training and neural repair.

7.1 Challenge level of a motor task affects motor training and perception of the task

In Chapters 2, 3 and 5 we presented results indicating that the challenge level of a motor training task had important effects on the motivation of the trainee and the long-term performance gains obtained from training.

In the first experiment on motor learning, unimpaired humans trained golf putting in a virtual golf environment. We showed that manipulating participants' performance errors—by reducing or amplifying them—had significant effects on how participants perceived the task. Specifically, while performance errors were being manipulated, participants whose errors were being reduced reported a positive perception of the task, while those whose errors were being amplified reported a negative perception. Remarkably, 1 to 3 days later, when participants trained in the same motor task, but this time without any error manipulation, those participants whose errors had been previously amplified once again reported a negative perception towards the task, even though their performance was comparable to the other participants.

These findings are in line with findings in psychology of sports research that indicate that athletes' perceptions of the difficulty of a task are influenced by their performance in the task. For example, golf players' perceive hole size to be larger when they have good recent performance at putting [116]. Other studies involving American-football [115] and softball [117] have found similar results in which the participant's perception of the target size for the task is influenced by their perceived ability to perform the task.

Such phenomena relate to the psychological concept of self-efficacy. Self-efficacy refers to a person's perception of their ability to achieve a specific goal [11]. Self-

efficacy theory was first introduced in the context of phobias, but has since been expanded into many other fields. Of special interest for this dissertation is the use of self-efficacy theory to explain why somebody may or may not participate in an exercise regime. Oman et al. 1998 showed that the degree of self-efficacy prior to starting an exercise regime predicted adoption and early adherence to the regime.

This theory of self-efficacy has important implications in the fields of robotic-based motor learning and rehabilitation robotics. Specifically, robotic devices may serve as tools that increase a participant's self-efficacy at a motor task. Much like they did for participants in the golf experiment whose errors were being reduced, robots can assist a participant to achieve a certain degree of success at the task, even if that level of performance does not match their skill level. For somebody with a motor impairment, who may have lost faith in his or her body's ability to perform a motor task as a result of a neurological injury such as stroke or spinal cord injury [92], a robotic-based intervention has the potential of increasing their self-efficacy. This idea of increased self-efficacy from robotic therapy could help explain why people may continue to improve even days, or months, after the intervention ([60]), or why bringing people above a certain threshold of hand function results in increased use of the impaired hand [102].

In the second experiment rats trained on a self-initiated pulling task with either a low or high challenge level, where the high challenge level was set with an adaptive algorithm from trial to trial based on the success of the previous trial. In this experiment we found that animals that trained with the low-challenge level, and experienced a significantly higher success rate than the high-challenge group, were more willing to execute the pulling task, as demonstrated by a total number of pull attempts that was twice as much as the high-challenge group. In this context we may ask, was this due to the animal's perception of its ability to succeed at the task? Are animal's behav-

iors consistent with the theory of self-efficacy? We currently do not have an answer for this latter question, and the idea of self-efficacy in animals is one that should be explored further.

In summary, the first major contribution of this dissertation is providing an increased understanding of how robotic interventions that modulate challenge level affect motivation and performance. Essentially, by making tasks more challenging, robots can improve performance gains, but discourage willingness to practice. Conversely, by making tasks less challenging, robots can reduce performance gains but encourage willingness to practice. These are some of the first findings that describe a psychomotivational dynamical effect of robotic training, and future research should continue to explore how robotic-based interventions can affect the psychological aspects of learning a new motor task, or re-learning after a neurological injury.

7.2 Development of robotic training devices for animal models of neural repair

A major focus in the field of robotic rehabilitation is retraining the upper extremity. For humans, there is a wide array of devices available to provide therapy (for a comprehensive list see [86]). In animal models, however, this number is limited to only a few for rodents ([112]; [104]), and none (to the best of our knowledge) for non-human primates. Thus, a major need in the field of rehabilitation research is the development of robotic devices that can be used to deliver controlled amounts of upper extremity training in animal models. Such devices will be essential tools for evaluating forthcoming neural repair strategies.

The second major contribution of this dissertation was the development of two robotic devices to train animals before and after a cervical spinal cord injury (cSCI). The first of these devices, the Robotic Rehabilitator for the Rodent Upper Extremity (RUE), provides self-initiated and unsupervised motor training for a rat model of cSCI. The second device, the Bimanual Vending Machine (BVM), provides in-cage, self-initiated, and unsupervised motor training for a nonhuman primate model of cSCI. This dissertation work showed how both devices can provide therapy-like exercises for animals before and after the lesion. In the case of RUE, we showed that requiring volitional movements from the animal led to functional assessments of forelimb strength that were significantly larger than those measured with the more conventional approach of the grip strength meter (GSM). We also showed that RUE measured functional capabilities of the forelimb within days after cervical spinal cord injury, something that the GSM was unable to replicate.

For the BVM, we showed that animals readily learned to use the device to achieve repetitive and quantifiable, in-cage, self-training of the impaired hand. Furthermore, we proved that animals that are highly impaired and show little spontaneous use of their impaired hand were able to engage in repetitive training while at their home cage.

These robotic devices have great potential to help in the current efforts to find neural repair suitable for human clinical trials. They could prove key tools for studying the interaction of motor activity and neural repair as part of combination treatments with stem cells and drug treatments. We will continue to work closely with collaborators from UC Irvine and the UC Spinal Cord Injury Consortium to further develop these devices to meet their needs.

7.3 The real-world challenge point framework: optimal challenge in unsupervised motor training

The final major contribution of this dissertation stems from the results of training with different challenge levels in RUE. As previously discussed, a crucial aspect in motor skill training and rehabilitation is the adherence to the training or therapy program outside of the training environment. In a rehabilitation clinic, or in a training facility, a primary responsibility of the trainer (physical therapist or coach) is to modulate the challenge level of the trainee in order to optimize performance and learning while maintaining a high level of motivation. Motivation in this context is thus derived from both extrinsic factors provided by the trainer, and intrinsic factors derived from the trainee. The problem with this approach is that once the trainee is out in the ‘real-world’, where training is largely unsupervised, motivation must come directly from the trainee. This level of motivation is heavily based on the trainee’s perception of his abilities, or his self-efficacy.

To optimize motor learning while training in highly motivating environments we propose the ‘Real-World’ Challenge Point framework. This framework, derived from the Challenge Point hypothesis framework by Guadagnoli and Lee [41], focuses on the implications that the challenge level can have on the motivation level of trainees. Namely, we seek to find the challenge level at which trainees will be highly motivated to participate in self-initiated training sessions while performing high number of repetitions at relatively high challenge levels (see Figure 7.1). Our working hypothesis consists of two parts: 1) there exists an inversely proportional relation between the challenge level and number of repetitions executed in a given period of training time; 2) there exists a proportional relation between the challenge level and the gain derived from each repetition performed. From these two parts we can define a non-

linear relation between the challenge level and the amount of learning/recovery in a given period of training time. We then hypothesize that there exists an optimal challenge level where trainees derive a maximum amount of learning/recovery in a fixed amount of training time. We show how robotic devices embedded with appropriate algorithms can both identify and control training experience around the real-world challenge point.

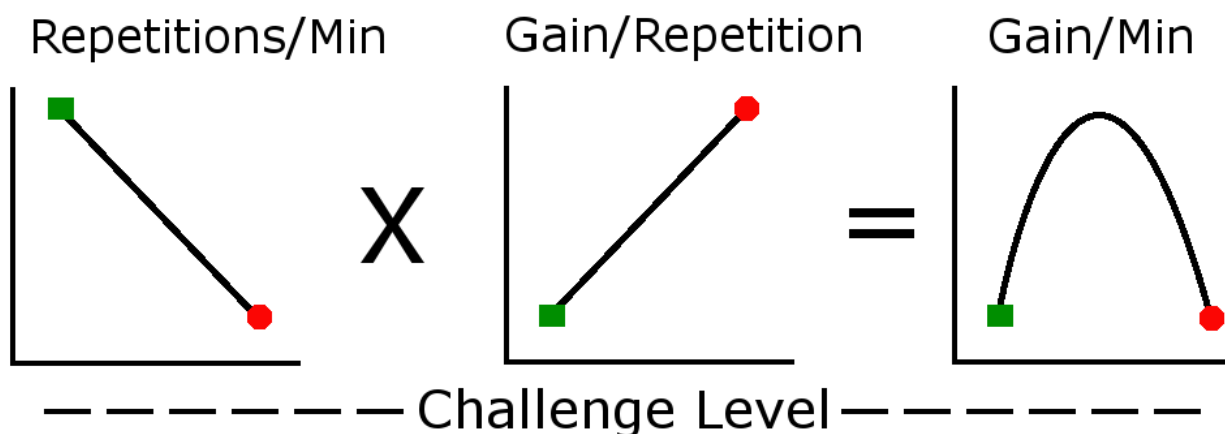


Figure 7.1: **Real-World Challenge Hypothesis** - The working hypothesis is that robotic training benefits are optimized at a specific challenge level because the willingness of the animal to practice, and the training gain per grasp movement vary oppositely to the challenge level. (A) The number of repetitions per minute is inversely proportional to the challenge level. (B) The benefit derived from each repetition is proportional to the challenge level. (C) Multiplying (A) and (B) yields a non-linear relationship from which we will derive the putative optimal challenge in relationship to the previously tested challenge levels; the optimal challenge level is the x-axis value at which recovery (gain/minute of training) is maximized.

As described in Chapter 5, the optimal challenge level for rats training in RUE was estimated at around 35% (i.e. a success rate of 65%). This framework needs to be tested at the newly predicted optimal challenge level and expanded to other tasks and training paradigms.

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