Learning in the Damaged Brain/Spinal Cord: Neuroplasticity

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Abstract

Neuroplasticity refers to the ability of the central nervous system (CNS) to undergo persistent or lasting modifications to the function or structure of its elements. Neuroplasticity is a CNS mechanism that enables successful learning. Likely, it is also the mechanism by which recovery after CNS lesioning is possible. The chapter gives an overview of the phenomena that constitute plasticity and the cellular events leading to them. Evidence for neural plasticity in different regions of the brain and in the spinal cord is summarized in the contexts of learning, recovery, and rehabilitation therapy.

Keywords

Recovery • Rehabilitation • Stroke • Spinal cord injury • Brain lesion • Plasticity

4.1 Learning in the CNS

Rehabilitation technologies that support movement recovery make use of different brain and body mechanisms, one of which is the brain's ability to learn. Likely, the learning of the damaged central nervous system that mediates partial or complete recovery of function is different from learning in the healthy state. But it is thought that recovery after stroke shares certain cellular and system mechanisms of neuroplasticity with healthy learning. Clearly, the main behavioral determinants of healthy learning of novel movements, activity and repetition, are also important in recovery.

Motor learning is a general term that encompasses many different processes. Distinct behavioral and neural mechanisms are engaged depending on the level of complexity of the movement to be learned and the stimulus driving learning. A few different forms of motor learning are briefly reviewed.

Motor adaptation is a type of motor learning that acts on a time scale of minutes to hours in

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order to account for predictable perturbations to a movement [1]. Adaptation occurs on a trial-by-trial basis, correcting a given movement from one trial to the next. It is driven by sensory prediction errors, which represent the difference between the brain's estimate of the sensory consequences of movement and the actual sensory feedback [2]. Once a movement has been adapted, it must actively be de-adapted (i.e., actively unlearned) when the predictable perturbation is removed.

Associative learning can also occur on a time scale of minutes to hours. Classical conditioning is perhaps the most commonly studied form of associative learning. It acts to link two previously unrelated phenomena in order to improve behavior. For example, in eyeblink conditioning, a "conditioned" stimulus like a sound or tone can be repeatedly paired with a second, slightly delayed "unconditioned" stimulus like a puff of air to the eye [3]. Early in the learning process, the eye blinks in response to the puff of air (i.e., unconditioned response). However, with repeated exposure, the eye begins to blink when the tone is sounded, therefore anticipating the air puff by closing the eye (i.e., conditioned response). This type of conditioning can be used to make associations between many types of behaviors.

Motor learning can also be driven by feedback, either positive in the form of reward-based learning [4] or negative in the form of avoidance learning [5]. These learning processes can occur on short or long time scales depending on the type and complexity of the movement. Motor skills can also be learned via implicit processes [6]. Small improvements after repeating a novel movement, e.g., when learning to play a piano piece, are often not obvious or consciously perceived. Indeed, the reward of playing the piece well is typically late and temporally unrelated to each training trial (e.g., the audience applauds). Thus, implicit motor learning may depend on use-dependent or Hebbian-like plasticity rather than reward-based mechanisms.

All of these forms of motor learning rely on networks of neural structures rather than single areas, but there are some key regions that seem to play especially important roles in each. Adaptation is known to be cerebellum dependent. Classical conditioning can involve the cerebellum and hippocampus depending on the specific timing between stimuli. Reward and avoidance learning are dependent on basal ganglia circuitry. Use-dependent learning likely occurs at many levels of the nervous system, including spinal cord, brain stem, and cerebral structures. Importantly, all forms of motor learning are dependent on cellular mechanisms of plasticity including long-term potentiation and long-term depression. As such, these mechanisms are reviewed below.

4.2 Mechanisms of Neuroplasticity in Learning and After Lesions

4.2.1 Gene Expression

Learning of a motor skill requires gene expression in the motor cortex [7, 8]. If this expression is pharmacologically blocked, learning is reduced. Gene and subsequent protein expression is a common requirement of various learning processes [9, 10] as well as for cellular equivalents of learning, i.e., the changes in neuronal structure [11] and synaptic strength in the form of long-term potentiation (LTP) and depression (LTD) [12]. For motor skill learning, proteins are not only expressed during training but also thereafter while the subject is resting [7]. This delayed synthesis can be regarded as reflecting intersession consolidation processes [13].

Gene expression is induced by ischemia, especially in the peri-infarct cortex [14]. Some of these genes could also promote cellular plasticity offering the potential for stroke-induced plasticity as self-healing mechanisms of the brain. These mechanisms still remain to be elucidated.

4.2.2 Cellular Plasticity

Long-term potentiation (LTP) and depression (LTD) are commonly seen as cellular equivalents of the brain's learning abilities [15]. Either by repetitive stimulation, seen as the equivalent to

repetitive training – or by synchronizing two signals that converge at one neuron, potentially reflecting associative learning phenomena – an increase in synaptic strength is induced that lasts from hours to days, termed LTP [16]. LTD is induced by low-frequency stimulation and leads to a lasting reduction in synaptic strength [15]. Both LTP and LTD have been described in various brain regions including primary motor cortex (M1) [17]. The observation that the ability of M1 neurons to undergo LTP and LTD is reduced in trained animals provides indirect evidence for the hypothesis that primary motor cortex LTP/LTD is involved in motor skill learning [18]. In other words, the cellular mechanism that may lead to the formation of a movement memory trace has been used up by the learning process and needs time to recover before new learning can be accomplished. Two months after a skill has been learned in a 2-week training period and is well remembered, the synaptic strengthening that is observed in M1 shortly after training persists. But, the ability to undergo has recovered and is now expressed on a higher level of synaptic strength [17].

In the context of recovery after brain or spinal cord injury, the role of LTP and LTD is unclear. LTP is facilitated in the peri-infarct cortex [19]. This result may be incompatible with the hypothesis that LTP is used up during recovery as it is after healthy skill learning; hence, LTP would be reduced in the peri-infarct cortex not facilitated. But, the study lacks information about recovery of function or lesion size, so a valid comparison to healthy learning is impossible, and the issue of LTP utilization during recovery is left unanswered. In hippocampus, short-term ischemia leads to a disruption of LTP formation [20]. In humans, preliminary evidence indicates that LTP-like phenomena elicited in M1 of the lesioned hemisphere (cortical or subcortical lesions) by repetitive transcranial magnetic stimulation (TMS) predict good recovery at 6 months [21]. Paired associative stimulation (peripheral muscle and TMS stimulation of M1) – a potential human equivalent of associative LTP – can be elicited in the affected hemisphere M1, especially in those patients with limited deficits [22]. Hence, the ability of the lesioned cortex to undergo LTP may be a requisite for recovery.

4.2.3 Systems Plasticity in the Brain

Plasticity phenomena not only exist on the level of single neurons or networks but also in distinct functional systems of the brain. The input-output organization and the somatotopy of M1 undergo persistent changes during motor skill learning. Skill learning leads to an expansion of the cortical representation of the trained limb [23, 24]. Longitudinal motor cortex mapping experiments in rats show that this expansion is transient and is reversed after training ends although the skill is maintained [25]. In humans who continuously train new motor skills, e.g., professional pianists, task-related activation is smaller in area and more focused [26, 27]. Musicians also have enlarged gray matter volumes in various areas of cortex including the motor cortices [28]. The M1 of musicians contains memory traces of practiced skills that can be probed by TMS [29].

Representations in primary motor cortex are also modified while recovering from a stroke. Initially, large areas of motor and adjacent cortices are recruited in the attempt to accomplish a movement as detected by functional magnetic resonance imaging (fMRI) [30, 31]. If M1 itself is lesioned, expanded activation is found in peri-infarct cortex [32] or in premotor cortex [33]. As subjects recover, this overactivation is reduced, and movement-related activity focuses in the ipsilesional hemisphere contralateral to the moving limb [34–36]. If recovery is unsuccessful, more cortices remain overactivated in the lesioned as well as the nonlesioned hemisphere which has been interpreted as a sign of a frustrating attempt to recover meaningful movement [37]. But, recovery is not only accompanied by cortical activation changes. Larger activation in the cerebellum ipsilateral to the moving limb [34] and smaller activation in the contralateral cerebellum are associated with better recovery [35].

While movement-related activation observed with functional imaging methods demonstrates the brain areas that are involved in the control of

this specific movement, TMS can directly assess the output efficacy and the viability of descending pathways in the lesioned hemisphere. Larger motor evoked potentials in response to TMS and absence of ipsilateral responses to stimulation of the intact hemisphere are correlated with good functional recovery [38, 39].

4.2.4 Plasticity in Spinal Cord

There is convincing evidence in animals with a transected spinal cord that a use-dependent plasticity of neuronal circuits within the spinal cord exists [40, 41]. When stepping is practiced in spinal cat, this task can be performed more successfully than when it is not practiced [42, 43]. The training effects of any motor task critically depend on the provision of sufficient and appropriate stimuli to initiate a reorganization of neural networks within the spinal cord. This is usually achieved by a functional training. In contrast, the loss of motor capacity following neural injury becomes enhanced when locomotor networks are no longer used, for example, following an SCI or stroke [40].

4.2.4.1 Spinal Reflex Plasticity

The isolated spinal cord can exhibit some neuronal plasticity. Evidence for such plasticity at a spinal level has been obtained for the relatively simple monosynaptic reflex arc [44]. Monkeys could either be trained to voluntarily increase or decrease the amplitude of the monosynaptic stretch reflex in response to an imposed muscle lengthening [44], as well as of its analogue, the H-reflex [45]. The fact that the training effects persist after spinal cord transection [46] indicates that some kind of learning by neuronal circuits within the spinal cord is possible. Similarly, humans can be trained to change the gain of the monosynaptic stretch reflex ([47]; for review, see [48]).

The idea that the spinal cord can learn is also supported by studies of spinal reflex conditioning. Simple hind limb motor responses to cutaneous or electrical stimulation are enhanced in animals with transected spinal cords via classical reflex conditioning (i.e., pairing the stimulus with another stimulus that evokes a stronger motor response) [49]. These reflex responses are enhanced within minutes of conditioning indicating that synaptic efficacy along the reflex arc has changed, perhaps through long-term potentiation [49].

4.2.4.2 Task-Specific Plasticity

Today, it is obvious that there is also a considerable task-specific plasticity of the sensorimotor networks of the adult mammalian lumbosacral spinal cord (for review, see [40, 41, 50]). The detailed assessment of the modifiability of neuronal network function was the focus of research on central pattern generators (CPGs) underlying stepping movements [51–54]. The lumbosacral spinal cord obviously can execute stepping or standing more successfully if that specific task is practiced. Observations in spinal cats indicate that if the training of a motor task is discontinued and no other task is subsequently trained, then the performance of the task previously trained is degraded [40]. Consequently, plasticity can be exploited by rehabilitative purposes using specific training approaches following a neural injury.

In the cat, recovery of locomotor function following spinal cord transection can be improved using regular training, even in adult animals [55, 56]. The provision of an adequate sensory input during training is of great importance to achieve an optimal output of the spinal neuronal circuitry. Correspondingly, in association with hind limb exercise, reflex activity becomes normalized in adult rats following spinal cord transection [57]. Exercise obviously helps to normalize the excitability of spinal reflexes.

Several neurotransmitter systems within the spinal cord (glycinergic and GABA-ergic systems) are suggested to be involved in the adaptation to repetitive task performance [40]. In animals with a spinal cord transection, stepping can be induced by the administration of the noradrenergic agonist clonidine, which enhances the activity in spinal neuronal circuits that generate locomotor

activity [58–60]. Furthermore, serotonin seems to be involved in the production of locomotor rhythms [61].

Training paradigms of stepping and standing can modify the efficacy of the inhibitory neurotransmitter, glycine [40]. For example, when glycine is administered to a chronic spinal cat that has acquired the ability to step successfully, there is little change in its locomotor capability. If it is administered to a stand-trained cat, it becomes able to successfully step with body support [40, 50]. These findings suggest that the effect of strychnine is in so far specific in its action as it enables spinal networks to integrate sensory input by reducing inhibition [59, 60].

4.2.5 Subcortical Contributions to Movement Learning

The cerebellum is thought to use adaptive learning mechanisms to calibrate internal models for predictive control of movement. Such models are needed because sensory feedback is too slow for movements that need to be both fast and accurate – corrections would be issued too late. Instead, the brain generates motor commands based on internal predictions of how the command would move the body [62]. This feedforward control requires stored knowledge (i.e., "models") of the body's dynamics, the environment, and any object to be manipulated to be constantly calibrated though adaptation.

Many studies have shown that the cerebellum is essential for adapting a motor behavior through repeated practice – it uses error information from one trial to improve performance on subsequent trials. It is important to note that cerebellum-dependent motor learning is driven by errors directly occurring during the movement, rather than other types of feedback, such as knowledge of results after the fact (e.g., hit or miss). Studies have suggested that the type of error that drives cerebellum-dependent learning is not the target error (i.e., "How far am I from the desired target?"), but instead what has been referred to as a sensory prediction error (i.e., "How far am I from where I predicted I would be?") [2]. Damage to the cerebellum impairs the ability to adapt many types of movements, including: reaching [63], walking [64], balance [65], and eye movements [66].

The microcircuit involved in cerebellar adaptation was first proposed by Marr [67], Albus [68], and Ito [69]. These works continue to provide the basis for many of the current theories of cerebellar function. Central to the idea of cerebellar involvement in learning was the discovery that Purkinje cell output can be radically altered by climbing fiber induction of long-term depression (LTD) of the parallel fiber-Purkinje cell synapse [70]. Hence, climbing fiber inputs onto Purkinje cells can be viewed as providing a unique type of teaching or error signal to the cerebellum. More recently LTD, LTP, and non-synaptic plasticity have all been shown to exist at numerous sites within the cerebellum, both in the cortex as well as the deep cerebellar nuclei [for review, see 71]. Thus, there are multiple avenues for activity-dependent plasticity to occur within the cerebellum over relatively short time scales. It is presumed that the plastic changes in cerebellar output are responsible for changing motor behavior during the process of adaptation.

Another subcortical brain region involved in motor learning is the ventral tegmental area (VTA). This site is more involved in motor skill learning rather than motor adaptation. Ipsilateral dopaminergic projections from VTA to M1 [72] are specifically necessary for acquiring but not for performing a skill once acquired. Elimination of dopaminergic terminals in M1 [73] or destruction of dopaminergic neurons in VTA impairs the acquisition of a reaching skill in rat [74]. Dopamine modulates the excitability of M1 [75] and S1 [76] and, more importantly, is necessary for the formation of LTP in layer II/III synapses [73] that link different cortical regions (such as M1 and S1) via horizontal connections. The same synapses are the ones at which LTP can no longer be elicited after skill learning – LTP is used up as described above [18]. It is likely that the VTA-to-M1 projection relays signals of the same nature

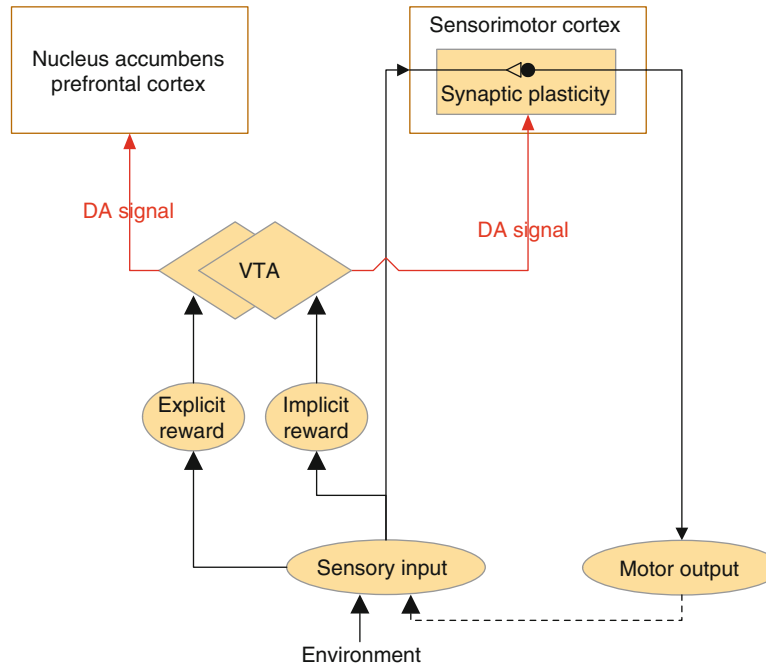

Fig. 4.1 Schematic representation of the integration of a postulated "implicit reward" into the simplified circuit that is required for motor learning. Via the dopamine (DA) signal, the reward could directly modulate synaptic plasticity in sensorimotor cortex synapses to store a new motor program

as compared to those that activate dopaminergic neurons from VTA to nucleus accumbens and prefrontal cortex. The latter encode rewarding feedback to behavior [77] (Fig. 4.1).

4.3 Learning and Plasticity During Rehabilitation Therapy

4.3.1 Lesions of Cortex and Descending Pathways

Rehabilitative training is associated with neurophysiological adaptations that are related to the improvement in motor function observed in individual stroke survivors [78]. Although correlation is no prove for causation, these studies provide an argument for neuroplasticity being a mechanism by which rehabilitative training can operate. It is likely not the only one. While bilateral arm training was associated with an increase in premotor cortex activation in both hemispheres that correlated with functional improvement in the Fugl-Meyer [79] and Wolf tests [80], conventional physical therapy (based on Bobath exercises) did not show altered brain activation despite being equally effective [80]. Conventional physical exercise may have utilized a mechanism other than those detectable by fMRI, e.g., by inducing changes in muscle, peripheral nerves, or spinal cord.

Lower extremity repetitive exercises in the form of aerobic treadmill training likely utilize yet another form of brain reorganization to improve gait. As compared with stretching exercises, improvements by treadmill training were related to increased activation of cerebellum and brainstem as detected with fMRI of paretic knee movement [81]. Interestingly, the areas recruited in cerebellum and brainstem corresponded to regions that control spinal pattern generators (cerebellar and midbrain locomotor region). These regions may have compensated for the loss of corticospinal projections that were injured by the stroke. It has also been shown that individuals with cerebral stroke can improve walking symmetry using adaptive mechanisms of learning on a split-belt treadmill [82, 83]. Here again, the hypothesis is that intact cerebellar mechanisms are responsible for this form of motor learning. Hence, subcortical reorganization may be the mechanism to target in lower extremity, and particularly walking, rehabilitation.

The availability of treatments that operate through distinct mechanisms may provide the rehabilitationist with an instrumentarium to individualize therapy for the particular patient. It seems likely that different patients with different brain injury and lesion profiles will require different therapeutic approaches.

4.3.2 Cerebellar Lesions

Recovery from a first ischemic cerebellar stroke is often very good, with minimal to no residual deficits in up to 83% of patients [84–86]. On the other hand, individuals with degenerative cerebellar disorders tend to have persistent or progressively worsening clinical signs and symptoms [87]. One study has shown that people with damage to the deep nuclei do not recover as well as those with damage to only the cerebellar cortex and white matter [88]. Thus, the etiology of the lesion and extent of damage are major indicators in recovery.

There is limited information on the effectiveness of rehabilitation interventions for individuals with primary cerebellar damage; there have been no randomized controlled trials published. Of the few studies on the effects of rehabilitation interventions in this patient population, all have been nonrandomized, noncontrolled small group [e.g., 89] or case study designs [e.g., 90]. Most work has been done on walking rehabilitation with common interventions including combinations of exercises targeting gaze, static stance, dynamic stance, gait, and complex gait activities [89, 90]. Dynamic balance activities in sitting, kneeling, and quadruped have also been advocated [89]. Ilg found that 4 weeks of an intensive coordination training followed by 8 weeks of home exercise could improve walking coordination and static and dynamic balance scores. It is not known whether such changes actually translate to improved real world function.

Locomotor training over ground and on treadmills, and with and without body weight support, has also been used with some success in single case examples [91, 92]. It is not clear how imbalance is corrected in the body weight support environment, however. With all gait and balance activities, it seems critical that the exercise be sufficiently and increasingly challenging, so as to facilitate plasticity in other intact areas of the nervous system [93, 94].

4.3.3 Spinal Lesions

4.3.3.1 Plasticity of Spinal Neuronal Circuits: Rehabilitation Issue

On the basis of the knowledge gained from animal experiments, the aim of rehabilitation after stroke or SCI should be concentrated on the improvement of function by taking advantage of the plasticity of neuronal centers and should less be directed to the correction of isolated clinical signs, such as the reflex excitability. For the monitoring of outcome and for the assessment of the effectiveness of any interventional therapy, standardized functional tests should be applied.

4.3.3.2 Functional Training in Persons with a Spinal Cord Injury

The coordination of human gait seems to be controlled in much the same way as in other mammals [95]. Therefore, it is not surprising that in persons with a complete or incomplete paraplegia, due to a spinal cord injury, locomotor EMG activity and movements can be both elicited and trained similar as in the cat. This is achieved by partially unloading (up to 60%) the patients who are standing on a moving treadmill ([96, 97]; for review, see [98]). In severely affected patients, the leg movements usually have to be assisted externally, especially during the transmission from stance to swing. In addition, leg flexor activation can be enhanced by flexor reflex stimulation of the peroneal nerve during the swing phase [99]. The timing of the pattern of leg muscle EMG activity recorded in such a condition is similar to that seen in healthy subjects. However, the amplitude of leg muscle EMG is considerably reduced and is less well modulated. This makes the body unloading necessary for the locomotor training. There are several reports about the beneficial effect of locomotor training in incomplete paraplegic patients (for review, see [56, 100, 101]),

and patients who undergo locomotor training have a greater mobility compared to a control group without training [102]. The neuronal networks below the level of an SCI can be activated to generate locomotor activity even in the absence of supraspinal input [59, 60, 103]. The analysis of the locomotor pattern induced in complete paraplegic patients indicates that it is unlikely to be due to rhythmic stretches of the leg muscle because leg muscle EMG activity is, as in healthy subjects, equally distributed during muscle lengthening and shortening [104]. In addition, recent observations indicate that locomotor movements induced in patients who are completely unloaded do not lead to leg muscle activation [105]. This implies that the generation of the leg muscle EMG pattern in these patients is programmed at a spinal level and requires afferent input from load signaling receptors.

During the course of daily locomotor training, the amplitude of the EMG in the leg extensor muscles increases during the stance phase and inappropriate leg flexor activity decreases. Such training effects are seen both in complete and incomplete paraplegic patients [96]. These training effects lead to a greater weight-bearing function of the leg extensors, i.e., body unloading during treadmill locomotion can be reduced during the course of training. This indicates that even the isolated human spinal cord has the capacity not only to generate a locomotor pattern but also to show some neuroplasticity which can be exploited by a functional training [106–109]. However, only persons with incomplete paraplegia benefit from the training program in so far as they can learn to perform unsupported stepping movements on solid ground [96]. In complete paraplegic patients, the training effects on leg muscle activation become lost after the training has been stopped [103].

4.3.3.3 Prerequisites for a Successful Training

The spinal pattern generator has to be activated by the provision of an appropriate afferent input and proprioceptive feedback to induce plastic neuronal changes [105].

Afferent input from receptors signaling contact forces during the stance phase of gait is essential for the activation of spinal locomotor centers [105, 109–112] and is important to achieve training effects in paraplegic patients [96] (Fig. 4.2). Furthermore, hip joint–related afferent input seems to be essential to generate a locomotor pattern [105]. For a successful training program for stroke and SCI subjects, spastic muscle tone has to be present as a partial compensation for paresis [113].

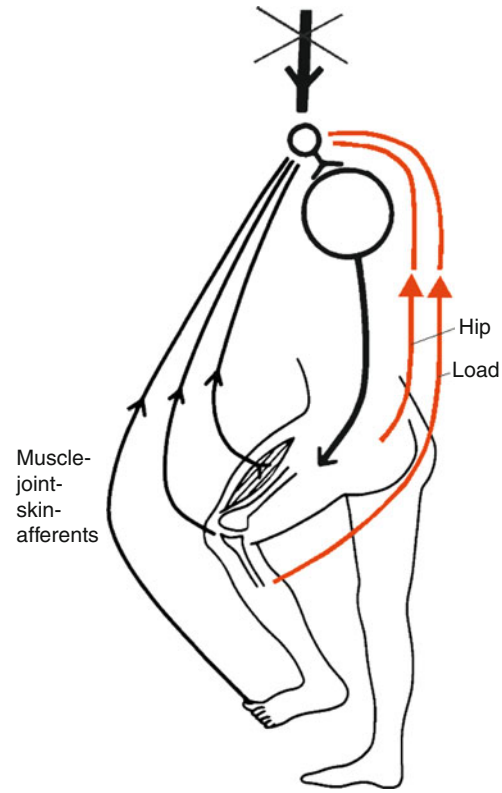

Fig. 4.2 Schematic demonstration of proprioceptive input during locomotor training in SCI subjects. The input from load and hip joint afferents was shown to be essential to achieve training effects

Only in patients with moderately impaired motor function a close relationship between motor scores (clinical assessment of voluntary muscle contraction) and locomotor ability exists. More severely affected SCI subjects with a low motor score undergoing a locomotor training can achieve an improved locomotor function without or with little change in motor scores [108, 114, 115]. In these cases, a relatively low voluntary force level in the leg muscles (reflected in the ASIA score) is required to achieve the ability to walk.

A considerable degree of locomotor recovery can be attributed to a reorganization of spared neural pathways ([116]; for review, see [117]). It has been estimated that if as little as 10–15% of the descending spinal tracts are spared, some locomotor function can recover [118, 119].

The improvement of locomotor activity could be due to a spontaneous recovery of spinal cord function that can occur over several months following a spinal cord injury [117, 120]. However, several observations indicate that the increase of leg extensor EMG activity also occurs independently from the spontaneous recovery of spinal cord function, as assessed by clinical and electrophysiological means [97, 107, 115, 117, 121]. Thus, functional training effects on spinal locomotor centers most likely contribute to an improvement of locomotor function in incomplete SCI subjects [97, 121]. However, part of the recovery in locomotion might also be attributed to changes that occur in the muscles during the training period, similar as observed in the rat [40].

4.3.3.4 Outlook

Unfortunately, patients with complete or almost complete paraplegia do not, as yet, profit from locomotor training for their mobility. In the future, these patients may profit from a combination of regeneration and exploitation of neuronal plasticity, as the research in spinal cord regeneration appears to be quite encouraging (for review, see [122]).

Furthermore, robotic rehabilitation devices become increasingly important and popular in clinical and rehabilitation settings for functional training and standardized assessments. Such devices allow a prolonged training duration, increased number of repetitions of movements, improved patient's safety, and less physical demands for the therapists. Novel sensor-, display-, control-, and feedback-information technologies have led to an improvement of training effects. By increasing patient's challenge and participation and by improving the assessments of clinical measures and performance, robots successively become an essential part of neurorehabilitation. In the future, rehabilitation robots offer a platform for the implementation of advanced technologies, which will provide new forms of training for patients with movement disorders. With the use of cooperative control strategies, e.g., by virtual reality technologies, not only the patient's engagement (especially of children) might become enhanced during training sessions but also the motivation to participate in the training can be improved.

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