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Learning in sensorimotor circuits

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The study of plasticity in the central nervous system is a major and very dynamic neuroscience research field with enormous clinical potential. Considerable advances in this field have been made during the past 10 years. It now appears that most circuits in the brain and spinal cord show plasticity and that they can be modified by experience. Knowledge of the mechanisms of plasticity in the nervous system is therefore essential for the understanding of how the nervous system is wired during development and how it adapts in response to changes in the body and environment. Recent findings indicate that functional sensorimotor modules probe the sensory signals from the body that are generated as a consequence of module specific activity and use this sensory feedback to calibrate the strength in its input–output connections. This experience-dependent signal adapts the circuitry in the sensorimotor module to the body anatomy and biomechanics.

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Abbreviations

LTP	long-term potentiation
NMDA	*N*-methyl-D-aspartate
NWR	nociceptive withdrawal reflex
RE	reflex encoder

Introduction

To be useful in motor control, somatosensory information must be encoded (weighted) with respect to body anatomy and movement patterns produced by the sensorimotor circuits. This is a difficult task because the multisensory information (nociception, pressure, temperature, joint angles, and muscle force and length) arises from a complex body constitution. The amount of information processing that needs to be performed is therefore staggering. Moreover, sensorimotor circuits must be adapted to changes in the body anatomy and biomechanics that occur over an organism's lifetime. Understanding how the basic sensorimotor system functions are adapted to the body anatomy and biomechanics is therefore a major task and the focus of this review. Such information might indeed have clinical relevance. Although there is a growing hope that substantial regeneration will be possible after spinal lesions, a difficult challenge will be to achieve functional recovery [1,2]. Regeneration tends to be rather chaotic and therefore does not usually re-establish normal connections without functional adaptation. This review focuses on self-organizing adaptive plasticity in spinal sensorimotor circuits. I begin by briefly reviewing recent data on adult plasticity in the spinal cord and then discuss recent evidence for a modular organization of the spinal cord and mechanisms that adapt the sensorimotor individual modules to the body constitution during development.

Adult plasticity in sensorimotor circuits

Although the major tuning of sensorimotor connections occurs during development, there is a substantial plastic capacity in the adult spinal cord that can compensate for altered conditions such as body growth, injury of the body, changes in muscle power and learning of skilled movements requiring co-contraction in synergistic and antagonistic muscles. For example, the gain in the stretch reflex elicited by Ia afferents appears to be increased in athletes and decreased in ballet dancers [3]. This might reflect a functional adaptation to altered biomechanical properties and movement patterns. There are also both short and long-term adaptations to changes in load [4].

It is well known that spinal cord functions are relatively well preserved if the spinal cord is lesioned early during development. However, damage of supraspinal control caused by spinal cord lesioning later in life often causes reduction or loss of motor function and maladaptive changes leading to increased reflexes, appearance of mass reflexes, and spasticity. Thus, although descending connections from the brain are needed for some forms of spinal plasticity (e.g. corticospinal pathways are necessary for operant conditioning of monosynaptic Ia-reflexes, [5]), the remaining spinal circuits in the isolated spinal cord still possess marked plastic properties. For example, spasticity develops slowly after injury and reflects an increased gain in the Ia-monosynaptic reflex and decreased gain in reciprocal Ia inhibition [6,7]. Allodynia (phenomenon of normally innocuous stimulations being painful) or hyperalgesia (increased pain on noxious stimulation) are other phenomena that can occur after spinal injury and involve plastic changes in the remaining networks [8]. Hence, although the adult spinal cord possesses a considerable capacity for plastic changes in the absence of descending control, this plasticity no longer leads to

functional adaptation. Nevertheless, specific training can strongly influence the spinal circuits even in animals with no descending control, termed spinal animals. Thus, adult cats with complete spinal transection can be trained on a treadmill to substantially improve their locomotor capability [9,10]. Similarly, spinal cats can be trained to stand [11]. Importantly, these improvements are entirely training-dependent and seem to be specific for the trained behavior: animals trained to walk were able to walk, whereas animals that were trained to stand were able to stand. Timoszyk *et al.* [12] have recently found that the spinal cord adapts to robotic loading applied during stance, indicating that the adaptive plasticity is dependent on the sensory feedback. The findings that adaptive learning is task specific further indicate that the individual circuits are in a 'learning mode' only when active. It is therefore tempting to speculate that when a spinal circuit is engaged by a supraspinal command, it is switched into a learning mode, similar to what appears to happen when learning is promoted by the spontaneous movements generated during development [13•]. If this is true, then sensory feedback to sensorimotor circuits is used both for correcting the ongoing sensorimotor transformation in response to a supraspinal command and for updating the long-term input–output transformation.

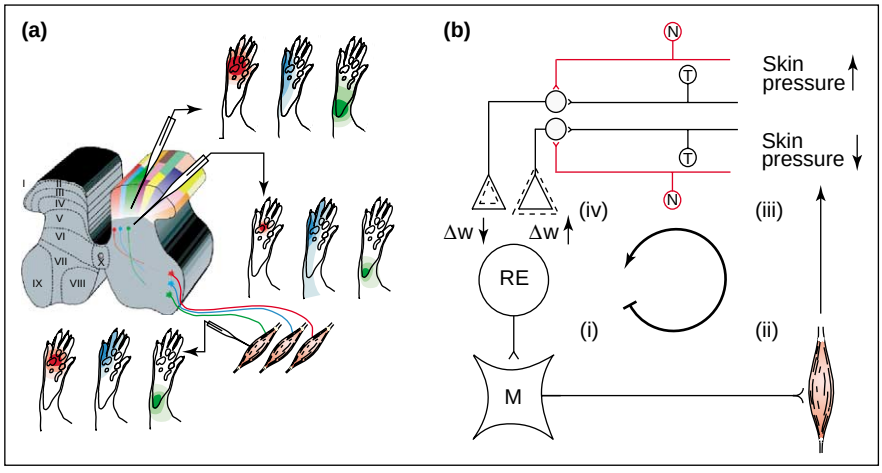
The cellular mechanisms underlying adaptive learning in the adult spinal cord are not understood. Most studies of adult spinal plasticity have used intense and often unphysiological primary afferent fiber stimulation or extensive conditioning protocols to provoke plasticity. These studies have shown that the withdrawal reflex system exhibits both short and long-term potentiation (LTP) after nociceptive stimulation. In particular, long lasting potentiation of nociceptive pathways has recently been demonstrated after intense nociceptive stimulation [14•] or overtly damaging stimuli [15]. These changes appear to be generated by mechanisms similar to LTP in hippocampus [16]. Other studies have shown that long-term depression (LTD) [17] and also classical conditioning [18] can be elicited in spinal circuits, suggesting a large potential for learning in the adult spinal cord. Besides these forms of afferent induced plasticity, several compensatory changes in sensorimotor circuits occur after injury to the primary afferent fibers [19•,20]. The plastic mechanisms disclosed after intense afferent stimulation or altered input after nerve lesions might well be an integral part of the mechanisms adapting the spinal circuits to biomechanical changes of the body (e.g. change in weight). It should be kept in mind, however, that for adaptation to body constitutional changes to take place, it is not the afferent input *per se* that is important (a strong afferent input might have nothing to do with the performance of the individual circuits), but rather the sensory feedback information resulting from activity in the sensorimotor system. Adaptive learning might thus utilize other, or additional, mechanisms than those disclosed by intense afferent stimulation. This would predict that, in the case of adaptive learning, postsynaptic activity in interneurons precedes the presynaptic input. This time sequence of events can lead to either LTP or LTD in the afferent synapses [21–23].

Modular organization of sensorimotor circuits in the spinal cord

To understand the cellular mechanisms underlying functional adaptation in the spinal cord, knowledge of the functional organization of the neural circuits is essential. During the past 10 years the concept of a modular organization of the spinal cord has gained in popularity. The idea of a modular organization of motor circuits is not new and was proposed in 1981 by Grillner [24] for locomotor circuits (unit bursters causing rhythmic activity around a joint), and a few years later by Stein and co-workers and Berkowitz [25–27] for circuits controlling scratch reflexes in the turtle. However, although a modular organization appears likely, it is not yet clear what constitutes a module in these rhythm-generating systems, the extent to which the different modules overlap, and how sensory information is related to the function of these modules [28].

A modular type of reflex organization in the mammalian spinal cord was first demonstrated for the nociceptive withdrawal reflex (NWR) system [29,30]. In this review, the word 'modular' is used synonymously with the term 'functional unit' of a system, that is, not alluding to the existence of different motor systems, such as stepping, standing, scratching or withdrawal reflex systems. For the NWR system, each excitatory module preferentially acts on a single muscle and performs a detailed sensorimotor transformation resulting in a graded withdrawal of the limb (or part of the limb) from its receptive field (Figure 1). For each excitatory NWR module, the input strength has a characteristic pattern on the skin that mimics the pattern of withdrawal efficacy when the output muscle of the module contracts [31]. In a sense, the pattern of withdrawal efficacy is 'imprinted' on the receptive field of the module. A corresponding set of inhibitory reflex modules also exists. In this case, the receptive fields correspond to the graded movement of the skin area towards external stimulation (i.e. increase in load) on contraction of the muscle in the module [32]. As a result of this organization, the excitatory and inhibitory modules are engaged to a degree that is proportional to their respective withdrawal or loading efficacy on skin stimulation. On the basis of microstimulation in the dorsal horn of the spinal cord, a somewhat different modular organization of sensorimotor circuits acting on synergistic muscle groups was later proposed in frogs and rats by Bizzi and co-workers [33–35]. According to these authors electrical and glutamatergic stimulation of the deep dorsal horn often results in a movement towards an equilibrium point independent of the starting position of the limb. In their

Figure 1



Self-organizing modular organization in the spinal cord. **(a)** Schematic of proposed modular organization of spinal withdrawal reflex circuits. Columns of the dorsal horn receive a cutaneous input that has a specific weight distribution. This weight distribution is the same as that of nociceptive input to reflex encoders (REs; interneurons that can encode the withdrawal reflex strength of individual modules) in deep dorsal horn. The REs are assumed to project to single muscles and weigh the input according to the withdrawal efficacy of the output muscle. On the left half of the spinal column there is a schematic indication of Rexed's laminae (Used with permission from [30].) **(b)** A proposed self-organizing circuitry that uses tactile information related to withdrawal efficacy to adjust the strength of nociceptive connections. One 'learning' cycle consists of the following chain of events. **(i)** Spontaneous bursts in 'reflex encoders' lead to motor neuron (M) activation. **(ii)** M activation leads to a muscle twitch. **(iii)** Increased or decreased skin pressure results in altered sensory input to pre- RE interneurons. Bold and thin lines represent afferents from skin areas on the tail from where an increase (↑) and decrease (↓) in low threshold mechanoreceptor input would occur. Strength of erroneous connections (receiving increased mechanoreceptive input) between pre-RE interneurons and RE is weakened (Δw↓) and that of appropriate ones (receiving reduced mechanoreceptive input) is strengthened (Δw↑). Abbreviations: N, nociceptive afferents; T, tactile afferents. (Modified with permission from [46•].)

proposal, the modules include activity in synergistic muscles. In a recent study Avella and co-workers suggested, by analyzing electromyographic (EMG) activity, that a combination of a limited number of synergistic units were used for 'kicking' in frog hindlimbs [36•]. Whether or not these findings reflect a fundamentally different organization than that of the withdrawal reflex system, as defined by us [30], is not clear at present.

The generality of the modular principle is further supported by data on the spino–olivo–cerebellar pathways [37]. For example, the C3 zone in the anterior cerebellar lobe is divided into microzones, in which each microzone is defined by its climbing fiber input from a specific spinal withdrawal reflex module [38]. Hence, the modular organization of the spinal cord is reflected in the organization of at least one of the major supraspinal motor centers.

Functional adaptation of sensorimotor circuits during development

Given that the adult sensorimotor transformations performed by the spinal cord reflect precisely weighted connections in modules, how can this weighting be achieved during development? Because the gross topographical organization of interneurons of the spinal cord is probably guided by gradients of trophic substances during development [39], it is difficult to see how such mechanisms could encode the detailed strength of every connection in the networks. Recent studies on the NWR system provide some clues to this problem. The sensorimotor transformations performed by its modules are functionally adapted during the first postnatal weeks in the rat [40] and can during this time adapt to both altered innervation of the skin and altered movement patterns caused by tendon transfer in the neonatal rat [41]. These changes in reflex sensorimotor transformations are paralleled by activity-dependent changes in the somatotopic organization of the spinal cord, including changes in laminar termination patterns of tactile afferents. For example, Fitzgerald and co-workers [42] have demonstrated that tactile fibers temporarily terminate in substantia gelatinosa during the first postnatal weeks in the rat and have recently found that this process is dependent on *N*-methyl-D-aspartate (NMDA) receptors [43]. NMDA receptors also seem to be involved in the rostro–caudal shrinkage of tactile afferent fiber termination in the dorsal horn during development [44]. The recent finding that the adult tactile somatotopy in the lower lumbar cord is related to the withdrawal reflex organization [45] suggests that these developmental changes are, at least to some extent, related to the functional adaptation of the sensorimotor circuits.

Recently, it was found that tactile feedback ensuing on spontaneous motility in spinal sensorimotor circuits is used to tune the connection strengths in nociceptive

withdrawal reflex modules during postnatal development [13•,46•]. Thus, tactile inputs arising in conjunction with the spontaneous movements and originating from the skin area that would normally be withdrawn by the movement had an adaptive effect on the reflex modules (Figure 1). This learning took place over postnatal days 12–17. Uncorrelated input (given at random time points) did not cause a learning effect. Because this process results in an imprint of the withdrawal efficacy on the reflex modules, it was termed 'motor directed sensorimotor imprinting'. Notably this novel form of unsupervised learning occurs during active sleep, characterized by atonia in the musculature. This state might be particularly advantageous for learning because the sensory feedback from muscle contraction stands out from a more or less silent background.

Spontaneous movements are a ubiquitous phenomenon during embryonic development in all vertebrates and mammals. Their role in sensorimotor learning has, however, not been discovered. The activity appears to be caused by spontaneous endogenous activity in neuronal circuits in the spinal cord and brain stem [47]. Although present classifications tend to lump the spontaneous motility broadly into a few categories, detailed studies in humans distinguished 16 different types [48]. The prevalence and complexity of these movements lead us to suggest that all major spinal motor systems contribute to the spontaneous movements during development [13•]. Furthermore, because this adaptive learning is highly effective, it might well be that all major groups of spinal motor systems learn relevant aspects of the body anatomy and biomechanics during development by probing the sensory feedback after spontaneous endogenous activation.

Concluding remarks

To summarize, recent studies indicate that spinal sensorimotor systems have a modular organization. Each module performs a specific function that is adapted to the body anatomy and biomechanics. The adaptation is based on self-organizing learning mechanisms that utilize sensory feedback generated by spontaneous endogenous activity in single modules during development. In the adult, sensory feedback from activation of the modules by the brain might take a similar adapting role, thus updating the connection weights to changes in the body constitution. Besides providing insights into how the wiring of the spinal cord is accomplished, these findings might well have clinical relevance. If adaptive mechanisms that decrease the gain in erroneous connections and increase the gain in adequate connections can be utilized, true functional recovery might be attainable also from chaotically regenerated connections. Certain rules for this adaptive process can be given: to modify the connection strengths of a motor module, sensory stimulation of its normal receptive field should be given in phase with the activity of the system. Uncorrelated afferent stimulation or passive movements are likely to be less effective. I suggest that a therapy, formed on the basis of pharmacological treatment that dis-inhibits regeneration, combined with training, using feedback stimulation to tune the regenerated connections, will be extremely useful.

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