Chapter 8

Motor learning principles for neurorehabilitation

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INTRODUCTION

The human motor system has the capacity to learn through practice and experience. Motor learning is a loosely defined term that encompasses motor adaptation, skill acquisition, and decision-making (Shadmehr and Wise, 2005; Krakauer, 2006; Krakauer and Mazzoni, 2011; Wolpert et al., 2011). This chapter will focus on what we, and others, consider to be two distinct types of motor learning (Agostino et al., 1996; Huang and Krakauer, 2009; Reis et al., 2009; Krakauer and Mazzoni, 2011; Shmuelof et al., 2012): adaptation and skill acquisition. In adaptation, the motor system responds to altered environmental conditions to regain a former level of performance in the new setting. For example, when one first puts on prism goggles and attempts to reach to a target, there is a misalignment between the actual and visually perceived position of the target, resulting in reach errors. Through adaptation, the discrepancy between the predicted position of the arm at the end of the reaching movement and the observed position of the arm is gradually reduced until one can reach the target as well as one could before putting on the goggles. Adaptation can therefore be understood as the learning of a new relationship between well-learned movements and a new spatial goal (Krakauer, 2009). In contrast, skill learning (e.g., learning to ride a bike or to play tennis) involves acquiring new patterns of muscle activation and achieving a higher level of performance by reducing errors without a reduction in movement speed (Hallett and Grafman, 1997; Reis et al., 2009; Shmuelof et al., 2012).

This chapter will first review the basic principles underlying motor adaptation and skill learning, with a focus on studies involving the upper extremity, although similar principles are likely to underlie learning with the lower extremity. The second part of the chapter will discuss the relevance of these learning principles to neurorehabilitation for stroke patients and their application through rehabilitative techniques.

MOTOR ADAPTATION

Motor adaptation occurs in response to both external perturbations and changes in the body that cause errors in movements. The most commonly used laboratory paradigms to study adaptation include use of a visuomotor rotation or a force field to create a discrepancy between the predicted hand trajectory and the executed trajectory in visual space, and a mismatch between proprioceptive and visual feedback in the case of visuomotor rotation (Shadmehr and Mussa-Ivaldi, 1994; Flanagan et al., 1999; Krakauer et al., 1999, 2000). Healthy subjects learn to alter their movements from trial to trial based on error feedback, reaching near-baseline performance within a single session (Shadmehr and Mussa-Ivaldi, 1994; Krakauer et al., 2005; Lackner and DiZio, 2005). The prediction error, the difference between the brain's predicted movement outcome and the observed outcome of the movement, is believed to be the driving force behind adaptation (Mazzoni and Krakauer, 2006; Tseng et al., 2007). Studies suggest that adaptation is learned implicitly, without subject awareness of what is to be learned. In fact, when subjects were given an explicit strategy to use in a visuomotor rotation task (i.e., to aim for a different target location), their performance worsened (Mazzoni and Krakauer, 2006). In this study, the motor system adapted to the rotation at the expense of the reward of accomplishing the task goal.

An important feature of learning is that it results in a change that outlasts the period of training (Schmidt and Lee, 2005). Two forms of memory have been demonstrated in adaptation paradigms. Once subjects have adapted to a perturbation and the perturbation is

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subsequently removed (e.g., switching off the rotation), transient "after-effects" occur, with trajectories in the direction opposite to that observed during initial adaptation (Shadmehr and Mussa-Ivaldi, 1994; Fernandez-Ruiz and Diaz, 1999). The presence of after-effects demonstrates that subjects do not merely react to the perturbation but have learned to alter their planned movements in the new environment, using a feedforward control strategy. Memory in adaptation paradigms is also evident in the form of savings: when subjects are re-exposed to the same rotation or force field after some time interval, adaptation occurs more rapidly (Kojima et al., 2004; Krakauer et al., 2005; Smith et al., 2006; Zarahn et al., 2008).

One definition of consolidation is the process by which a motor memory becomes resistant to interference by another task as a function of time. Shadmehr and Brashers-Krug (1997) showed that learning of an opposite force field (task B) interfered with savings when learned immediately after learning initial force field (task A), but this interference no longer occurred if a sufficient time interval (> 5.5 hours) had elapsed between task A and task B. Similarly, for visuomotor rotation adaptation, resistance to interference has been demonstrated when a counter-rotation is learned 24 hours, but not 5 minutes, after learning of an initial rotation (Krakauer et al., 2005). These interference effects appear to depend more on task context than on consolidation processes *per se*; subjects could learn opposite visuomotor rotations without interference if there was a change in effector (from wrist to arm), which suggests that proprioceptive feedback or motor commands themselves may themselves serve as contextual cues (Krakauer et al., 2006). Thus evidence from adaptation paradigms suggests that timing between perturbations and implicit contextual cues (Howard et al., 2010) are important considerations in the design of adaptation-based training paradigms in neurorehabilitation.

Another important aspect of learning is how much of what is learned in one task generalizes, or transfers, to another task or context. Improvements in reaching performance after training in the laboratory or the clinic are not so meaningful if the improvements do not transfer to reaching in everyday activities. Adaptation studies have demonstrated that generalization can occur to varying degrees across different limb configurations, movement directions, and effectors (body parts) (Gandolfo et al., 1996; Krakauer et al., 2000, 2006; Baraduc and Wolpert, 2002; Sainburg and Wang, 2002; Criscimagna-Hemminger et al., 2003; Wang and Sainburg, 2006). Errors can be attributed to changes in the body (intrinsic) or the world (extrinsic), and the degree of generalization may reflect the nervous system's belief in the source of these errors (Berniker and Kording, 2008).

SKILL LEARNING

Motor skill is easier to recognize than to define. Definitions of skill such as: the "ability to achieve an environmental goal with maximum certainty and minimal expenditure of energy and time" (Schmidt and Lee, 2005) are not wrong, but suffer from a certain vagueness. Here we will operationally define skill at the level of motor execution, i.e., the ability to reliably deliver accurate execution. A way to capture and quantify skill at the level of motor execution is the speed−accuracy tradeoff function, which refers to the relationship between movement speed and accuracy for a particular task. Subjects tend to make more errors as movement speed increases and, conversely, to slow down in order to be more accurate. Thus, an increase in accuracy alone does not indicate improved skill; true skill acquisition requires a systematic change in the learner's speed−accuracy tradeoff function (Reis et al., 2009; Shmuelof et al., 2012). Unlike adaptation, which can occur within a single experimental session, motor skill acquisition can be achieved only through extended practice and can take several days, weeks, or even years, depending on the complexity of the task. Performance gains are seen within-session (online effects) and between training sessions (positive offline effects) (Karni et al., 1998).

According to the "power law of practice," acquisition of skilled performance is determined solely by the number of times a task is practiced (Korman et al., 2003). While increasing the number of repetitions may be the most effective method to improve within-session performance, other factors in the practice schedule appear to affect performance and retention. It is well established in the literature that inserting longer rest intervals between task repetitions (distributed practice) and introducing task variability (e.g., reaching to pick up a glass at varying distances rather than at a fixed distance) lead to improved retention compared with blocked practice of a single task (Lee and Genovese, 1988; Shea and Kohl, 1991). Given that, in real situations, even a task as simple as reaching for a glass will likely be performed under varying conditions due to differences in initial posture and location of the glass, it would seem imperative to learn how to deal with variability within a task. Indeed, variable task training has been shown to increase generalization of learning to new tasks (McCracken and Stelmach, 1977; Catalano and Kleiner, 1984; Braun et al., 2009). Another key concept in task scheduling is that of contextual interference: a random ordering of several tasks within a training session leads to greater retention of each of the tasks than practicing a single task at a time, even when performance during acquisition is better in the single-task training session (Shea and Morgan, 1979; Tsutsui et al., 1998). It is postulated that the

random schedule may aid learning because the variability of tasks requires the learner to treat each movement as a problem to be solved (Krakauer, 2006; Winstein and Stewart, 2006; Grafton et al., 2008). The learner must determine the requirements to complete each task successfully and plan a movement accordingly, rather than merely memorizing and replaying a set of muscle activation patterns (Conditt et al., 1997).

Different types of feedback can also modulate skill acquisition and retention. Intrinsic feedback provided through sensory systems allows a learner to evaluate his/her own performance for each movement. For example, after shooting a basketball, the thrower gets visual feedback on whether or not the ball went through the basket. Extrinsic feedback, or augmented feedback, from an external source provides additional information during or following the movement. Augmented feedback can take the form of knowledge of results, defined as feedback about the movement outcome defined in terms of an environmental goal, or knowledge of performance (KP), defined as feedback about the patterns of movement (Schmidt and Lee, 2005). The type of feedback, which features of performance to emphasize, and timing and frequency of feedback are all variables to be considered. For example, feedback can take the form of verbal encouragement, a display of kinematics (e.g., movement path or peak velocity), dynamics, or even muscle activation patterns using EMG signals. Therapists and coaches can use KP to influence an aspect of movement of which the learner might be unaware (e.g., the position of the elbow during a tennis serve). In supervised learning paradigms, subjects can be provided with a desired movement trajectory and then given feedback about how well they followed this "normal" or "optimal" pattern of movement. This method may be useful in reducing impairment in patients, by emphasizing reacquisition of movement patterns seen in healthy subjects. Providing augmented feedback during learning can facilitate acquisition of a skill task, but subjects can become dependent on this feedback for the performance of the task, thus leading to poorer performance post-training when the feedback is removed. Multiple studies support decreasing feedback frequency over time in motor learning protocols (Winstein et al., 1994; Goodwin et al., 2001). Reinforcement learning, a subfield of machine learning, is based on the selection of actions that are predicted to result in better cumulative rewards (Sutton and Barto, 1998). Subjects are free to explore different strategies to arrive at a solution on their own using intrinsic or extrinsic reward feedback. Thus, in contrast to adaptation, where the training signal is an error vector, the training signal is a scalar reward. In patients, reinforcement learning may lead to adherence to compensatory movement patterns, themselves perhaps learned

through adaptation, which may or may not be optimal for their level of impairment. For example, a patient who has lost the ability to extend the arm at the elbow will quickly learn to flex their trunk to reach for an object. This ability to make the correct directional adjustment of the trunk to prevent a reaching error is an example of adaptation. If this strategy leads to successful reaching then it will be reinforced. If this strategy is used even after extension at the elbow has recovered then it can be considered a habit. Reinforcement learning may be applied in rehabilitation through the use of assistive devices (e.g., robotic arm), or assistance by a therapist, to reward a patient with task completion when the proper movement is initiated by the patient (Huang and Krakauer 2009).

Many skilled motor behaviors, such as playing the piano, are comprised of a sequence of movements. Sequence learning encompasses at least two distinct components: the effector-independent acquisition of the order of elements in the sequence, and the effector-dependent achievement of skilled performance of each element in the sequence. Experimental paradigms of sequence learning include the serial reaction time task, in which subjects are unaware of a repeating sequence embedded within the task, and learning is measured as a reduction in response time (Nissen and Bullemer, 1987; Goedert and Willingham, 2002). In another commonly used paradigm, subjects are asked to learn a short sequence of movements, and learning is measured as an increase in speed and accuracy of the movements (Karni et al., 1998; Walker et al., 2003). A third approach combines the two components of sequence learning by asking subjects to explicitly learn a sequence of movements, thereby allowing for separate quantification of both the explicit acquisition of sequence order and performance (speed/accuracy) measures (Hikosaka et al., 1995; Ghilardi et al., 2009).

Hikosaka and colleagues (2002) observed that sequence order was acquired faster than the performance component, suggesting that sequence learning is a serial process. Others have proposed that the two components are learned concurrently, but the effector-specific performance component takes longer to develop (Nakahara et al., 1998; Bapi et al., 2000). Once subjects acquire explicit knowledge of a sequence, they shift from a reaction time mode to an anticipatory mode with a simultaneous increase in movement accuracy (Ghilardi et al., 2003, 2008, 2009). This increase in accuracy is likely due to prolongation of movement time and a more complete specification of movement parameters (Hening et al., 1988; Ghez et al., 1997). The relationship between learning how to better concatenate discrete movements into a sequence and learning to make more skilled continuous single movements is unclear, but the

boundary is likely to be blurred. For example, for prehension one has to start with a proximal-muscle driven reach and end with a distal-muscle controlled grasp, in essence a sequence. More fundamentally, even single movements to a single target require sequences of activation in agonist and antagonist muscles. Thus the learning principles obtained from laboratory-based sequence tasks may generalize to movements and tasks that are not overtly sequential.

The literature is divided regarding consolidation of sequence learning, with some studies demonstrating consolidation (Walker et al., 2003) while others did not (Goedert and Willingham, 2002). The emphasis on either the explicit or implicit component of sequence learning in these studies may have contributed to the seemingly contradictory findings. Ghilardi and colleagues (2009) demonstrated a dissociation in consolidation between the explicit and implicit components, using a task that combined both. Explicit recall of the initial sequence (sequence A) was interfered with to the same degree regardless of whether a second sequence (sequence B) was learned 5 minutes or 24 hours after sequence B. Implicit learning of sequence A, however, showed a window of susceptibility to interference by sequence B, which was evident when the interval between sequence A and B was 5 minutes but not at 24 hours. Both components of sequence learning showed resistance to interference with more prolonged training of the initial sequence. A similar beneficial effect of prolonged training on retention and consolidation has been suggested by studies of motor adaptation (Yin and Kitazawa, 2001; Krakauer et al., 2005), skill acquisition (Matsuzaka et al., 2007), and explicit learning (Hauptmann and Karni, 2002; Hauptmann et al., 2005). The benefit of prolonged performance at asymptote may relate to the observation that repeated testing itself enhances retention, as demonstrated by Karpicke and Roediger (2008) using an explicit learning task.

Thorndike and Woodworth (1901) proposed that transfer of motor skills depends on how many "identical elements" are shared by the practiced task and the new task. For example, one would expect that a tennis player would be more skilled at racquetball the first time he or she plays because the two sports share common elements. However, what constitutes a "similarity" and what "elements" are important in a motor skill is still poorly understood (Schmidt and Lee, 2005). In sequence learning, one would expect explicit knowledge of sequence order to transfer to other limbs or workspaces, whereas effector-dependent sequence skill would not necessarily transfer. Most investigations of transfer of sequence learning have not made a distinction between the two components and use diverse paradigms for testing of sequence learning. This may have led to the contradictory findings of complete (Panzer et al., 2009) versus incomplete (Berner and Hoffmann, 2009) transfer of learned motor sequences between the two arms, and transfer in visuospatial coordinates (Kovacs et al., 2009) versus motor (joint angle) coordinates (Panzer et al., 2009).

MOTOR LEARNING IN PATIENTS

The first part of this chapter discussed some of the basic principles of motor learning derived from laboratory studies in healthy subjects. Neurorehabilitation is based on the assumption that these motor learning principles can be applied to motor recovery after injury, and that training can lead to permanent improvements in motor function in patients with motor deficits (Krakauer, 2006). Several key issues must be addressed in the development of rehabilitation interventions based on motor learning principles. First, it is still unclear whether and to what extent motor learning mechanisms themselves may be impaired in patients. Second, the goals of rehabilitation should be clarified with respect to recovery of impairment versus functional compensation, as learning may make differential contributions to these two processes. Third, it is necessary to consider which type(s) of motor learning are most relevant to patients. Finally, it needs to be appreciated that recovery is not synonymous with motor learning; endogenous processes triggered by ischemia can themselves lead to recovery (Murphy and Corbett, 2009). The interaction between learning and spontaneous biological recovery is only beginning to be investigated (Biernaskie et al., 2004; Carmichael, 2010).

Motor learning deficits in patients

Very few studies have examined the effects of neurological injury on motor learning processes. Areas of the brain believed to be involved in motor control and/or motor learning include the cerebellum, parietal cortex, premotor cortex, motor cortex, and the basal ganglia (Shadmehr and Krakauer, 2008). Patients with cerebellar lesions have consistently been shown to have impaired motor adaptation (Lewis and Zee, 1993; Maschke et al., 2004; Morton and Bastian, 2006). In contrast, patients with basal ganglia diseases such as Huntington and Parkinson disease seem to have relatively intact adaptation (Contreras-Vidal and Buch, 2003; Smith and Shadmehr, 2005) but whether these patients are impaired at skill learning, understood as more accurate and precise execution, remains subject to investigation (Siegert et al., 2006; Ghilardi et al., 2008).

Studies of motor learning in patients with hemiparesis after stroke have yielded mixed results. Given the heterogeneity of stroke patients, it may be difficult to demonstrate a specific learning deficit in this

population. Furthermore, patients' movements are often more variable than controls, which may limit the expression of learning. Despite this limitation, several studies have claimed preserved motor learning in stroke patients. Hemiparetic stroke patients could successfully adapt to force field perturbations with both affected and unaffected arms using a similar strategy to healthy subjects (Scheidt and Stoeckmann, 2007). Winstein and colleagues (1999), using a novel extension—flexion elbow reversal task to investigate skill learning in the unaffected arm, found no significant differences in acquisition, offline forgetting, and retention between healthy subjects and patients with middle cerebral artery territory strokes. In the affected hand, Raghavan and colleagues (2006) demonstrated impaired learning despite preserved execution ability; stroke patients had impaired anticipatory scaling of grip force and load force rate to the object weight in a grasping task, although they could do so after performing the task with their unaffected hand. Given the differences in tasks, amounts of practice, effectors, and patient characteristics in the above-mentioned studies, it is difficult to draw unifying conclusions from these results. Patients may retain the ability to learn certain tasks but not others, depending on the information and processing requirements of the task, and training with the unaffected side may offer a way to acquire the information needed to perform the task with the affected side.

The results also highlight the importance of discriminating between absolute performance level and the change in performance of a task in studies of motor learning (Kitago and Krakauer, 2010). Patients generally have greater variability in their performance compared to the controls even after training, despite seemingly preserved ability to adapt to a perturbation or learn a new task (Winstein et al., 1999; Scheidt and Stoeckmann, 2007). Whether this increased variability reflects a ceiling effect due to execution noise, or a deficit in motor planning that is not improved by training, remains unknown. It is possible that training with a focus on reducing variable errors or prolonged training is required to improve the level of performance.

Recovery of impairment versus functional compensation

The distinction between impairment and function is important to consider in the patient population (Levin et al., 2009; Raghavan et al., 2010). Recovery of impairment means that the same movements patterns used before injury are regained after injury, whereas the recovery of function can either occur through recovery of impairment or through compensatory mechanisms. For example, a patient with hand weakness can reacquire the ability to write through regaining normal movements of their affected hand, by using alternative muscles on their affected side, or learning to write with their unaffected hand. Many studies use functional tests, such as the Action Research Arm Test (Yozbatiran et al., 2008), or assessments of patients' ability to perform activities of daily living (ADLs) as their outcome measures. However, because these tests do not consider the quality of movements, they cannot discriminate between impairment recovery and the development of compensatory strategies. The Fugl-Meyer Motor Assessment (Fugl-Meyer et al., 1975) is commonly used to measure recovery of impairment. Quantitative and qualitative movement analysis can further discriminate between compensation and recovery, and can shed light on the how impairment is changing during the recovery process. For example, using a biometric rating scale to evaluate skilled reaching in a rat stroke model, Moon et al. (2009) were able to show that both compensatory mechanisms and partial recovery of impairment contributed to early improvements in skilled reaching. One of the benefits of robotic devices and virtual reality interfaces is their ability to reliably measure movement kinematics and/or dynamics over the course of recovery, permitting insight into the underlying mechanisms of recovery. A thorough understanding of these mechanisms is critical to the development of new techniques that can enhance recovery in patients, i.e., we need to ask not only whether a novel therapy works but how it works (Kitago et al., 2012).

Longitudinal studies of stroke patients have shown that recovery of impairment reaches an asymptote around 3 months (Jorgensen et al., 1995; Kwakkel et al., 2006). Despite the assumption that motor learning processes contribute to recovery, the interaction of motor learning with spontaneous recovery processes has not been adequately studied. Spontaneous recovery processes may enhance learning mechanisms, which could lead to greater benefits of training during this time period, or training itself could directly enhance spontaneous recovery processes. In animal studies, rehabilitation initiated at 5 days poststroke was found to be more effective than waiting 1 month before beginning rehabilitation (Biernaskie et al., 2004), and a period of enhanced motor learning was demonstrated early after stroke in the unaffected limb (Hsu and Jones, 2005). The latter finding may actually facilitate learning of compensatory strategies with the unaffected side, which may interfere with learning of normal movement patterns with the affected side. A window of enhanced learning has yet to be demonstrated in humans after stroke.

Learning is required for both true recovery and compensation. Early training appears critical to promoting

recovery of impairment and brain reorganization after injury. Lesion studies in monkeys demonstrated that forced skilled hand use prevented loss of hand territory adjacent to the infarcted area and was accompanied by recovery of skilled hand use, whereas without training there was further loss of cortex with reliance on compensatory proximal movements (Nudo and Milliken, 1996; Nudo et al., 1996). While some degree of compensation may appear immediately after injury (e.g., limping after development of leg weakness), the ability to compensate involves the discovery and practice of alternative strategies that can be used to accomplish a task. In fact, in a rat stroke model, compensatory reaching strategies lead to higher success rates than premorbid reaching strategies in some animals (Metz et al., 2005). The learning rates for the improved reachers poststroke in this study were comparable to the learning rates for reaching prior to the infarct, suggesting that similar learning mechanisms were in play during the two periods.

We have shown that the impairment level in the arm at 3 months is well predicted by the magnitude of their impairment in the first week after stroke (Prabhakaran et al., 2008; Zarahn et al., 2011), suggesting that conventional neurorehabilitation has little impact on recovery of impairment. Conventional therapy has largely focused on teaching compensatory strategies, towards a goal of achieving early functional independence. It is possible that this focus on compensation during the early poststroke period is limiting potential long-term recovery at the level of impairment. Patients may learn not to use or explore with their affected limb and rely on compensatory strategies acutely poststroke, even as spontaneous recovery is occurring. Without practice with the affected limb during this early poststroke period, spontaneous recovery may go unnoticed. In constraint-induced movement therapy (CIMT), the unaffected arm is restrained for a majority of waking hours while the affected arm is trained intensively (Mark and Taub, 2004; Wolf et al., 2006), thereby encouraging re-exploration and optimization of strategies using the affected arm. Presently, it is not known whether neurorehabilitation protocols that emphasize recovery of impairment during the first 3 months poststroke can alter the time course of recovery. Future studies investigating the acute to subacute stroke recovery period are needed to clarify this issue.

Relevance of learning principles for patients and their relationship to timing of intervention

Intensive practice remains one of the most important components of training to promote learning (Winstein and Stewart, 2006). Despite this widely acknowledged principle, patients hospitalized after stroke spend the majority of their days lying or sitting in bed (Bernhardt et al., 2004). It is possible that conventional rehabilitation has limited impact on impairment because the dosage of therapy is too low (Lang et al., 2009). Robotic devices provide a means to deliver high-intensity therapy at lower costs than with conventional therapy, and CIMT and virtual reality (VR)-based interventions also incorporate repetitive task practice in their design. VR-based rehabilitation presents simulations of the real world via a human−machine interface to provide patients with engaging, interactive tasks and experiences designed to enhance motivation and attention (Deutsch et al., 2004). In addition to promoting repeated task practice, robot-assisted rehabilitation and VR-based interventions also allow complete control over task timing, environmental stimuli, and use of augmented feedback to enhance motor learning.

What kind of motor learning paradigm should be applied to promote recovery after stroke? Motor adaptation in healthy subjects is learned rapidly and the after-effects are transient, which could limit its use in inducing permanent behavioral improvements desired in patients. In a force field adaptation reaching study in hemiparetic stroke patients, after-effects lasted for only 30 to 60 movements after approximately 600 movements of training (Patton et al., 2006). Nevertheless, adaptation paradigms using error enhancement can be beneficial for patients by inducing after-effects that follow a "normal" movement pattern (Bastian, 2008; Huang and Krakauer, 2009). Reisman and colleagues (2007) used a split-belt treadmill task, with one belt running faster than the other, to transiently achieve after-effects that normalized gait asymmetry in stroke patients. Gradual introduction of the change in belt speeds was important in promoting adaptation in this study; a sudden change did not elicit after-effects. Similarly, in a visuomotor rotation study, Kagerer et al. (1997) demonstrated that a gradual increase in rotation up to the final value elicited more complete adaptation and longer after-effects compared to a sudden change (step perturbation). It has been proposed that longer after-effects are seen in subjects after incremental adaptation because learners attribute the errors to themselves, rather than to an external source (Michel et al., 2007).

Reaching after-effects lasting 2−4 hours have also been shown after prism adaptation in hemineglect patients (Rossetti et al., 1998; Frassinetti et al., 2002; Pisella et al., 2002; Rode et al., 2003; Striemer and Danckert, 2010). The reasons for the prolonged after-effects in patients compared to healthy subjects remain unclear. It is possible that patients are learning in a qualitatively different way to controls, or that their rates of adaptation and forgetting are slower than in controls, although to our knowledge no study has directly compared learning and forgetting rates in prism adaptation in patients and

controls. Another possibility is that patients have a deficit in identifying changes in context, which could lead them to generalize their adapted behavior to the nonperturbed condition. Regardless of the reasons, the prolonged duration of after-effects could permit training during this period to reinforce them, with potential therapeutic benefits.

Thus far we have spoken about various adaptation paradigms that have been used to promote recovery after stroke. What about skill? To acquire a motor skill takes considerably longer than adaptation. For example, one may adapt fairly quickly to being on skis to avoid falling down but it will take years of practice to slalom. According to the theory of optimal feedback control, the steps required in order to make a movement include: system identification (the prediction of the sensory consequences of motor commands), state estimation (the combination of these predictions with sensory feedback to form an idea about the state of the body and the world), and optimal control (the adjustment of the sensorimotor feedback loops to maximize some measure of performance) (Shadmehr and Krakauer, 2008). After a stroke, the brain must learn the new properties of the hemiparetic limb to predict the sensory consequences of motor commands accurately. This process of system identification can be likened to adaptation, and the learning principles derived from adaptation experiments in the laboratory may be applied to enhance this phase of recovery. Following this step, the motor system must become more skilled in the new setting through practice, which may correspond to a process of learning a reoptimized control policy (Izawa et al., 2008) and increased accuracy and precision implementing the new control policy. Guidance from a therapist or a coach may be required for all these motor learning steps, as even healthy subjects do not always adopt the optimal training strategy on their own (Huang et al., 2008; Huang et al., 2011 and Shmuelof et al., 2012). The way to optimize neurorehabilitation after stroke may be to combine the principles derived from error-based learning paradigms and reward-based reinforcement learning paradigms (Han et al., 2008; Huang et al., 2011 and Shmuelof et al., 2012) to design training strategies leading to the reacquisition of normal movement patterns in true recovery and/or the optimization of the alternative strategies used for compensation. For example, the studies described above that used adaptation paradigms to induce after-effects to make patients' movements more like those they made premorbidly show that these paradigms work only transiently (Reisman et al., 2007). One way to proceed might be to use reinforcement and practice protocols *during* this after-effect period, i.e., help patients become skilled at the use of their after-effect. This serial approach is hindered by short length of stays in acute

rehabilitation and by the adoption of compensatory habits in the chronic stage. The most obvious solution seems to be to apply motor learning protocols in the acute and subacute stroke period that focus on impairment. The prediction would be that this approach will prevent premature development of "skilled" compensatory strategies and greater generalization of what is learned. Results of studies in chronic patients and studies in animals lend some support to these predictions. When training focuses on functional activities, as in CIMT, patients show greatest gains in function and minimal gains in impairment (Page et al., 2008; Massie et al., 2009), whereas when training focuses on impairment, as in robotic interventions, patients show reductions in impairment but these are still likely too modest for them to have an impact on function or ADLs (Prange et al., 2006; Kwakkel et al., 2008). Nevertheless, the differential effect of CIMT and robotics on impairment and functional scales, respectively, is proof of the principle that the two therapies target different kinds of recovery, compensatory in one case and true recovery in the other. In animal models enriched environments, forced use, and increased practice greatly augment recovery in the first 4 weeks after stroke, suggesting a crucial interaction between learning signals and endogenous brain repair mechanisms (Biernaskie et al., 2004; Jones et al., 2009). The current idea is that learning serves to usefully direct and constrain plasticity mechanisms (Carmichael, 2010).

These results from studies in chronic patients and the data from animal models serve as clues as to what to do in the period of spontaneous recovery early after stroke, a period which in humans perhaps lasts 3 months poststroke, although this is not yet known precisely. Many, perhaps most, patients demonstrate large reductions in impairment (Sunderland et al., 1989; Duncan et al., 1992) in this period, which suggests that applying training regimens that target impairment, e.g., robotic therapy, in the first months after stroke may lead to even larger reductions in impairment than are currently seen, changes that are very likely to generalize to functional and ADL scales (Krakauer et al., 2012).

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