CHAPTER 7

The applicability of motor learning to neurorehabilitation

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Introduction

Statements to the effect that recovery is a form of learning or relearning are commonplace in the field of neurorehabilitation. In this chapter, motor training will refer to what is done to the patient and motor learning will refer to what the patient may do in response. This distinction is important—just because training is happening does not mean that anything is being learned. The relearning premise for neurorehabilitation is based on three other a priori assumptions. First, that the nature of the deficit to be rehabilitated through learning is known. Second, that the kind of motor learning that should be targeted by training is known. Third, that patients after stroke have an intact learning capacity despite impaired performance. In this chapter the focus will be mainly on rehabilitation of arm paresis after stroke, which results from damage to motor cortical areas and/or their descending pathways. This narrower focus is essential if the topic of learning and neurorehabilitation is to remain within the bounds of a single chapter. That said it is hoped that the general principles introduced here, which will be emphasized over details, are broadly applicable across the range of post-stroke impairments and to other neurological conditions.

Arm paresis after stroke refers to loss of strength and motor control, along with changes in phasic and tonic muscle tone [1]. Non-neural peripheral changes in muscle, joint and tendon properties can also contribute to the paresis phenotype. In this chapter it will be assumed that treatments for strength, tone (spasticity) and contractures are not based on motor learning principles and so will not be addressed further. Note again that one can *train* for strength but this is not motor *learning*. Thus, the starting point for this chapter is that when learning is invoked it implies either improving motor control or finding alternative compensatory strategies with effectors/joints/muscles in which motor control remains relatively intact; in either case, response to training is assumed to have mechanistic commonalities with motor learning in healthy subjects. It will become apparent after reading this chapter that the assumption that one can equate recovery and motor learning is subject to several fundamental caveats.

A taxonomy for motor learning

The fundamental problem for motor learning is to find the appropriate motor commands that will bring about a desired task outcome. Motor learning is a fuzzy category that encompasses action selection guided by instruction, reward, or error, and subsequent improved execution of the selected actions. Skill is a very popular term but is hard to define. Here, it will suffice to say that one is skilled at a task when practice has led to it being performed better than baseline because of selection of optimal mean actions that are then executed with high speed and precision. We will briefly describe the motor learning components in the following section. A question that should always be kept in mind is whether these components of motor learning are relevant or effective in reversing identified motor deficits after stroke or any other neurological condition.

The role of *instruction* in selecting task-appropriate actions has been surprisingly under-emphasized in the motor learning literature despite the ubiquity of coaching and teaching in sport, music and dance; all quintessential motor skill-requiring activities. Similarly, the existence of physical and occupational therapists attests to the crucial role of instruction in rehabilitation. We have recently posited [2] that neglect of the crucial roles of knowledge and instruction for motor learning originates in part from an over-emphasis on simple implicit adaptation tasks due to the classic result in the patient H.M., who retained memory of mirror-drawing ability across days despite no explicit memory of ever having performed the task [3]. This led, in our view, to over-generalization of the notion of procedural learning/memory from this simple task to all motor skills. We have recently argued instead that everyday motor skills such as cooking or driving cannot be extrapolated from motor adaptation tasks and cannot be learned without knowledge and instruction [2]. In agreement with our position, a recent paper has shown that a motor task with redundant structure cannot be learned without explicit awareness of this structure [4]. We, and others, have recently shown that even adaptation tasks have a crucial explicit component [5, 6].

In *reinforcement learning*, actions are selected with increased or decreased frequency based on rewards and punishments, respectively. Reward can be intrinsic, based on self-perceived success or failure, or it can be based on extrinsically provided loss or gain in points or praise. Rewards can be short-term or long-term, and the balance between these is of central computational importance in the field of reinforcement learning. A local action solution can be found based on short-term rewards that is ' just good enough', which then becomes habitual, even though with more time and

exploration, a more optimal action could have been found. For example, if a person is given a pair of skis and told to get down a mountain, they may well find a way to do so on their own but they are very unlikely to discover the best technique, which would require instruction and more extended practice. Later in the chapter we will argue that compensatory strategies after stroke often represent precisely this kind of premature adoption of habitual 'just good enough' actions. Constraint-induced therapy is an attempt to prevent adoption of the bad habit of choosing the unaffected arm to perform tasks rather than doing the harder work of improving the affected side [7].

Sensorimotor adaptation refers to reduction of errors in response to a perturbation. Sensorimotor adaptation tasks have been extensively studied experimentally and modeled computationally [8–11]. The prevailing idea is that adaptation occurs through cerebellar-dependent reduction of errors through updating of a forward model via sensory prediction errors [12, 13]. The relevance of adaptation to rehabilitation remains unclear, however, because although imposed errors can lead to fast and large changes in behaviour, these changes do not seem to last once the perturbation is removed. For example, the paretic arm can be made adapt to a viscous force field set to amplify baseline directional reaching biases. When the force field is switched off, aftereffects are now in a direction that negates the biases [14]. A similar 'error augmentation' approach has been used using a split-belt treadmill to reduce step asymmetry in hemiparetic gait [15]. In both cases, however, the desirable aftereffects are very short lived. In the case of force-field adaptation of the arm, after effects lasted for only 30–60 movements after 600 training movements [14]. More recently it has been shown that repeated exposure over multiple sessions prolongs split-belt treadmill over-ground after-effects in patients with stroke [16]. Interestingly, repeated exposure is also required for prism adaptation in the treatment of neglect after stroke [17]. One explanation for the short-lived nature of adaptation is that newly adapted behaviours are out-competed by baseline behaviours that have been reinforced over much longer periods of time and have become habits. In support of this idea is the recent finding that if a newly adapted behaviour, once it has reached asymptote, is reinforced by switching from error to binary feedback, the adapted behaviour is retained for longer [18]. Thus, if adaptation paradigms are going to be used to have patients quickly converge on desired behaviours, then error-based and reinforcement-based learning mechanisms will likely need to be combined. A potential way to do this would be to adapt a patient first and then reinforce the after-effect.

We have recently introduced the term 'motor acuity', drawing a direct parallel with perceptual acuity, for the component of motor skill by which movement variability and smoothness improve with practice [19]. This kind of learning probably occurs in the same motor cortical areas that are responsible for the motor commands themselves [20]. Motor acuity increases with repeated practice and could potentially be modelled as a form of statistical learning.

Finally, there has been a great deal of recent interest in *use-dependent plasticity* (UDP). It will be argued here that the assumption that UDP is a form of motor learning or motor memory relevant to neurorehabilitation is likely incorrect. The core problem is the tendency to blur the distinction between plasticity and learning. Plasticity refers to the capacity of the nervous system to change its input–output characteristics with various forms of training. These input–output relationships can be assayed in a variety of ways, which include single-unit recording in animal models and non-invasive brain stimulation in humans. Learning does imply that a plastic change has occurred but a plastic change does not imply that learning of a new behaviour has occurred. Thinking otherwise is to commit the classic logical fallacy called 'affirming the consequent': (1) If P, then Q. (2) Q. (3) Therefore, P. Unfortunately, a sizable literature appears to consider UDP important to neurorehabilitation, based largely on this logical fallacy. To appreciate the misunderstanding, consider the classic paper in this area by Classen and colleagues [21]. Transcranial magnetic stimulation (TMS) of the motor cortex was used to evoke isolated and directionally consistent thumb movements through activation of the abductor pollicis brevis muscle. Subjects were then required to practice thumb movements for 30 minutes in the direction approximately opposite to that elicited by TMS. The critical finding was that subsequent TMS was found to evoke movements in or near the direction practiced rather than in the pre-training baseline direction. This is a very interesting result with regard to how movement repetition (it is not really training in so much as the goal is not to improve performance in any way) can lead to changes in cortical representation. Indeed, a very similar mechanism is likely at play in the series of controversial papers published by Graziano and colleagues showing that long duration trains of intracortical microstimulation of monkey motor cortical areas elicit movements that look like natural movements performed at high frequency in everyday life [22]. More recently, it has been shown that TMS in piano players elicits different finger postures than in non-piano players [23].

The crucial point when considering all these UDP-like results is that it is not at all clear what they mean for *voluntary* movements. To appreciate this objection, consider the thumb experiment; although TMS after training causes the thumb to move in a direction roughly similar to the one practised, if a subject is asked to move their thumb in the original pretrained direction they do not suddenly find themselves going in reverse! That is to say, the plastic changes assayed with TMS have not changed voluntary behaviour. Now it is true that when looked for, movement repetitions in one direction can lead to small biases in other directions [24–26] but these biases are only a fraction of the trained direction and can be easily over-ridden in a few trials. Thus at the current time, experiments that induce UDP are informative about how the brain changes with repetition but these changes do not lead to learning of new task-relevant behaviours. Further support for this conclusion comes from the many reported failures of haptic and robotic guidance to benefit training [27, 28]. It appears that the interest in these cortical epiphenomena is out of proportion to their practical usefulness for neurorehabilitation.

To learn complex everyday tasks almost certainly requires that instruction and knowledge combine with adaptation, reinforcement, and acuity mechanisms. For example, instruction and imitation can help select the mean movement that then becomes more precise and reinforced with repeated practice. All these normal learning mechanisms, if intact after stroke, could be used to increase the acuity and accuracy of compensatory movements without any recovery per se.

Table 7.1 Types of motor learning

Type	Anatomy	Example	Relevance
Instruction	Prefrontal cortex	Transfer from bed-to-chair	High
Error-based adaptation	Cerebellum and parietal cortex	Split-belt treadmill for gait	Medium
Reward- and failure-based reinforcement	Motor cortex and basal ganglia	Constraint-induced therapy of arm	High
Motor acuity	Motor cortex	None as of yet	Unclear
Use-dependent plasticity	Motor cortex	None as of yet	Low

Thus far, we have spoken about the different ways that new actions can be acquired and improved. As has already been alluded to for the case of adaptation, acquisition is not of great use if what is learned is not retained across sessions. In addition to retention, it is hoped that training the limb on a task in the rehabilitation clinic will generalize to other activities of daily living. It is surprising how little investigation there has been of retention and generalization of motor learning in the context of neurorehabilitation. One possible reason is that, as we argue here, rehabilitation is mainly compensatory and does not generalize because learning to compensate suffers from the same 'curse of task specificity' as normal motor learning [29]. A notable exception, as already mentioned, is work performed by Bastian and colleagues looking at retention of split-belt treadmill adaptation and its generalization to over-ground walking [16].

All the kinds of motor learning described here (see Table 7.1) for healthy subjects are predicated on the existence of normal neural substrate for the expression of learning, that is, that the motor system can execute the chosen motor commands. It should be immediately apparent that if the neural substrate that generates motor commands is damaged, for example the corticospinal tract (CST) after a capsular infarct, then learning might not be expressible, even if normal [30]. This example should already make it clear that learning is not, on the face of it, an obvious mechanism for reversal of a stroke's effect on performance. It will be argued here that motor learning in response to rehabilitative training after stroke can only operate within the residual performance envelope that the remaining nervous system is capable of after spontaneous biological recovery is complete. That is to say, based on reasoning and current empirical data, the null position taken in this chapter is that motor learning in response to training in the period after spontaneous biological recovery is complete cannot reverse the loss of motor control but is only relevant to learning of compensatory strategies.

Motor learning in the sensitive period after stroke: interaction with spontaneous biological recovery

There is now extensive evidence in both humans and in non-human animal models that almost all recovery of motor control (impairment) occurs in a time-limited window or sensitive period post-stroke; such training-independent recovery is often referred to as spontaneous biological recovery [31]. The sensitive period lasts about 3 months in humans [32, 33] and 1 month in rodents [34]. Evidence suggests that most recovery occurs within the sensitive period because of a unique plasticity environment that is initiated by ischaemia and falls off as a function of time and distance from the infarct. This post-ischaemic environment can be characterized by unique changes in gene expression, in the structure and physiology of synapses, and in excitatory/inhibitory balance [31, 35–37]. The crucial point to be made here is that spontaneous biological recovery in the sensitive period is not motor learning per se but an endogenous repair process that presumably relies on residual intact neural architecture as a template for reorganization. That the repair process may interact with and be augmented by training is of great importance, but task-specific training is not necessary for spontaneous biological recovery [38] and training alone cannot reproduce spontaneous biological recovery outside of the sensitive period. A clear demonstration that recovery can occur in the absence of directed training is the predictable change in the Fugl-Meyer Scale (FMS) between the first week after stroke and 3 months later [33, 39]. The FMS tests the ability to isolate joints and to make multi-joint movements in and out of synergy. As the FMS does not have functional components it is never used for training, nevertheless the FMS can dramatically improve in the sensitive period (Figure 7.1).

The obvious question is how to combine the task specificity of training with the general recovery allowed by spontaneous biological recovery in the sensitive period? Experiments in animal models suggest that the response of the brain to training in the sensitive period is uniquely enhanced and that this responsiveness diminishes as the interval between the stroke and training is increased. In one influential experiment in rats, it was demonstrated that starting re-training 5 days after stroke was much more effective than waiting 2 weeks. By one month the efficacy of task-specific training was not greater than social housing alone. These results, and others, strongly suggest that motor learning in the sensitive period is qualitatively different from motor learning in the chronic state and in healthy animals, and bears similarities to conditions early in development [31, 40]. In primates, a partial ischaemic lesion in motor cortex leads to loss of hand dexterity that recovers fully if training is initially early but is lost completely if delayed [41]. As of this writing, two crucial questions remain unanswered in the case of humans: (1) Does any form of rehabilitation in the sensitive period enhance the generalizing effects of spontaneous biological recovery? (2) Is the response to any given amount of task-specific training greater inside versus outside the sensitive period? These questions are a challenge to address and so it is not so surprising that we do not yet know the answers to them. One problem is that studies need to be adequately powered to detect additional changes riding on top of spontaneous biological recovery. Another is that it is almost certainly necessary to provide high intensity and dosage of training to exploit enhanced plasticity mechanisms, levels that current practice does not come close to achieving in the relevant time window.

A recent study determined that patients were active only 13% of the time and were alone 60% of the time during inpatient rehabilitation [42]. Lang and colleagues, in a study of how much movement practice is provided during rehabilitation (inpatient

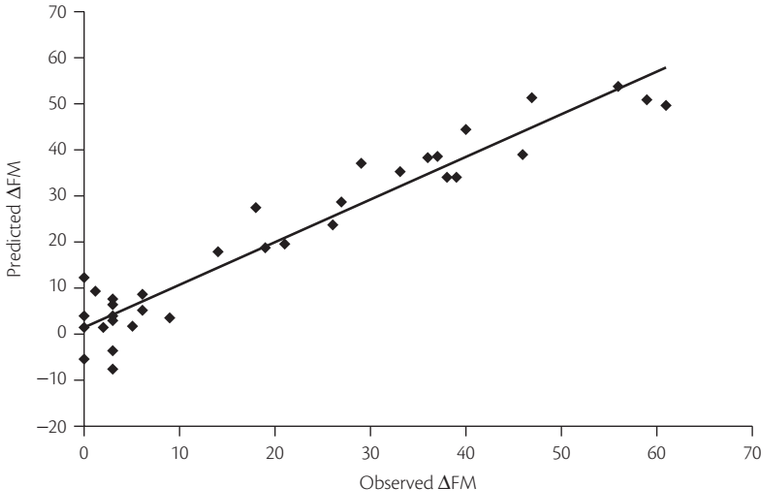

Fig. 7.1 The observed change in Fugl-Meyer Scale (ΔFM) from the first 72 hours after stroke to 3 months is very predictable in most patients using a regression model with initial FMS as a predictor.

and outpatient), found that practice of task-specific, functional upper-extremity movements occurred in only 51% of the rehabilitation sessions that were meant to address upper-limb rehabilitation and that even then the average number of repetitions per session was only 32 [43]. Data from the animal literature suggest that this dosage of repetitions is too low; changes in synaptic density in the primary motor cortex occur after 400 but not 60 reaches [44, 45]. In most rodent stroke recovery studies that use reaching as part of the rehabilitation protocol, there is often no limit imposed on the amount of reaching allowed; rats will typically reach 300 times in a training session. In a recent experiment, the amount of reaching rats were permitted was varied, and it was found that there was a threshold for the amount below which recovery did not occur [46].

Thus current rehabilitation in humans does not come close to reproducing either the dosages or intensities achieved in rodent and primate studies. Further support for the idea that current therapy early after stroke is too under-dosed to have an impact on impairment is the predictability of recovery at 3 months in the FMS after just 48 h: subsequent intervening therapy does not seem to be changing the trajectory of spontaneous biological recovery. On a more hopeful note, a recent feasibility study found that it is possible to deliver a similar number of upper-limb repetitions to stroke patients in a 1-hour therapy session as occurs in typical animal rehabilitation studies [47].

Whenever discussion turns to early intense rehabilitation after stroke, the objection of a possible adverse effect is raised both with respect to exacerbation of lesion volume and a worse behavioural outcome in the affected limb. This objection originates from a series of well-cited studies by Schallert and colleagues in the rat, in which they reported that immobilization of the unaffected forelimb with a hard cast for 15 days post-lesion induction led to less use of the affected side once the cast was removed from the unaffected side compared to when the affected side itself had been immobilized for the same duration. Immobilization of the unaffected limb not only had an adverse effect on behaviour but was also accompanied by expansion in lesion volume [48, 49]. What is less well appreciated is that in these early studies, the lesions were electrolytic rather than ischaemic, making their relevance to stroke questionable. Subsequently, however, the same group of investigators asked the same question for ischaemic lesions using a middle cerebral artery occlusion (MCAO) model in the rat. Here the results are more equivocal. In the case when 45 minutes of MCAO caused moderate cortical ischaemia, 10 days of casting of the unaffected limb did not lead to exaggeration of infarct volume but did lead to worse behavioural performance [50]. For more severe cortical ischaemia, induced by 90 minutes of three-vessel occlusion, there was no deleterious effect on lesion volume or outcome. In a distal MCAO model that caused subcortical (striatal) infarction, forced non-use but not over-use of the affected forelimb led to detrimental behavioural outcomes but without exaggeration of lesion size [50]. More recently, the same investigators failed to show a behavioural consequence of casting the unaffected limb despite exaggerations of cortical lesion volume [51]. Indeed in this study, as in the earlier subcortical study, it was *disuse* of the affected forelimb that had detrimental effects. Importantly, in these later experiments the cast was smaller and lighter and the rats were housed in larger cages with littermates. Carmichael and colleagues have revisited the effects of overuse. They induced overuse of the affected forelimb one day after the stroke by using Botox in the unaffected limb; there was no increase in infarct size with this approach [52] but the same authors have demonstrated that there is instability in cortical excitability for about 3 to 5 days post-stroke [36, 53].

All the studies cited thus far with respect to deleterious effects of early over-use of the affected limb have been in rodents. Support for a similar effect in humans came from the VECTORS study, in which 52 patients with stroke were randomized at about 10 days post-stroke to two levels of intensity of constraint-induced movement therapy (CIMT) or standard upper- extremity therapy [54]. It should be stated that intense here meant 3 hours versus 2 hours of shaping therapy per day. The surprising result was that at 90 days, affected upper-extremity functional outcome measured with the Arm Research Action Test was worse for the more intensive CIMT group. An impairment

measure was not reported in VECTORS. Interestingly, over 60% of the high intensity group had involvement of the dominant limb versus only 30% for the low intensity group. There have been reports of asymmetries in degree of bilateral and non-affected limb use with right and left hemispheric strokes [55], so other factors could have played a role in the results. Finally, longitudinal magnetic resonance imaging (MRI) in a subset of the patients did not show any enlargement of the brain lesion that could be related to intensity of treatment, so there was no evidence for infarct expansion, which was the putative explanation for intensity-related worsening in the early rodent models [48]. A study similar to VECTORS enrolled 23 patients within one week after stroke onset but with only one CIMT intensity level. In this case, the trend favored CIMT, although in the control group, therapy was more intensive than usual in order to match the CIMT group [56].

It is hard not to conclude that as rodent experiments have become more sophisticated, the purported detrimental effects of early affected limb use have become less convincing. In addition, the more recent experiments raise the possibility that immobilizing the unaffected limb can *reduce* practice with the affected limb; in none of these studies was actual frequency or total use of the affected side ever documented, it was just inferred indirectly. Thus it cannot be ruled out that it is immobilization of the unaffected side that is the problem rather than overuse of the affected side. A conservative approach, to allay lingering fears about early exacerbation, might be to ramp up the dose and intensity over the first 5 days post-stroke in the case of large cortical infarcts. It should also be emphasized that CIMT is not the only way to instigate early use of the affected side. For example, increased dosage and intensity of training could be accomplished by robotic therapy of the affected side without any need to immobilize the unaffected side but there have been very few studies of robotics in the first 3 months after stroke to date.

To summarize this section, evidence in humans and in animal models demonstrates that there is a sensitive period after stroke in which most recovery from impairment occurs and in which there is heightened responsiveness to motor training. Future advances in reduction in impairment will almost certainly exploit this sensitive period.

Motor learning in chronic stroke: it's all about compensation

This section is predicated on the assumption that in chronic stroke—that is when patients are 6 months or more post-stroke—brain plasticity and the response to training are no different to what is seen in healthy subjects, with the consequence that treatment effects on impairment are minimal and only compensatory responses can be expected to lead to meaningful improvements in function. Significant decreases in impairment occur almost exclusively in the first 3 months after stroke as a result of an interaction between spontaneous biological recovery and training in this sensitive period. As already outlined, conventional neurorehabilitation in the sensitive period is so low in dose and intensity that it fails to exploit the unique potential for motor learning. Instead, patients are prematurely made to learn compensatory strategies when they should be focusing on reducing impairment in the short time available.

There is undeniable irony in the course taken in neurorehabilitation research thus far—training at the doses and intensities that would potentially be highly beneficial in the sensitive period have instead been attempted almost exclusively outside of it, when it is too late for such training to have an effect on impairment and so only compensation is possible. Here, the term compensation will be restricted to changes in effector, joints and muscles, and not to use of external aids such as walkers, canes, or orthoses. In this framework, motor learning in patients with chronic hemiparesis is in no way different to a healthy person learning to write with their non-dominant arm after breaking their dominant arm, or learning to lean forward and shuffle when walking on a slippery surface. The failure to distinguish between the unique learning conditions that pertain to the sensitive period and the ordinary motor learning that occurs during the rehabilitation of patients with chronic stroke, has led, in our view, to significant conceptual confusion and the design of ill-conceived trials.

The two major forms of neurorehabilitation of the paretic arm in chronic stroke based on motor-learning principles are CIMT, and robotics. There are other learning-based approaches, which include action observation [57, 58], bilateral priming [59], Arm Ability Training [60], electromyography (EMG)-triggered neuromuscular stimulation [61], and virtual reality [62]. We will not cover these other approaches here in any detail because they have received less experimental attention and because the principles that will be discussed here, in our view, apply to them to a large degree.

Constraint-induced movement therapy

CIMT was the focus of the first multicentre randomized trial in neurorehabilitation, EXCITE [7]. The technique has two components: (1) Restraint of the less affected arm and/or hand with a sling or mitten for 90% of waking hours. (2) Task-oriented practice with the affected side using a form of training called *shaping*. The weightings for the two components and the length of the overall treatment have varied considerably in studies since the original trial. It is perhaps under-appreciated that EXCITE was based on some well-thought-out principles first established in de-afferented monkeys by Taub and colleagues. A chapter on motor learning and rehabilitation is a good place to consider the learning principles underlying CIMT in more detail and ask whether they were well suited to application to hemiparesis after stroke in humans.

Taub and colleagues wrote an influential paper in 1994 titled: 'An operant approach to rehabilitation medicine overcoming learned non-use by shaping' [63]. In this paper, the authors presented their new rehabilitation framework based on experiments in monkeys that had been deafferented in one forelimb via dorsal rhizotomy. The key observation was that the monkeys did not resume use of the de-afferented limb even after spinal shock had resolved and use of the limb was again possible. The explanation was that early on when the limb was severely impaired, the monkeys learned that it was useless through negative reinforcement. This learning became a habit despite return of a latent capacity that was not explored. The authors discovered that the habit of non-use could be overcome if the good limb was restrained over days. In addition to use of the restraint, the authors also re-trained the limb in two different ways. In conditioned response training, the monkeys were made to make isolated repetitive movements across single joints and resist against loads. It was noted that these exercises

did not generalize to functional tasks (the relevance of this finding to much conventional human neuro-rehabilitation cannot go unnoted). A second, more effective training method, which they called shaping, was to incrementally reward successive approximations to a functional behaviour. In essence, shaping attempted through reward to reverse the non-use that had developed through failure. In the same paper, some promising preliminary data were presented in three patients with stroke. We can now fast forward to EXCITE, a clinical trial predicated on the ideas of restraint and shaping developed in these early studies by Taub and colleagues.

EXCITE showed that patients who received CIMT for 2 weeks had greater responses in a test of motor function and in self-report of performance quality in common daily activities. There was no assessment of motor impairment [7]. What is CIMT accomplishing? Evidence suggests that it is not leading to either significant reductions in impairment or a return to closer to normal levels of motor control [64]. Instead patients seem to be learning to compensate better for their deficit by practising particular tasks using intact residual capacities. The subtle but critical point is that, unlike in the case of a monkey's recovery from spinal shock, patients are not discovering a capacity that they lost and then latently regained. Instead compensatory strategies in the chronic state are performed with capacities that were present from the time of the stroke or were recovered in the sensitive period; they just had not been incorporated into functional tasks through practice. Thus while it seems that an operant approach, as in de-afferented monkeys, does teach useful compensatory strategies in patients after stroke, the mechanistic parallels between CIMT after stroke and after de-afferentation are limited. Learned non-use has never been documented in humans, nor is there evidence of a latent return of capacity in the chronic state. Mention of plasticity and reorganization in the setting of CIMT is misleading unless these terms are thought to apply equally to healthy subjects. For example, to also occur when a healthy person's elbow is splinted into flexion so that within a few attempts they flex their trunk to make a reaching movement. To summarize, CIMT is a rehabilitation approach based on reinforcement through verbal instruction. It relies on the existence of residual actions that can be selected through rewarded practice and incorporated into functional tasks. CIMT has not been shown to lead to the recovery of lost motor control.

Robotic therapy

It is of historical interest that the most popular robotic device for therapy of the upper limb after stroke evolved from the same planar robot used in initial ground-breaking studies of a form of motor learning, force-field adaptation [8]. Two distinct approaches have since been used with robots in the setting of therapy. One approach has been to have the robot guide or constrain the arm to more normal straight trajectories (i.e. shaping). Alternatively, robot-applied force fields may be used to make patients' trajectory errors even larger than their baseline errors (error augmentation [14]). Here, the idea is that when the force field is switched off, immediate after-effects will be more similar to normal movements. Thus two very different kinds of motor learning have been used with the same robotic device: incremental reinforcement (shaping) versus fast error-based learning (adaptation). Interestingly, the data suggest that the former approach has small but lasting effects [65], whereas the latter has impressive but short-lived effects [14]. Similarly, an increasingly investigated split-belt treadmill paradigm used for gait rehabilitation has shown rapid improvements in gait symmetry in patients with hemiparesis after stroke, presumably through cerebellar-dependent error-based learning but these improvements revert back to baseline asymmetry fairly rapidly (25 strides) when patients return to over-ground ambulation [15]. Planar movements have a unique solution in joint space if the trunk is restrained, which means that it is not compensatory movements that are being trained but instead an attempt is being made to have subjects regain more normal motor control. Thus, robotics is quite different from CIMT. It is important to be clear on what kind of motor learning is being targeted by an approach and whether the goal is impairment reduction or compensation. It is of interest that although not intentional, both CIMT and robotics have reinforcement as their core learning mechanism but ended up having differential efficacy on function and impairment, respectively.

There have been 67 robotic stroke trials between 1997 and 2011. The learning principles underlying the trials are rarely overtly described. The largest robotics trial to date treated patients with chronic stroke (> 6 months) using the MIT-Manus device [66] with results that were essentially negative: patients who received robotic therapy gained only 2 Fugl-Meyer points over the usual care group. A minimum meaningful effect size for the FMS is a change of 7 [67]. A meta-analysis of robotic therapy has also reported a very small FMS change overall [65]. Despite unimpressive results, there are very important lessons to be learned from the Veterans Association ROBOTICS study. First, the study showed that standard of care has no effect at all on impairment, disability or quality of life. This observation alone cries out for the need for new treatments. Second, therapists outside of a research setting would not be able to consistently provide doses of assisted arm movements of around 1,000 per session (the average in real-world settings is 20–45). Third, there were no serious adverse events in 49 patients who performed 1,024 movements per session with the robot, three times a week for 12 weeks.

The reason why the effect sizes on impairment for robotic studies have been so disappointing is that, as previously stated, almost all recovery from impairment occurs in the sensitive period. This window had closed by the time patients were enrolled in almost all the robotic studies to date. Only five robotic trials have been conducted in the first 3 months after stroke, with only one of these showing a FMS change of 5 or more (68). It is not enough, however, to provide robotic therapy in the first 3 months; the kinds of movement will also almost certainly matter. The MIT-Manus robot trains patients to make non-ecological horizontal planar movements; the shoulder and elbow are level with each other. In a very interesting study, six healthy subjects were given a wearable motion-tracking system to record their arm movements as they went about their daily life [69]. Despite the large range of possible movements, the investigators found that during most normal everyday tasks the arms are confined to a small volume of space around the body and movements are predominantly in the vertical, not the horizontal, plane across a variety of tasks. Thus it could be objected that trials with the MIT-Manus and other single joint or planar devices may have failed not because they were outside the sensitive period, but because patients were not trained on functional movements. This possibility has now been addressed in a recently published trial in chronic stroke that used a 3D exoskeletal robot with 7 degrees of freedom [70]. Patients in

the study (77 randomized) had fairly severe impairment with a mean FMS of 20/66. Patients received 45 minutes of robotic or standard therapy, three times a week for 8 weeks. Not much detail is provided about either the robotic protocol used or of the motor learning framework it was embedded in. It should be said that it is fairly typical for rehabilitation studies to provide little in the way of methodological detail or conceptual justification with respect to theories of learning. The change in FMS was 4.7 in the case of robotic assistance and 3.1 points after conventional therapy. The difference of 0.78 reached significance but unfortunately this is clinically trivial.

At the current time the most parsimonious conclusion is that no amount of training alone, no matter what motor learning mechanism is recruited, is going to reverse impairment in the chronic state after stroke. It is a biological not a technological limit. It is to be hoped that there will not be a loss of faith in robotic therapy just because it has for the most part been deployed in the wrong time frame after stroke.

Does stroke have an effect on motor learning?

The question of whether learning and not just motor control is impaired after stroke is asked surprisingly infrequently [71]. The question itself can be misunderstood and is also very difficult to answer for methodological reasons. First of all, the relevant question is not whether or not certain strategically localized strokes can cause learning deficits, because the answer is clearly yes. For example, we know that cerebellar and parietal infarcts can have detrimental effects on visuomotor adaptation [72–74]. The critical question is whether the infarcts in motor cortical areas and/or their output pathways that cause hemiparesis also cause a learning deficit. At the time of writing, it has not been convincingly demonstrated that there is a learning deficit in the paretic arm after stroke [71]. One reason that the question is very difficult to answer is that there is a no assumption-free way to compare learning rate, retention or generalization between patients and controls when the levels of initial performance are not matched, as is the obviously case in the setting of hemiparesis. Any attempt to match through normalization, either additive or multiplicative, makes unproven assumptions and can lead to contradictory results [75]. The only way forward is to either have a good justifiable a priori learning model that is predicated on either additive or multiplicative effects, or to try and stratify patients who overlap performance-wise with controls. Such stratification is treacherous because of regression to the mean—one may be conditioning on noise rather than comparing true overlapping high values from one group and low values from another, and therefore requires good estimates of the measurement noise in the learning task chosen. Alternatively one can ask what the degree of retention or generalization is for patients based on what is considered desirable for them rather than making any comparison to controls.

Conclusions and future approaches

Here the case has been made that training has a unique effect on learning and repair in the first 3 months after stroke. In this time window, true reductions in impairment occur both through spontaneous biological recovery and interactions between post-ischaemic plasticity and training. In the chronic phase, motor learning is normal and only leads to task-specific compensatory effects rather than any true reversal of the paretic deficit. It is to be hoped that in the future, pharmacological agents (e.g. selective serotonin receptor inhibitors [76]), trophic support from stem cells, and brain stimulation techniques will augment [77], extend and even re-open the sensitive period in the chronic period [78, 79]. Most clinicians can provide anecdotes about patients who made true progress at the impairment level way beyond the 3-month sensitive period; such patients are also to be found in reported clinical trials. Whether these late responding patients comprise a special subset remains to be investigated but several possibilities suggest themselves. One is that these patients are outliers with respect to the sensitive period. Another is that their main deficit is not classic CST hemiparesis—for example, they have proprioceptive loss, dystonia, or apraxia. Another may be biomechanical or peripheral, for example, fixing one part of the system (e.g. painful or stiff shoulder) allows apparent reduction in impairment elsewhere (distally). Finally, perhaps something has allowed them to reopen their sensitive period to training. In the mean time, the best hope for patients with hemiparesis after stroke is to greatly increase the dose and intensity of impairment-focused therapy for the first 3 months after stroke based on the new findings with regard to learning, plasticity, and neural repair in this sensitive period.

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