ANNUAL REVIEWS

Annual Review of Neuroscience

Closing the Loop: From Motor Neuroscience to Neurorehabilitation

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Annu. Rev. Neurosci. 2018. 41:415–29

First published as a Review in Advance on April 30, 2018

The *Annual Review of Neuroscience* is online at neuro.annualreviews.org

https://doi.org/10.1146/annurev-neuro-080317-062245

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Keywords

motor learning, motor control, rehabilitation, gait, reaching, neurorehabilitation

Abstract

The fields of human motor control, motor learning, and neurorehabilitation have long been linked by the intuition that understanding how we move (and learn to move) leads to better rehabilitation. In reality, these fields have remained largely separate. Our knowledge of the neural control of movement has expanded, but principles that can directly impact rehabilitation efficacy remain somewhat sparse. This raises two important questions: What can basic studies of motor learning really tell us about rehabilitation, and are we asking the right questions to improve the lives of patients? This review aims to contextualize recent advances in computational and behavioral studies of human motor learning within the framework of neurorehabilitation. We also discuss our views of the current challenges facing rehabilitation and outline potential clinical applications from recent theoretical and basic studies of motor learning and control.

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INTRODUCTION

In recent years, there has been an increased emphasis on translating behavioral and computational studies of normal human movement to the rehabilitation of patients with neurological damage. Often, studies of normal motor processes promise that the work is essential for informing and benefiting rehabilitation and training of patients. Conversely, many studies of rehabilitation look for mechanistic inspiration or justification of a given approach based on ideas from behavioral and computational work. Here, we discuss the bridge between these areas of study, highlighting ideas that have begun to successfully translate from theory to practice, and those that show promise for translation. We also discuss questions that are essential to improving this link and ultimately to transforming rehabilitation therapies for people with neurological dysfunction. This review focuses on studies of motor control and learning in humans with or without neurological damage, with an emphasis on work within the past several years. We focus exclusively on behavioral training and its mechanistic basis, as we think it is a powerful approach for changing how the nervous system controls movement. Of course, many other methods alter motor function, including invasive and noninvasive brain stimulation, robotics, brain machine interfaces, and pharmacological interventions. These methods are important in their own right but are beyond the scope of this review.

BRIDGING STUDIES OF MOTOR LEARNING TO REHABILITATION

The notion that understanding normal motor learning leads to better rehabilitation techniques is not new. Historically, there has been a great deal of emphasis on how to, for example, structure practice sessions to optimize day-to-day retention and generalization to other tasks (Schmidt & Lee 2005). This work is well summarized in a variety of reviews and textbook chapters dating back more than 30 years and thus is not focused on here. Instead, we discuss some examples of more recent thinking on this topic and show how some of this work has begun to translate to rehabilitation of people with neurological damage.

Motor learning is not a unitary process. Many types of motor learning depend on different brain systems and are driven by unique behaviors (Krakauer & Mazzoni 2011, Taylor & Ivry 2014). Motor learning also occurs at different timescales—some motor patterns can be learned in minutes, whereas proficiency in others can take months or even years. Given this, there is no one-size-fits-all method for optimally training individuals, regardless of whether they are neurologically impaired. Different individuals likely rely to varying extents on distinct learning mechanisms. This is influenced by many factors, including a person's age, motivation, experience, and presence of pathology in the body or brain.

A general approach for optimizing neurorehabilitation is to try to understand which motor learning mechanisms are intact versus impaired within an individual, and then use the intact mechanisms to train new movement patterns. This approach makes a couple of important assumptions. First, it assumes that we can independently measure whether different learning mechanisms are intact by using sensorimotor testing. Isolating each process behaviorally is difficult because, in any situation, it is unlikely that one motor learning mechanism is the only one operating. That said, certain training methods can engage one mechanism more than others, as we discuss below. Second, this approach assumes that different learning mechanisms can substitute for one another in order to improve different types of movements (e.g., hand control, walking) or different features of a movement (e.g., smoothness, efficiency). It is unclear the extent to which this is the case, as some brain areas are specialized for controlling different types of movements. Here, we discuss three forms of motor learning that have gained considerable attention in neurorehabilitation: adaptation, reinforcement learning, and instructive learning.

LEARNING FROM MOVEMENT ERRORS VIA MOTOR ADAPTATION

Adaptation is an error-driven form of motor learning that changes a movement pattern over time in response to a perturbation (e.g., wearing prism glasses that shift gaze or adding a mass to the arm during reaching; Martin et al. 1996). Once a movement has been adapted, people show a characteristic after-effect, or error in the opposite direction, when the perturbation is removed and conditions return to normal. This after-effect is a hallmark of adaptation; following adaptation, people cannot simply switch back to the original movement pattern; instead, the adapted movement must be actively de-adapted before returning to its original form (Kitago et al. 2013). The timescales of adaptation and de-adaptation are of the order of minutes to hours (de-adaptation typically occurs slightly faster than adaptation; Smith et al. 2006), often requiring tens to hundreds of movements to accumulate any beneficial effect from this type of learning.

Adaptation across many kinds of movements has been extensively studied in human behavioral laboratories, and as such is considered a prototypical motor learning mechanism. Here, we focus on adaptation of reaching in response to either visual or mechanical perturbations and on adaptation of walking in response to mechanical perturbations. As mentioned, adaptation is driven by error feedback. However, errors such as misreaching for a glass of water and spilling it, or misstepping onto a curb and stumbling, are not the types of errors thought to drive adaptation. Instead, adaptation is driven by sensory prediction errors, defined as the difference between the expected and the actual sensory consequences of a movement (Tseng et al. 2007). In other words, did your movement go where you expected it to go? Sensory prediction errors can occur even if one does not miss the target (e.g., knock over the water glass or stumble onto the curb) as long as there is a mismatch between the expected and the actual sensory feedback that one receives.

That said, the most commonly studied perturbations used to drive adaptation cause both types of errors: The postmovement sensory feedback does not match what one expected and they miss the target. So, most of the time the target error is a good proxy for the sensory prediction error. However, a set of careful studies in both reaching and walking have disentangled these two error signals. Subjects encountered situations in which they experienced a sensory prediction error but still reached the target or stepped correctly (Mazzoni & Krakauer 2006, Long et al. 2016). In these situations, adaptation occurred uninterrupted, as evidenced by normal after-effect when the perturbation was removed (i.e., during de-adaptation). This point is important—in rehabilitation there may not always be consistent reductions in observable errors during adaptation, yet the subject might still be adapting. The clearest way to test for adaptation is to look for after-effects once the perturbation is removed.

Adaptation appears to depend more on some brain regions than on others; that is, it is potentially useful for rehabilitation in certain neurological populations but not others. Cerebellar damage impairs adaptation across many movement types—reaching (Smith & Shadmehr 2005, Tseng et al. 2007), walking (Morton & Bastian 2006), eye movements (Lewis & Zee 1993), and postural control (Horak & Diener 1994). This suggests that the cerebellum is an important part of the brain circuit for this type of learning. Adaptation may be a useful learning mechanism for neurological patients without cerebellar damage. Indeed, people with cerebral stroke show largely intact adaptation of reaching and walking, though adaptation is sometimes slower (Reisman et al. 2007, Scheidt & Stoeckmann 2007). Likewise, individuals with Parkinson's disease show unimpaired reaching and walking adaptation (Fernandez-Ruiz et al. 2003, Roemmich et al. 2014a), although the after-effects following adaptation may be modestly smaller in the absence of dopaminergic medication (Fernandez-Ruiz et al. 2003, Roemmich et al. 2014b). People with damage limited to the cerebrum and basal ganglia might benefit from adaptation learning mechanisms. Of course, the exception would be if these patients could not perform some approximation of the desired movement from the start (e.g., the patient is unable to walk).

How might adaptation be helpful for rehabilitation? One example comes from work on prism adaptation and hemispatial neglect. Laterally displacing prisms shift the direction that the eye must look in order to see something straight ahead. If one wears prisms that shift the gaze 20° to the right, one also reaches 20° to the right when asked to reach to an object placed straight ahead because the direction of arm movement depends heavily on gaze direction. However, people adapt by slowly shifting their reach direction to the left of their gaze over tens of movements to reach the object. When the prisms are removed, people show an after-effect and continue to reach to the left of their gaze until they de-adapt. Nearly 20 years ago, Rossetti et al. (1998) reported that a single prism adaptation session in patients with left hemispatial neglect induced after-effects that helped their sensorimotor and cognitive spatial functions for about 2 h. Subsequent work has shown that repeated prism adaptation induces longer effects that last days to weeks (Rode et al. 2015). A randomized clinical trial is currently under way to determine the short- and long-term effects of prism adaptation in a large population in a realistic clinical setting (Ten Brink et al. 2015). Importantly, this trial goes beyond assessing specific impairments tested in the laboratory, instead testing whether prism adaptation can affect a person's function and activities of daily living.

Adaptation has also been used to improve walking in neurological populations. Split-belt treadmills (i.e., treadmills with separate belts for the right and left legs) allow the experimenter or therapist to perturb the walking pattern by making the legs walk at different speeds (**Figure 1*a***) (Dietz et al. 1994, Reisman et al. 2005). In a typical split-belt treadmill adaptation experiment, subjects walk for periods of time with the belts tied at the same speed in a baseline period, split at two different speeds in an adaptation period, and tied again in a de-adaptation period. When the treadmill belts are split, people initially limp by taking one long step and one short step (Reisman et al. 2005). **Figure 1*b*** shows individual step lengths, or the distance between the feet at heel strike for each foot, and **Figure 1*c*** shows the difference between left and right step lengths for adjacent steps. Notice that the step lengths are asymmetric early in adaptation, but after approximately 100 steps they converge (**Figure 1*b***) and are equal (**Figure 1*c***). During de-adaptation, when the belts are tied again, subjects show the opposite asymmetry. People then show an after-effect in which they walk with the opposite asymmetry when the treadmill belts return to moving at the same tied speed (like a normal treadmill)—the leg that initially took a short step during adaptation now takes a long step and vice versa for the other leg. An interesting and important feature of split-belt adaptation is that people cannot explain what it is they are changing—they feel like walking is easier as they adapt, but they cannot describe how they are changing their walking pattern.

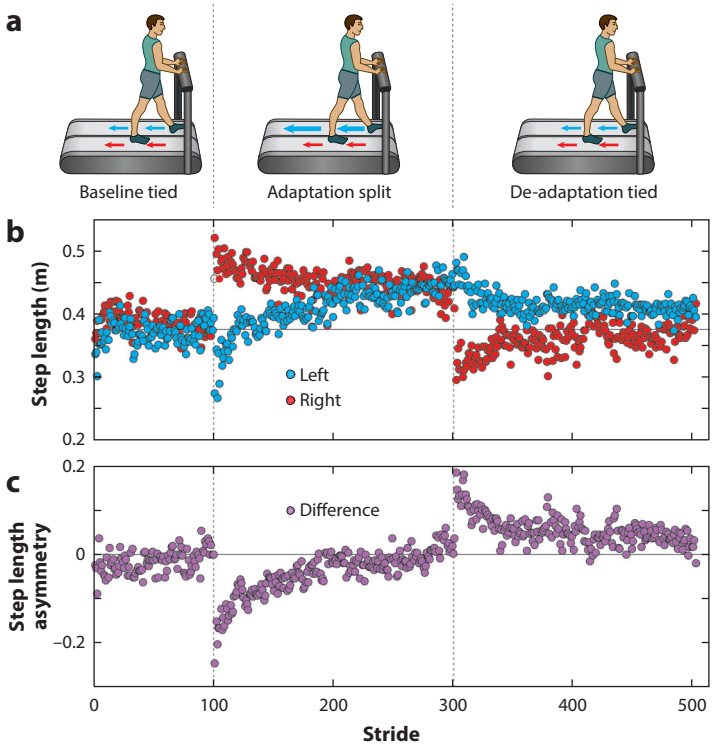

Figure 1

(*a*) Schematic of a typical split-belt treadmill adaptation experiment. The belts move at tied speeds during a baseline period, split at different speeds (2:1 speed ratio) during an adaptation period, and then return to tied speeds during de-adaptation. (*b*) Individual step lengths, which are calculated as the fore-aft distance between the feet when either the right (*red*) or left (*blue*) foot hits the ground. (*c*) Step length difference during baseline, adaptation, and de-adaptation. Healthy adults generally walk with symmetric step lengths during baseline. During early adaptation, the leg on the slow belt (right leg, in this example; *red*) takes a longer step than the leg on the fast belt (left leg; *blue*). Note that the right slow step length is initially longer owing to the trailing fast leg being pulled back rapidly on the fast belt. Over a couple hundred steps, the slow leg step gradually shortens and the fast leg step length increases to converge on a symmetric stepping pattern (*purple*). During de-adaptation, the leg that previously walked on the slow belt (right; *red*) takes a short step and the leg that was previously on the fast belt (left; *blue*) takes a longer step. Again, the right and left step lengths eventually converge to symmetry over time (*purple*).

Split-belt walking adaptation (**Figure 2*a***) has been used to improve the gait of people with hemiparesis from cerebral damage (e.g., stroke, hemispherectomy) who walk with unequal steps (Reisman et al. 2007, 2013; Choi et al. 2009). For these individuals, adaptation can induce after-effects that make their step patterns more symmetric (**Figure 2*b***). When a split-belt perturbation augments the limp, making it larger than normal, this drives the nervous system to learn to reduce the asymmetry. Importantly, the asymmetry does not go away completely during the adaptation—people tend to adapt back to their own baseline asymmetry. Symmetry then occurs in the after-effect when the belts are tied (**Figure 2*c***), and this generalizes to improve walking symmetry overground (Reisman et al. 2009) over both short (i.e., minutes; Reisman et al. 2007) and long (i.e., months; Reisman et al. 2013) timescales. The long-term study trained chronic stroke survivors for 4 weeks and tested for retention of a new overground walking pattern 3 months later. A key feature of this study is that adaptation was used only to induce a beneficial after-effect (i.e.,

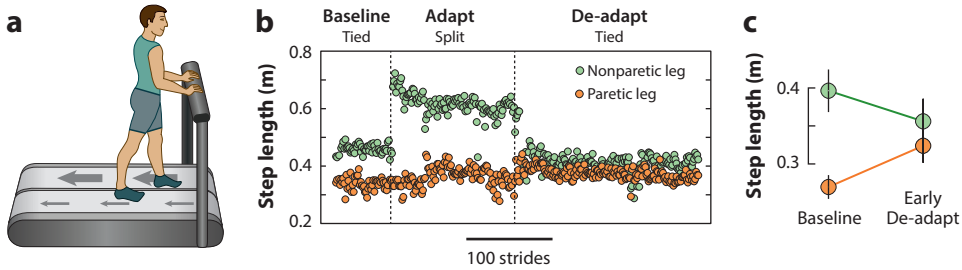

Figure 2

(*a*) Schematic of the split-belt treadmill during adaptation in which the left leg is walking faster than the right leg. (*b*) Example data from a stroke survivor adapting step lengths on the split-belt treadmill. This individual had step length asymmetry of approximately 0.1 m at baseline in which the nonparetic leg took a longer step than the paretic leg (i.e., this individual had difficulty advancing his paretic leg). During split-belt adaptation, the step length asymmetry was made even larger by making the paretic (left) leg move faster and the subject adapted back toward their baseline asymmetry. This led to an after-effect in the de-adaptation period that caused step lengths to be more symmetric. For this particular individual the beneficial after-effect persisted, in which the steps were symmetric for hundreds of strides compared to baseline walking at the same speed. (*c*) Group data from stroke survivors showing that symmetry is due to both legs changing their step lengths from baseline to the after-effect in the de-adaptation period. Figure adapted from Reisman et al. (2007).

symmetry), which was then practiced and reinforced as subjects walked overground. Thus, it is likely that both elements of training, adaptation on the treadmill and reinforced practice during overground walking, were important.

There are clear benefits to using adaptation for rehabilitation. First, the therapist is in control of the perturbation (or environmental change) that drives adaptation. The perturbation can be customized depending on the deficit of each individual patient. For example, a recent case series used individualized robotic force fields for adaptation in stroke survivors and showed positive effects after several days of training reaching movements in the robotic environment (Bittmann et al. 2017). Second, adaptation does not require the individual to think about how to correct their movement. Once a perturbation is applied, adaptation occurs without any voluntary effort to correct for it. As mentioned above, people can voluntarily aim (reaching) or step (walking) and this does not interfere with the adaptation process (Mazzoni & Krakauer 2006, Long et al. 2016, Roemmich et al. 2016). For example, when subjects receive feedback that helps them speed or block expression of an adapted walking pattern, it does not interfere with the after-effect or de-adaptation, suggesting that the feedback response functions separately (**Figure 3*a–c***). Third, multiple features of movement can adapt simultaneously, which theoretically means that multiple impairments can be targeted all at once (Statton et al. 2016). Specifically, we showed that healthy people can adapt their step length symmetry on a split-belt treadmill while undergoing a visuomotor adaptation of their knee or hip kinematics (**Figure 3*a–c***) (Statton et al. 2016). It is not yet known whether more than two adaptations can occur simultaneously, whether the adaptations must be in different domains (i.e., visuomotor versus mechanical force perturbation), or whether patients have a similar capacity for simultaneous adaptation.

There are also notable unanswered questions about and limitations of using adaptation for rehabilitation. One important question is how to optimize generalization of adapted movements to different contexts or untrained movements. For example, our group has shown that walking adaptation on the split-belt treadmill normally generalizes incompletely and transiently to more natural overground walking (Reisman et al. 2009, Torres-Oviedo & Bastian 2010), which can limit its usefulness for gait training. One reason for this might be the so-called credit

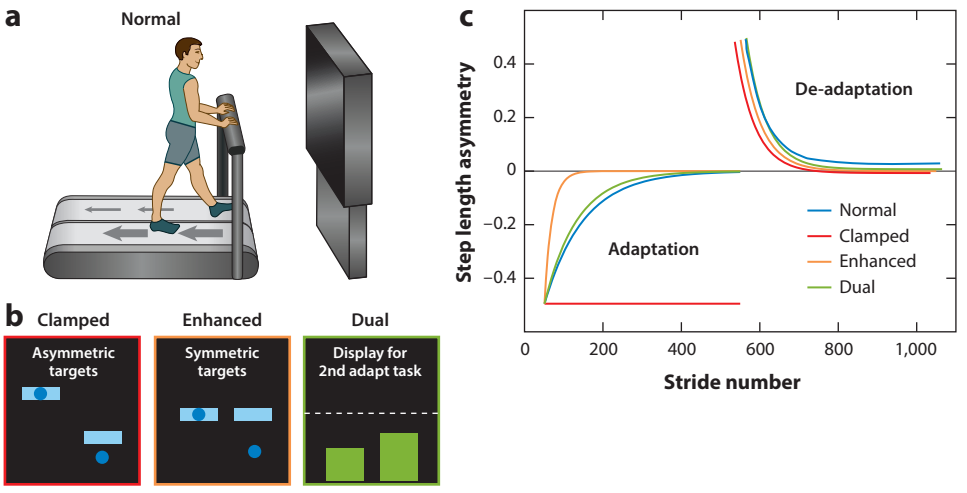

Figure 3

(*a*) Schematic of split-belt treadmill walking with a visual display screen. In the normal condition, the screen is blank. (*b*) Illustrations of the screen for different visual feedback conditions. In the clamped condition, subjects' fore-aft foot motions are displayed as blue dots and subjects are asked to step with the blue dots in two asymmetric target zones. This acts to clamp their step asymmetry to the initial level of the perturbation. In the enhanced condition, subjects see a similar display but are now asked to step into two symmetric targets. This acts to reestablish symmetry more quickly. In the dual condition, subjects are asked to adapt to the split-belt treadmill perturbation while performing a visuomotor adaptation involving knee motions. Each green bar represents how flexed the knee is, and subjects are asked to hit the white dotted line during the swing phase of walking. Adaptation is driven by changing the left bar so that the left knee must flex more than the right knee in order to hit the white target line. (*c*) Schematic of adaptation and de-adaptation for the four different conditions. In this panel, step length asymmetry is plotted—this is the difference in consecutive right and left steps normalized to their sum. Thus, a value of −0.4 indicates the right step is approximately 40% smaller than the left step, and vice versa for 0.4. A value of 0 indicates the steps are symmetric. Note that no matter which condition subjects adapted in, the de-adaptation curves look identical. This suggests that the voluntary control strategies or a dual adaptation does not alter adaptation.

assignment problem—if a perturbation is large, the credit or origin of that error might be assigned to the treadmill and learning might be specific to the environment (i.e., walking on the treadmill). Smaller errors that can be induced through more gradual adaptation—particularly those within an individual's normal motor variability—seem more likely to be credited to the person and not the environment, thus improving generalization of the adapted motor pattern (Torres-Oviedo & Bastian 2012). Adult stroke survivors also generalize split-belt treadmill adaptation to overground walking more than control adults, even when they receive an abrupt perturbation (Reisman et al. 2009). We currently do not understand why this is the case, but it suggests that one must test generalization in the clinical population of interest rather than assuming that they will behave like healthy control subjects.

An important limitation of adaptation is that both the time course of adaptation and the subsequent after-effects occur on a relatively short timescale. One cannot simply train for one adaptation session and expect for the after-effects to be long lasting. The fast (i.e., on the timescale of minutes) rates of adaptation and de-adaptation are both beneficial and detrimental to the use of adaptation in rehabilitation: New movement patterns can be learned quickly through adaptation, but they de-adapt even faster. Relying on adaptation alone to drive long-lasting improvements in movement patterns is somewhat paradoxical because it requires the learning mechanism that adapts the

movement to fail to subsequently de-adapt the movement. It will likely be important for future work to understand how to use adaptation in combination with other learning mechanisms so that adapted movement patterns persist over longer timescales.

THE ROLES OF REINFORCEMENT AND REWARD IN CHANGING MOVEMENT PATTERNS

As discussed above, effective rehabilitation relies on the ability to make long-lasting improvements in movement patterns. Many approaches succeed at teaching new movement patterns in the clinic; however, most approaches result in patterns that fade once the patient leaves therapy. In this section, we discuss recent advances in reinforcement concepts and techniques that aim to ingrain movement patterns for long-term use. Note that this review is not intended to be a historical review of reinforcement and reward-based learning. We do not discuss in detail, for example, the seminal findings of Pavlov (1927) and Skinner (1953) on classical and operant conditioning, Thorndike's (1911) law of effect, the temporal difference models of Sutton & Barto (1998), or the neurophysiology of reward-based learning commonly studied via reward prediction error signaling in dopaminergic neurons (Schultz 1998). We instead focus on the implications of recent behavioral studies of movement reinforcement in humans on rehabilitation.

Newly learned movement patterns are most likely to persist when the pattern has value to the learner. This value is often created by forming associations between a certain movement and a subsequent reward. If a basketball player tries a new shooting form and consequently makes a basket, they are more likely to continue to use the new form. As any coach can attest, transitioning these movement-reward associations into habitual movement patterns is a considerable and complicated challenge, especially when the pattern is complex (Bernstein 1967). It is not so simple that the basketball player changed their movement and achieved success. They must understand—either explicitly or implicitly—how they changed their form to result in a successful shot, how to reproduce the new movement pattern, how likely it is that the pattern will result in future success, and how much value to place on the reward.

Behavioral studies of motor learning and motor control have provided insights into how humans process and register these types of information to reinforce successful movement patterns. In a study of reaching movements, Izawa & Shadmehr (2011) showed that healthy adults could learn a new movement pattern from a simple binary feedback that indicated only whether the movement was a success or failure. An important finding of this study was that learning via binary success/failure feedback resulted in the desired movement pattern but, unlike adaptation, did not result in sensorimotor recalibration. Therefore, a different mechanism must have led the learner to the successful movement.

Several subsequent studies attempted to elucidate this mechanism and suggested that effective reinforcement learning is driven by an exploratory component of movement variability (Wu et al. 2014, Therrien et al. 2016). All our movements are executed with a certain amount of variability—even the world's best athletes cannot produce two consecutive identical pitches in baseball or identical serves in tennis. Movement variability is not purely noise in the sensorimotor system (Skinner 1953) but may play a key role in the exploration of new movement patterns, a process that may have therapeutic value (Stergiou et al. 2006). Indeed, the structure of movement variability appears to facilitate exploration of new, potentially desirable movements (Wu et al. 2014) and is responsive to reward (Pekny et al. 2015). However, not all variability is tuned toward exploration. Learning from binary success/failure feedback depends not only on exploitation of exploration variability but also on contamination from noise in the sensorimotor system (Therrien et al. 2016). Noise introduces a difficult problem for the nervous system because the system must estimate

where to assign credit for the resulting reward or lack thereof. For example, weighing exploration and noise contributions to variability enables us to determine whether a movement failure was a result of our own movement or a change in the environment (McDougle et al. 2016).

Reinforcement mechanisms not only are important for reward-based motor learning but can also ingrain movement patterns that have been learned via other mechanisms. For example, recall that we suggested that learning via adaptation may be longer lasting if supplemented with another learning mechanism. Indeed, a new sensorimotor mapping can be learned through motor adaptation and reinforced with binary feedback (Shmuelof et al. 2012). This approach holds considerable promise for rehabilitation, as one learning mechanism could be used to facilitate acquisition of a new movement pattern and another could be leveraged simultaneously to make the pattern more permanent. However, approaches that combine adaptation and reinforcement mechanisms have yet to be tested in long-term clinical studies.

There is a clear need to test reinforcement principles in clinical populations, as current studies with direct applications for rehabilitation are limited. One interesting study of persons poststroke aimed to encourage use of the paretic arm by providing participants with augmented reward feedback during a reaching task (Ballester et al. 2016). The idea behind this study was that persons poststroke often avoid using the paretic arm because hemiparesis makes it difficult to execute tasks (and, subsequently, obtain rewards). The investigators hypothesized that amplifying arm movements in a virtual environment such that rewards were easier to achieve with the paretic arm would encourage the participants to use the arm more often in daily life. Although this novel protocol only marginally outperformed a control group that did not receive virtual movement amplification, and the contribution of potential adaptation in response to the perturbed virtual environment must be considered, refinements of this type of training in which reward is used to encourage increased use of impaired limbs may hold promise. Similarly, although not within the motor domain, providing reward may reduce spatial neglect after stroke by rewarding stroke survivors for attending to the neglected side (Malhotra et al. 2013).

Up to this point, we have focused primarily on a role for reinforcement in discrete, goal-directed reaching movements. These are relatively simple movements with clear objectives. In daily life, though reach trajectories are subject to principles of optimization (Huang et al. 2012, Shadmehr et al. 2016), the primary goal of a reach is to move the hand to its intended target. The way that we reinforce successful reaches is then generally simple and intuitive: The participant receives a reward if the hand reaches its target (or, in some cases, moves along a specified shape or trajectory), and obtaining this reward is paramount to any competing objective. However, reinforcement of continuous movement patterns is seemingly more complicated. Walking, for example, is thought to be influenced by several objectives, including stability, energy optimization, and pain avoidance (Kuo & Donelan 2010). This adds complexity to the reinforcement of new walking patterns, because although healthy adults can learn new walking patterns using binary success/failure feedback (Hasson et al. 2015), it is unclear how the nervous system prioritizes rewards of external (i.e., provided by a clinician or experimenter) versus internal (e.g., maintaining stability, saving energy) origin.

We suggest that understanding how people weigh external versus internal rewards is likely to be critical for gait rehabilitation. Clinicians and rehabilitation professionals commonly aim to restore patient function to normal. However, we think it crucial that normal function have some value to the patient if it is to be retained long-term upon leaving therapy (Latash & Nicholas 1996). Consider a patient that takes short, slow steps. A therapist could reward the patient for taking longer, faster steps (perhaps by using points on a game), but we suggest that this pattern will be unlikely to persist outside the clinic if longer steps are destabilizing or energetically costly for the patient. In other words, slow steps provide internal reinforcement for the patient because

they improve stability, and satisfying this internal objective may prevail over competing external reinforcement feedback provided by a clinician that has comparatively little value to the patient.

In summary, reinforcement is facilitated by movement exploration in which specific movements are associated with rewarding outcomes. Reinforcement-based mechanisms show considerable potential for clinical use because current evidence suggests that they can be paired with other learning mechanisms to promote longer-lasting improvement. However, reinforcing a desired movement pattern is not trivial, as understanding the type of reward that effectively reinforces the desired pattern is critical. Successful rehabilitation requires a focus on identifying the key objective that is most rewarding to the patient and, instead of simply striving for normal function, should design treatments that reward the identified objective to improve function.

LEARNING NEW MOVEMENT PATTERNS THROUGH INSTRUCTION AND PRACTICE

Instructive learning is arguably the most common motor learning mechanism used in motor rehabilitation. Therapists and clinicians often provide explicit instructions to drive voluntary changes in movement (e.g., "take a bigger step," "bend your knee") over repeated sessions of therapy. Although the concept of instructive learning is seemingly simple—a clinician instructs the patient how to change their movement pattern and then the patient practices the new pattern repeatedly—many features of the training type and structure can affect patient outcomes. Indeed, decades of research in psychology, kinesiology, and behavioral neuroscience have provided insights into how humans refine voluntary movement patterns and learn new motor skills with practice (Schmidt & Lee 2005, Krakauer & Mazzoni 2011). We focus on (*a*) recent studies that have identified important factors to consider when designing instruction-based rehabilitation protocols for clinical populations, and (*b*) recent work in human motor learning that has explored the role of voluntary control in the acquisition of new movement patterns.

Before an instructive learning approach for rehabilitation is used, it is important to assess the patient's ability to voluntarily correct the targeted movement deficit and produce the desired pattern. Many common motor deficits observed in clinical populations can indeed be corrected voluntarily with instruction and feedback. For example, persons with Parkinson's disease often exhibit slow movements that are diminished in amplitude, but retain the ability to amplify movement kinematics voluntarily with instructive therapy (Ebersbach et al. 2010). Similarly, persons post-stroke can often walk faster than they do in their daily lives when instructed to do so (Lamontagne & Fung 2004). Even much finer features of pathological motor control can often be controlled voluntarily, as children with dystonia or cerebral palsy can use electromyographic feedback from individual musculature to reduce co-contraction (Young et al. 2011) and improve arm function (Bloom et al. 2010).

If a patient is capable of voluntarily correcting the targeted movement deficit, we must then understand how to best deliver training to facilitate lasting improvement. In particular, the effects of training dose and timing on patient outcomes have garnered considerable attention. It had long been assumed that higher-dose, longer-term training led to better patient outcomes (Bell et al. 2015, Lang et al. 2015); however, evidence led researchers to question this assumption (Lang et al. 2016). Prolonged doses of upper extremity training for persons with chronic stroke did not lead to improved functional capacity compared with the improvements gained over much smaller doses of therapy (Lang et al. 2016). Whether this is also true in the acute phase of stroke—when training may be able to take advantage of heightened plasticity in the nervous system (Zeiler & Krakauer 2013)—is unknown. The importance of training dose and timing in other populations with damage to the nervous system (e.g., spinal cord injury, traumatic brain injury) or neurodegenerative disease

(e.g., Parkinson's disease, multiple sclerosis) is also not well understood, nor is the importance of dose and timing in rehabilitation of lower extremity movements.

Facilitating patient engagement is another key consideration when developing effective training protocols that require extensive practice. The rapid rise of interactive gaming and virtual reality technology has increased the emphasis on developing training methods that are fun and engaging. Studies have shown that these technologies can increase patient involvement (Brunner et al. 2016) and enjoyment (Cameirão et al. 2016) compared with conventional therapy and may lead to greater improvements on specific tasks (Laver et al. 2015). However, large clinical trials comparing gaming-based and conventional therapies have reported similar improvements in gross motor function regardless of training modality (Saposnik et al. 2010, 2016). Incorporating gaming and virtual reality into training regimens appears to be a good way to increase patient adherence to home-based rehabilitation but may not consistently outperform conventional therapy when available.

Training may also be more effective when instructive learning is paired with other learning mechanisms. Several studies of motor learning in healthy adults have revealed that voluntary changes in movement can co-occur with other learning mechanisms without interference (Taylor & Ivry 2014). This finding provides researchers an opportunity to combine mechanisms that rely on voluntary and involuntary control to drive improvements in movement patterns. As discussed above, motor adaptation in reaching persists even when the participant is explicitly told how to move to counteract the perturbation (Mazzoni & Krakauer 2006, Taylor & Ivry 2014), and humans can use feedback during walking to intentionally block changes in their gait patterns in response to mechanical perturbations (Long et al. 2016) or voluntarily change how they walk (Roemmich et al. 2016) with little effect on gait adaptation (**Figure 3*a–c***). Implicit, subconscious mechanisms can function in parallel with explicit, voluntary control to change movement patterns, offering patients the potential to tap into these mechanisms simultaneously without interference during rehabilitation.

We have discussed the considerable strengths of instructive learning—it can result in quick changes in movement patterns, it can combine with other learning mechanisms, it can make therapy more enjoyable, and it can target a variety of movement deficits—but there are also notable challenges. Effective instruction-based rehabilitation requires that therapy targets the deficit in such a way that the resulting improvements generalize outside the clinic. This is not always straightforward and intuitive. It is commonly assumed in rehabilitation research that improved movement quality results in participants having a better movement pattern for use in daily life. However, Waddell et al. (2017) found that this is not necessarily true for persons poststroke. These authors showed that intensive, task-specific upper extremity training of the paretic limb resulted in improved limb capacity, yet this did not generalize to increased paretic limb use in daily life (Waddell et al. 2017). Furthermore, generalization is limited because, upon leaving the clinic, patients must attend to everyday life and cannot focus entirely on reproducing the desired movement pattern. Driving lasting improvements through instructive learning is thus often a significant challenge because the resulting changes in movement depend on the presence of instruction or external feedback that ceases once the patient goes home.

Last, designing effective and efficient rehabilitation approaches with any of the above learning mechanisms depends on the clinician's ability to understand the potential for improvement on a patient-specific basis. When persons poststroke were trained to perform a skilled elbow flexion task with the paretic arm, many eventually improved performance to a level similar to that observed in untrained healthy adults (Hardwick et al. 2017). However, the key finding here is that this performance level had reached asymptote in the persons poststroke, whereas healthy adults showed considerable room for further improvement. This study showed that a point of diminishing returns

can be reached at different levels for patients with differing degrees of impairment. We must carefully consider each individual patient's potential for further improvement when determining whether to proceed with a particular treatment protocol.

CONCLUSION

In this article, we have reviewed the rehabilitation applications of recent human behavioral findings to motor learning and motor control. We have identified a particular need for developing rehabilitation strategies that simultaneously incorporate multiple motor learning mechanisms to drive fast, long-lasting improvements in movement patterns. More generally, we suggest that the most successful rehabilitation approaches result from understanding both (*a*) what approaches work and (*b*) why they are effective. Because clinicians, rehabilitation researchers, and basic scientists will have critical roles in the future of neurorehabilitation, we think it is important that we learn from one another to identify and understand the mechanisms that effectively drive changes in human movement while being mindful of the practicality and likelihood of translating these mechanisms to the clinic.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We thank K. Leech for helpful comments. This work is supported by National Institutes of Health grant no. R37 NS090610.

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