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Review

Plastic Spinal Motor Circuits in Health and Disease

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Abstract

In the past, the spinal cord was considered a hard-wired network responsible for spinal reflexes and a conduit for long-range connections. This view has changed dramatically over the past few decades. It is now recognized as a plastic structure that has the potential to adapt to changing environments. While such changes occur under physiological conditions, the most dramatic alterations take place in response to pathological events. Many of the changes that occur following such pathological events are maladaptive, but some appear to help adapt to the new conditions. Although a number of studies have been devoted to elucidating the underlying mechanisms, in humans and animal models, the etiology and pathophysiology of various diseases impacting the spinal cord are still not well understood. In this review, we summarize current understanding and outstanding challenges for a number of diseases, including spinal muscular atrophy (SMA), amyotrophic laterals sclerosis (ALS), and spinal cord injury (SCI), with occasional relations to stroke. In particular, we focus on changes resulting from SCI (and stroke), and various influencing factors such as cause, site and extent of the afflicted damage.

Keywords: spinal plasticity; spinal neuronal networks; spinal muscular atrophy; amyotrophic lateral sclerosis; spinal cord injury; stroke; spasticity

1. Introduction

Animals must adapt not only their behaviors to changing external environments, but their own internal enviornments as well. This requires learning from action outcomes and adapting to changes, at various different levels of organization and time scales and using as much sensory information as available. This in turn requires neuronal networks, including motoneurons (MNs) and their inputs, to be plastic. The structures subject to plasticity are numerous and distributed throughout the central and peripheral nervous system, even extending to the neuromuscular junction [1–4].

The musculo-skeletal system is complex and can communicate easily and elegantly with the rest of the nervous system. How could the two systems develop in perfect mutual interaction? The most promising theory has been suggested to be "...based on trial-and-error learning, recall and interpolation of sensorimotor programs that are good-enough rather than limited or optimal" [5]. But this theory must be realized by flexible mechanisms that are only partly understood.

Plastic adaptations occur throughout normal life, from birth to old age [1]. But dramatic examples are provided by adaptations to pathological events. The primary emphasis of this review lies on plastic processes in the spinal sensory-motor system during and after various pathological events, including spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS), and various lesions to the nervous system, particularly spinal cord injury (SCI).

2. Plastic Changes in Motoneuron Diseases

Neurological diseases change internal conditions within the body and force adaptive changes in the neuromuscular systems, among others. ALS and SMA are two pathological conditions that were originally considered to result from MN degeneration, but have been increasingly recognized to be multi-systemic diseases, affecting structures beyond the nervous system [6,7]. In addition, multifactorial mechanisms have emerged over time, taking into account the pathophysiology of MN diseases, and include a complex interplay between genetic factors and molecular signaling pathways [8] (Fig. 1).

ALS and SMA differentially affect α-motoneurons (α-MNs) innervating extrafusal muscle fibers, γ-motoneurons (γ-MNs) innervating intrafusal muscle-spindle fibers, or ß-motoneurons (ß-MNs) innervating both extra- and intrafusal muscle fibers [9–12]. For simplicity, α-MNs and ß-MNs will be referred to as α-MNs. In both SMA and ALS, the largest α-MNs innervating fast-contracting, fast-fatiguing muscle fibers (type FF)

Fig. 1. Major hallmarks of motoneuron dieseases (MND). MND were originally considered to result from selective degeneration of upper and lower motoneurons (MNs) but are now considered multi-systemic diseases affecting areas beyond the nervous system, with early and frequent impacts on cognition, behavior, sleep, vigilance, and pain. The pathophysiology of MND include a complex interplay between genetic factors and molecular pathways such as proteostasis, axonal transport, and energy homeostasis. In addition to MNs, other cells such as astrocytes, microglia, and oligodendrocytes are considered determinants of MND onset and progression. MN hyperexcitability resulting from increased glutamatergic excitation and monoaminergic influences, the second acting through persistent inward currents (PICs; sodium and calcium channels), occurs early in disease progression and leads to excitotoxicity via elevated intracellular Ca^{2+} concentrations.

are the most vulnerable and degenerate first, followed by the α-MNs innervating fast-contracting, fatigue-resistant muscle fibers (type FR) . The α-MNs innervating slowly contracting, fatigue-resistant muscle fibers (type S) are the last to degenerate [13–18]. In ALS, γ-MNs are affected less so or later in disease progression [19].

2.1 Spinal Muscular Atrophy

SMA is one of the most common neuromuscular disorders ocuring during childhood and is associated with a high morbidity and mortality [20]. It is characterized by degeneration of α-MNs in the spinal cord and brainstem (other cell types are also affected; for details see Quinlan *et al.* 2019 [21]). Approximately 90–95% of SMA cases involve a group of autosomal-recessive disorders caused by loss-of-function mutations in the survival α-MN 1 (*SMN1*) gene on *5q13* [22,23]. Thus, the majority of SMA cases are caused by low levels, but not the complete absence, of the essential SMN protein. *SMN1*-associated SMA (*5q-SMA*) comes in various degress of severity and incidence: severe (type I) has the highest disease incidence, and milder forms including intermediate (type II) and mild (type III) SMA have the higher prevalence. SMA leads to progressive symmetrical muscle atrophy, weakness, and hypotonia, leading to the inability to sit, stand, or walk [24–26]. Therapy has advanced towards the development of drugs, such as nusinersen, onasemnogene abeparvovec, and risdiplam [20], which when applied presymptomatically, allow affected individuals to achieve normal motor abilities and most other age-based development [26]. Non-*SMN1* SMA (or non-5q SMA) is a heterogeneous group of rare neuromuscular disorders associated with autosomal recessive and dominant, as well as X-linked recessive inheritance [22,27].

Mouse models of SMA have led to deeper insights into the pathophysiology of MN degeneration [28]. However, the precise cellular and molecular mechanisms mediated by SMN deficiency are still unclear. SMA is not a MN autonomous disease [29]. Its' pathology is not restricted to α-MNs and dysfunction is more widespread, particularly within the brainstem and spinal circuits in which the α-MNs are located. In a mutant *SMNΔ7* mouse model, α-MN degeneration leads to motor deficits, such as weakness and an inability to right themselves, and possible premature death around 2 weeks of age. Additionally, in this model the proximal muscles are more affected than the distal muscles, with the epaxial and hypaxial muscles being more severely weakened [14].

The vulnerability of α-MNs and their synaptic connections is further evidenced by the fact that increasing the expression of SMN restricted to α-MNs is sufficient to rescue α-MN survival, maintain excitatory synapses from sensory afferents onto α-MNs, and increase the lifespan in *SMNΔ7* mice. In systemic SMN reduction, deficiencies in other cell types also contribute to SMA pathology (for a more extensive review, see Quinlan *et al.* 2019 [21]). SMA is likely a non-cell autonomous disease with a critical impact on MN degeneration when considering the pathophysiology of the disease, through the interaction of MNs and other cell types in the nervous system, particularly glial cells [29–31]. Different glial cells exhibit functions in maintaining MN integrity, including trophic support, minimization of excitotoxicity, synaptic remodeling, and immune surveillance.

2.1.1 Changes in Motoneuronal Excitability

The excitability of α-MNs depends on a number of factors, including intrinsic properties such as MN size and input impedance, as well as extrinsic modulatory influences exerted by descending monoaminergic signals. Thus, serotonin [5-hydroxytryptamine (5-HT)] and noradrenaline (NA) enhance certain ion channels in α-MNs [32–34]. One way that serotonin influences α-MN excitability is via persistent inward currents (PICs).

PICs contribute to the operation of endogenous and conditional oscillators and increase the gain of the input/output relationship leading to an increase in the firing rate of α-MNs. PICs are activated by depolarization and carried by sodium (Na^+) and calcium (Ca^{2+}) ions through Nav1.6 and nifedipine-sensitive L-type Ca^{2+} channels, Cav1.3, respectively. The channels mediating the Na^+ PIC appear to be located on the soma and/or proximal dendrites and contribute to both the initiation of action potentials during rhythmic firing and maintenance of normal repetitive firing of α-MNs in the presence of sustained, depolarizing synaptic drive. Channels mediating the Ca^{2+} PICs are situated in close proximity to synapses in mid-dendritic locations, supporting a role for amplification of synaptic inputs. A higher innervation by serotonergic [5-hydroxytryptamine (5-HT)] and noradrenergic (NA) fibers occurs in extensor compared with flexor α-MNs. This could explain the bias toward extensor α-MNs for facilitating expression of PICs by an increase in monoaminergic effects [21,32,33].

In two mouse models of severe SMA, α-MN excitability was increased, as indicated by hyperpolarization of the threshold voltage for action potentials and faster action-potential firing rates, among other changes in α-MNs. In $Smn^{2B/-}$ mice at P9-10, the hyperpolarized action-potential threshold was most likely due to alterations in PICs [21]. Hence, in $Smn^{2B/-}$ mice, an increase in these currents is likely to underlie altered α-MN excitability. The PICs showed increased amplitudes and hyperpolarized threshold activation. In $Smn^{2B/-}$ mice at P9-10, α-MNs were larger in size, which might compensate for the greater excitability because of decreased input resistance. α-MN hyperexcitability and changes in α-MN size were also found in pre-symptomatic mouse models of ALS (Sect 2.2). It has been hypothesized that the hyperexcitability involves an altered function of aberrant voltage-gated Na^+ channels and likley occurs early in disease progression before α-MN loss, and could initiate a series of compensatory changes, including loss of glutamatergic synapses, changes in α-MN size, and eventual cell death (Fig. 1). Also, motor-unit loss occurred after these changes in α-MN properties at P9-10, at the earliest two weeks after birth [21].

2.1.2 Changes in Proprioceptive Reflexes

In SMA mouse models, α-MNs have reduced proprioceptive reflexes and this correlated with decreased number and function of synapses on α-MN somata and proximal dendrites [35]. One of the first pathological changes is a decline in the strength of synaptic input to α-MNs from group Ia afferents from muscle spindles. This decline is due to a decrease in the amount of glutamate released from the afferents onto α-MNs. In addition, in *SMN*Δ*7* mice, the number of vesicular glutamate transporter (VGLUT)2^+ terminals on α-MNs are reduced, which could be derived from local or descending glutamatergic interneurons. The decreased glutamate release from group Ia afferents triggers several secondary changes in the α-MN properties, including an increase in input impedance and a down-regulation of the Kv2.1 potassium channel, these responses being probably compensatory. In contrast to α-MNs, Renshaw cells (Sect 4.4) in *SMN*Δ*7* neonatal mice receive an increasing number of VGLUT1 primary afferent terminals, which disappear with age, and vesicular acetylcholine transporter (VAChT)+ terminals from α-MNs, which could be due to the sprouting of proprioceptive afferents and motor-axon collaterals on the remaining α-MNs, respectively. Restoration of the SMN protein in afferents, but not in α-MNs, normalized Kv2.1 expression and partially restored the firing of α-MNs to current injection. Although secondary, the motoneuronal changes contributed significantly to the motor deficits in SMA. Inhibitory inputs to α-MNs were less affected than excitatory inputs [14].

2.2 Amyotrophic Lateral Sclerosis

ALS is a complex, multi-factorial neurodegenerative disease often associated with pathobiological features of fronto-temporal lobe dementia [36,37]. About two thirds of patients have the spinal form of the disease, which initially manifests with arm or leg weakness (limb-onset) [38,39]. Most of the remaining cases are bulbar-onset, which initially manifests with speech and swallowing problems. Most commonly, ALS starts at advanced age (up to 80 years), with a mean age of about 60 years at onset of sporadic disease and about 50 years in familial disease. It presents as progressive muscle weakness and atrophy leading to paralysis, loss of the dexterity, ability to move, talk, eat, breathe, and is often accompanied by spasticity (Sect 3) and pain. Death typically occurs within 3 to 5 years of disease onset [39–44]. The term 'lateral sclerosis' refers to a hardening of the anterior and lateral spinal cord [45], indicating degeneration of mainly the cortico-spinal tract (CST) but also other tracts within antero-lateral spinal white matter [46,47]. There are two broad classes of etiologies: familial (arround 5–10%) and sporadic (idiopathic). Familial ALS is related to mutations in specific causative genes *(C9ORF72*, *SOD1*, *TARDBP*, *FUS*, among others), which directly induce α-MN degeneration, and sporadic ALS cases are considered to be secondary to the interactions between the individuals' genetic risk, developmental factors, and environmental conditions [6,43,48–52].

Traditionally, as of the first description by Jean-Martin Charcot in 1869 [45], ALS was considered an α-MN disorder characterized by the selective degeneration of upper and lower MNs [38]. More recently, views have changed such that ALS is now considered a multi-system disease in which degenerative pathology has also been detected in the cerebral cortex, cerebellum, basal ganglia, spino-cerebellar tracts, dorsal columns, serotonin-containing neurons in the raphé, noradrenergic neurons in the locus coeruleus, peripheral nervous system, neuromuscular junction, and other

synapses, as well as gastrointestinal, autonomic, and vascular systems. This condition has an early and frequent impact on cognition, behavior, sleep, pain, and fatigue [19,38,43,46,53–62] (Fig. 1). There is also evidence of immune dysregulation in the pathogenesis of ALS [46,63–65].

The underlying pathogenesis and pathophysiology of ALS are complex and incompletely understood, but probably affected by manifold genetic, epigenetic, developmental and environmental factors [37,49–52,66–70] (Fig. 1).

Impairment of several crucial cellular pathways, such as gene-processing disorders, proteostasis, axonal transport impairments, hyperexcitability, excitotoxicity, or functional deficits of surrounding glial cell (with immunological and trophic consequences for the motoneuronal integrity), have been associated with degeneration of α-MNs [31,38,46,50,54] (Fig. 1). In particular, energy homeostasis is compromised in patients with ALS, which has notable clinical implications such as weight loss, hypermetabolism, and hyperlipidaemia. More recently, alterations have been described in all the compounds of the neuro-vascular unit. In addition to MNs, considering the non-cell autonomous pathophysiology of ALS, other cells are considered determinants of ALS onset and progression, such as astrocytes, microglia, oligodendrocytes, Schwann cells, muscle cells, or as contributors, such as lymphocytes, pericytes, and interneurons [31,38,46,54] (Fig. 1).

A number of animal models have been developed to study the genetic and molecular mechanisms of ALS [38,49,59,71–73]. The first intraspinal changes in ALS appear to differ from those in SMA, at least in mouse models [13,14]. There are several mouse models, but the one on which most work has been done is the superoxide dismutase *SOD1-G93A* model. In addition to *G93A* mutation of *SOD1* gene, mice with other mutations of *SOD1*, such as *G37R* and *G85R*, are also commonly used, but to a lesser extent. The *SOD1-G93A* model survives up to 150 days, longer than the *SMN*Δ*7* model of SMA. In transgenic mouse models of ALS (expressing *mSOD1*), PIC amplitudes are altered and may contribute to α-MN dysfunction. Na^+ PICs are increased and show a rapid recovery from fast inactivation, allowing α-MNs to fire at higher rates [33].

2.2.1 Progression of ALS

In ALS, the successive death of α-MNs, from FF-type α-MNs over FR-type α-MN to S-type α-MNs, leads to consequent loss of muscle forces. Since the disease becomes symptomatic only after the degeneration of at least 30% of an α-MN pool, there should be some homeostatic mechanisms that compensate for the early loss. It is proposed that, in pre-symptomatic ALS, a key compensatory mechanism lies in increasing excitation of α-MNs by premotor circuits, which would lead to increased co-activation of functional α-MNs and γ-MNs [13].

Homeostatic mechanisms could include increased input to α-MNs from spinal segmental and supraspinal circuits to ensure that force production is preserved. Thus, the input to co-activated γ-MNs would also increase, leading to increased contraction of intrafusal muscle fibers out of proportion to extrafusal fibers. This α-γ imbalance would result in an increase in muscle spindle afferent input to α-MNs. The increasing glutamatergic excitation from these inputs would initially maintain the homeostatic response despite a reduction of activity of F-type α-MNs whose muscle fibers produce high forces. In particular the loss of type-F α-MNs would simultaneously, in motor pools with recurrent inhibition via Renshaw cells (Sect 4.4), reduce the recurrent inhibition of α-MNs and γ-MNs, which would be initially compensated by increased α-MN activity particularly from type-S α-MNs. Together, these processes would lead to increased glutamatergic excitation of vulnerable α-MNs and, hence, excitotoxicity, via elevated intracellular Ca^{2+} concentrations (Fig. 1). That is why ablation of primary afferents exerts a protective effect on α-MNs. In symptomatic stages, the processes that began during pre-symptomatic stages would continue, there would be runaway from homeostatic processes, and further excitotoxicity would lead to disease progression. It would no longer be possible to maintain muscle contraction, compounding the α-γ imbalance, and the resulting loss of input to Renshaw cells would reduce recurrent inhibition of α-MNs and diminish γ-MN inhibition, thereby contributing to increased excitation of remaining α-MNs but a further imbalance of α-γ output [13]. This hypothesis remains speculative and needs to be tested experimentally.

2.2.1.1 Proprioceptive Inputs to α-MNs.

"You can only control what you sense" [74]. The impact of different sensory inputs on central nervous system (CNS) networks are diverse and complicated, but sensory deficits severely interfere with motor control and kinesthesia. In particular, proprioception is of great importance for motor control [75] and kinesthesia [76,77]. Sensory impairments at early stages of ALS have been underestimated. In both ALS patients and mouse models, sensory neurons are abnormal [19,43,78].

Proprioceptive afferents of groups Ia and II from muscle spindles appear to be damaged in ALS, likely a result of their monosynaptic connections to α-MNs, as seen in cats: [79,80]. Group Ib afferents from Golgi tendon organs are not damaged. The latter may also apply to some group II cutaneous afferents which signal proprioceptive information on joint position and movements [81]. The degeneration of Meissner corpuscles requires further investigation as they do not monosynaptically connect to α-MNs.

In two lines of transgenic mice, *SOD1-G93A* and *TDP43-A315T*, there were no differences in the total number and size of proprioceptive sensory neuron somata in dorsal-root ganglia (DRG) between symptomatic (*SOD1-G93A*) and control mice. Group Ia and II sensory terminals around the equatorial region of intrafusal fibers of muscle spindles were altered at an earlier stage prior to

the symptomatic phase of the disease. During the symptomatic phase, these sensory endings underwent degeneration, in parallel with degeneration of the central endings on α-MNs, when the neuromuscular junction was denervated. By contrast, group Ib proprioceptive afferents from Golgi tendon organs and γ-MN nerve endings were mostly spared at all ages examined. Spinal nerve endings terminating on α-MNs were affected during the symptomatic phase and after peripheral nerve endings had begun to degenerate. This indicates that cells directly contacting α-MNs are preferentially affected in ALS. In muscles, α-MN terminals at neuromuscular junctions undergo bouts of degeneration and regeneration in young asymptomatic mice expressing mutant *SOD1*. Later in life, α-MN axons degenerate via a process termed 'dying back', resulting in the appearance of neurological symptoms from denervation of muscle fibers and loss of α-MNs [18,82]. Another crucial mechanism of α-MN degeneration, namely a 'dying forward' mechanism [83,84], has been proposed. The main assumption is that the anterograde glutamate-mediated excitotoxic process is responsible for α-MN degeneration.

In *SOD1-G93A* mice, large proprioceptive neurons in the DRG accumulated misfolded SOD1 and underwent degeneration that involved recruitment of macrophagic cells. Additionally, degeneration of sensory axons occurred in association with activation of microglial cells [46,85]. As large proprioceptive DRG neurons project monosynaptically to ventral horn α-MNs, it was hypothesised that a prion-like mechanism might be responsible for the transsynaptic propagation of SOD1 misfolding from ventral-horn α-MNs to DRG sensory neurons [60].

In regard to changes in the muscle-spindle loop, animal models of ALS have provided relevant data. In ALS mouse models, VGLUT1 immunoreactivity, presumably originating from proprioceptive afferents, was reduced in the ventral horn of the spinal cord at day 110 and was almost absent at day 130, indicating loss of muscle spindle afferent input to α-MNs. This may have been due to the initial degeneration of proprioceptive nerve endings in the periphery, which was followed by the loss of their central projections onto α-MNs. Proprioceptive afferents in the mesencephalic nucleus of *SOD1* mice were less excitable at P11 due to reduced expression of Nav1.6-type Na^+ currents, which could lead to compensatory increases in the excitability of their target α-MNs [14]. Elimination of group Ia fiber synapses protected α-MNs, suggesting that this excitatory input is involved in α-MN degeneration. The reduction of group Ia afferent activation by targeted reduction of γ-MNs delayed symptom onset and prolonged the lifespan. Together this suggests that group Ia excitatory inputs contribute to α-MN degeneration, such that silencing these inputs improves α-MN survival [86]. But there are other excitatory inputs to α-MNs.

2.2.1.2 Other Sensory Inputs. Transgenic mice expressing a human *SOD1* mutation (*hSOD1-G93A*) exhibited significant sensory damage, including Wallerian-like degeneration in axons of the DRG and dorsal funiculus, and mitochondrial damage in DRG neurons [87]. *SOD1-G93A* mice displayed small-diameter fiber pathology, as measured by loss of intra-epidermal nerve fibers and Meissner corpuscles [88,89].

Cutaneous Small-diameter Fibers are primarily involved in nociception and thermosensibility. One third of ALS patients reported cutaneous sensory symptoms. Sural sensory response amplitudes were reduced in a similar proportion of patients. Sural nerve biopsy showed that predominantly large-diameter myelinated fibers were affected, while small-diameter myelinated fibers were affected less frequently [90]. About 16% of ALS patients reported sensory disturbances with different distributions, and most ALS patients showed a loss of intra-epidermal small-diameter nerve fibers [91]. ALS patients showed a significant reduction in intra-epidermal nerve fiber density as well as a significant loss in Meissner's corpuscles [92,93].

Small-diameter fibers from skeletal muscles, which are also involved in nociception, thermosensibility and some mechano-reception of muscle events, have been shown to be affected in ALS as mentioned below.

Noxious stimulation of cutaneous or muscular free nerve endings with afferents in groups III and IV elicited motor (e.g., withdrawal reflexes), cardio-vascular, and respiratory reactions, as well as arousal, pain, and stress, the latter in turn influencing pain sensations. Primary causes of pain include pain with neuropathic features, spasticity, and cramps, with the latter being the major cause, while spasticity typically starts at advanced stages. Secondary causes develop during progressive paresis, which induces immobility and degenerative changes in connective tissue, bones, and joints, leading to musculo-skeletal pain [40,41,43,44]. Rhythmic stimulation, treadmill training, and cycling enhance the expression of brain-derived neutrophic factor (BDNF) and prevents the development of nociceptive sensitization [3].

While pain in ALS patients has attracted increasing attention, stress has not. Pain activates systems involved in the stress responses, such as anxiety, fear, and frustration. Chronic pain can indirectly contribute to these categories of stress. Conversely, stress may influence the generation, maintenance, and perception of pain. There are significant differences between acute and chronic states of pain and stress. While the acute states are frequently beneficial in ensuring survival, chronic pain and stress are generally detrimental and may have adverse effects on health. The effects of stress are dependent on various factors including genetic predisposition and early life experience [94–96]. The influence of stress on pain, and vice versa, warrants further research.

2.2.1.3 Ascending Sensory Systems. Spinal sensory tracts ascend through the dorsal (light touch, vibration, and

proprioception) and antero-lateral (pain and temperature) columns. Sensory evoked potentials (SEPs) and laser evoked potentials (LEPs) showed that, compared to healthy controls, a substantial proportion of ALS patients had prolonged nerve conduction latencies. Also, diffusion tensor imaging (DTI) and magnetization transfer (MT) magnetic resonance imaging (MRI) sequences have demonstrated spinal alterations in both dorsal and antero-lateral tracts [43]. DTI of the dorsal columns at C5-T1 levels and SEPs after median and ulnar nerve stimulations in ALS patients with moderate disability indicated anatomical damages of ascending sensory fibers in about 60% of patients [97].

Compared to control subjects, ALS patients have a smaller numbers of neurons in the primary motor (MI) and primary somato-sensory (SI) cortex [98]. The median survival time was significantly shorter in patients who had larger somato-sensory cortical amplitudes in SEPs, suggesting that sensory-cortex hyperexcitability predicts short survival [99]. Evidence suggests that the motor cortex is hyperexcitable in response to transcranial magnetic stimulation and that marked disinhibition is present in the somatosensory cortex more than 2 years after disease onset [100].

2.2.1.4 Interneuronal Inputs to α-MNs. Other excitatory inputs to α-MNs derive from interneurons. Loss of V2a interneurons in ALS has been suggested to deplete the direct connectivity to α-MNs, which could drive V2a loss. A similar mechanism might cause the loss of V0c interneurons, a small compact group of interneurons close to the central canal. This is supported by the finding that the percentage loss of V0c and α-MNs are tightly correlated. V0c neurons provide direct neuromodulatory input to α-MNs, being more frequent on FF-type α-MNs than S-type α-MNs via large so-called 'C-bouton' synapses, and thereby regulate α-MN excitability in a task-dependent manner by reducing afterhyperpolarization [14,101,102]. Changes in the C-boutons found in both ALS patients and in transgenic mice that carry the mutant form of superoxide dismutase 1 (*mSOD1-G93A*), suggest that they play a role in ALS disease progression. C-boutons are necessary for behavioral compensation in *mSOD1-G93A* mice. Symptomatic *mSOD1-G93A* mice showed significantly higher C-bouton activity than wild-type mice during low-intensity walking. Also, C-bouton silencing in combination with high-intensity training worsened gross weight but improved fast-twitch muscle weight and was beneficial for the behavioral capabilities of *mSOD1-G93A* mice. Their lifespan was prolonged compared to untrained *mSOD1-G93A* mice with silenced C-boutons, but not untrained *mSOD1-G93A* mice. The presence of C-boutons also significantly worsened fast-twitch muscle innervation over time. The V0c interneurons, and thus C-boutons, were active in a task-dependent manner and in symptomatic *mSOD1-G93A* mice.

Nonetheless, there is evidence to indicate that another alternative modulatory system must be involved in compensating for the loss of C-bouton modulation, namely the serotonergic system, for three reasons: (1) The serotonergic system modulates α-MN excitability by increasing PICs; (2) it slows disease progression and improves motor function in ALS; (3) the V0c interneurons also receive serotonergic input. Thus, the serotonergic modulatory system might be up-regulated when the V0c interneurons fail [103].

The role of Renshaw cells mediating spinal recurrent inhibition in ALS has been studied in humans and animals (Sect 4.4). There is evidence that recurrent inhibition is reduced in ALS patients (Sect 4.4). In animal models of ALS, the innervation of Renshaw cells by α-MNs is lost early on and is associated with a down-regulation of VAChT in α-MNs. Renshaw cells appear to produce axonal sprouting, leading to transient up-regulation of glycinergic synapses on α-MNs. However, as the disease progresses, Renshaw cells receive progressively less input from α-MNs, with some Renshaw cells being completely denervated. A proportion of Renshaw cells then die during disease progession. Thus, there is evidence that a reduction in α-MN inputs to Renshaw cells leads to a reduction in recurrent inhibition, but that Renshaw cells initially compensate by sprouting on remaining viable α-MNs [13,14]. It has been argued, however, that the loss of Renshaw cells plays a decisive role in making α-MNs more susceptible to glutamate excitotxicity, and moreover, that in cats and humans, it is sparse or absent in α-MN pools that innervate distal limb muscles in which initial wasting is prominent in ALS in humans [58].

In mutant *SOD1-G93A* mice, inhibitory spinal circuits exhibit abnormalities early on. For example, the gamma-aminobutyric acid (GABA) equilibrium potential in α-MNs is more depolarized than in wild-type animals, indicating an alteration in chloride homeostasis at E17.5. At this early stage, inhibitory synaptic terminals on α-MNs show a deficiency, which persists into postnatal life. The loss of glycinergic function appears to be specific for large α-MNs because it is not observed in small, fatigue-resistant (S-type) α-MNs and presumed γ-MNs. The reduced inhibitory input could be due to loss of inhibitory interneurons or to weaker inputs from inhibitory neurons [14].

Changes in inhibitory interneurons were also found in the spinal cord of mice (low-copy Gurney *G93A-SOD1* ALS model), in which the expression of markers of glycinergic and GABAergic neurons were reduced. This suggests that, in mutant *SOD1*-associated ALS, pathological changes may spread from α-MNs to interneurons early on. The degeneration of spinal inhibitory interneurons may in turn facilitate degeneration of α-MNs and contribute to disease progression [104]. *SOD1-G93A* α-MNs showed a decrease of surface postsynaptic glycine receptors, which may contribute to inhibitory insufficiency in α-MNs early in the disease process [105].

2.2.2 Comments and Questions

A MN is a neuron in the brainstem or spinal cord that innervates muscle fibers, either extrafusal and/or intrafusal. Any neuron that innervates MNs is a premotor neuron. What are 'lower' and 'upper' MNs and why do these cells die in ALS?

The question as to the origin of ALS processes has been speculated upon from the beginning.

About half of the ALS patients show cognitive-behavioral deficits. Together with other degenerative brain diseases, such as Alzheimer's disease and Parkinson's disease, ALS shares the histo-pathological phenomena of aggregation of abnormally altered endogenous proteins in the nervous system. A so-called staging model of the abnormally phosphorylated protein TDP-43 (pTDP-43) pathology in sporadic ALS proposes that four stages can be distinguished, where pTDP-43 inclusions are found in different places. Stage 1: agranular motor cortex and α-MNs of the brainstem and spinal cord. Stage 2: pre-frontal cortex (middle frontal gyrus), reticular formation, and pre-cerebellar nuclei. Stage 3: other areas of the pre-frontal cortex (gyrus rectus and orbito-frontal gyri), post-centrally located sensory cortex, and basal ganglia. Stage 4: antero-medial temporal lobe including the hippocampus. Accordingly, a cortico-fugal spreading of pathology has been hypothesized ('dying forward'), whereby pathology starts in the primary motor cortex and spreads from there via axonal projections to sub-cortical structures and α-MNs [62].

Another hypothesis suggests that pathology starts in the periphery, at the other end of the motor-control system, and harks back to the α-γ loop (Sect 2.2.1). It proposes that the primary target of ALS lies in the muscle, not only in extrafusal, but also intrafusal muscle fibers, resulting from oxidative stress, mitochondrial, and myogenic pathology. The ensuing reduction of neurotrophic factors would lead to the pre-symptomatic degeneration of motor and sensory axons as a 'dying-back' axonopathy ending in MN death [19].

Whether a third (intermediary) proposal, attempting an integrative view, will answer this question is uncertain. It poses synaptic failure as a converging and crucial player to ALS etiology. Homeostasis of input and output synaptic activity of MNs has been shown to be severely disrupted early on and to definitively contribute to microcircuitry alterations at the spinal cord. Several cells play roles in synaptic communication across the MNs network system such as interneurons, astrocytes, microglia, Schwann, and skeletal muscle cells [38].

So, the question of what comes first and what is the origin of it all remains open. But how can we be sure about the start within a multi-system disease whose elements and entagled interactions are not completely known as yet? Current basic and clinical research on biomarkers as well as on genetic causes and therapies of ALS will be instructive. Time may tell.

3. Brain and Spinal Cord Lesions

The following discussion will focus on SCI The consequences after SCI in humans go through several stages, beginning with acute effects.

3.1 Acute Effects of SCI

A SCI is caused by a primary mechanical insult, e.g., acute compression, sharp injury, missile, laceration, shear etc. This is followed by a secondary injury, comprised of an acute, a sub-acute, and a chronic phase. The primary insult of SCI arises from the loss of directly damaged gray matter and neural pathways, as well as surrounding tissue damage. The acute phase, which occurs within the first 48 hours following primary injury, is associated with spinal ischemia, vasogenic edema, and glutamate excitotoxicity. The sub-acute phase, occuring within the first two weeks following primary injury, involves mitochondrial phosphorylation and neuro-inflammation. The chronic phase then extends from days to years and includes apoptosis, necrosis, acute axonal degeneration, and glia scar formation [106,107].

At the cellular level, the following changes occur. Immediately after injury, dying neurons release death signals which exacerbate the injury. The immediate tissue damage activates the innate and adaptive immune response [106]. Monocyte-derived macrophages and activated microglia remove the debris from the initial primary insult [108] (Fig. 2). These immune cells remain after debris is removed and continue to release inflammatory cues that initiate secondary injury in areas rostral and caudal to the injury epicenter. Reactive astrocytes limit the spread of inflammation, compensate for a leaky blood-brain barrier, and reduce lesion expansion by forming a glial scar, which may also prevent axonal regeneration through the lesion [108] (Fig. 2). Evidence demonstrates astrocyte-release of growth-promoting factors, such as laminin, however the cumulative effect is detrimental to recovery. Other processes also contribute to the inability of damaged axons to regenerate after injury. Wallerian degeneration of the distal axons and myelin results in debris releasing Nogo (or Rtn4), myelin-associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (OMgp or Omg), which have all been shown to inhibit regeneration and sprouting. Collectively, these impediments limit the efficacy of spontaneous recovery following a SCI [109,110].

The acute effect of a complete SCI in humans is a spinal shock in which neither locomotor nor spinal reflexes can be evoked. Muscles are paretic and flaccid [33,111]. The main reason for spinal shock is the sudden loss of supraspinal influences on spinal networks; that is, the damage of CST glutamatergic signalling, as well as the loss of bulbo-spinal monoaminergic pathways and their powerful descending modulation of spinal excitability [34,112].

In animals, spinal shock is associated with a dramatic reduction of extensor muscle tone and spinal reflexes, including postural limb reflexes (PLRs). One factor respon-

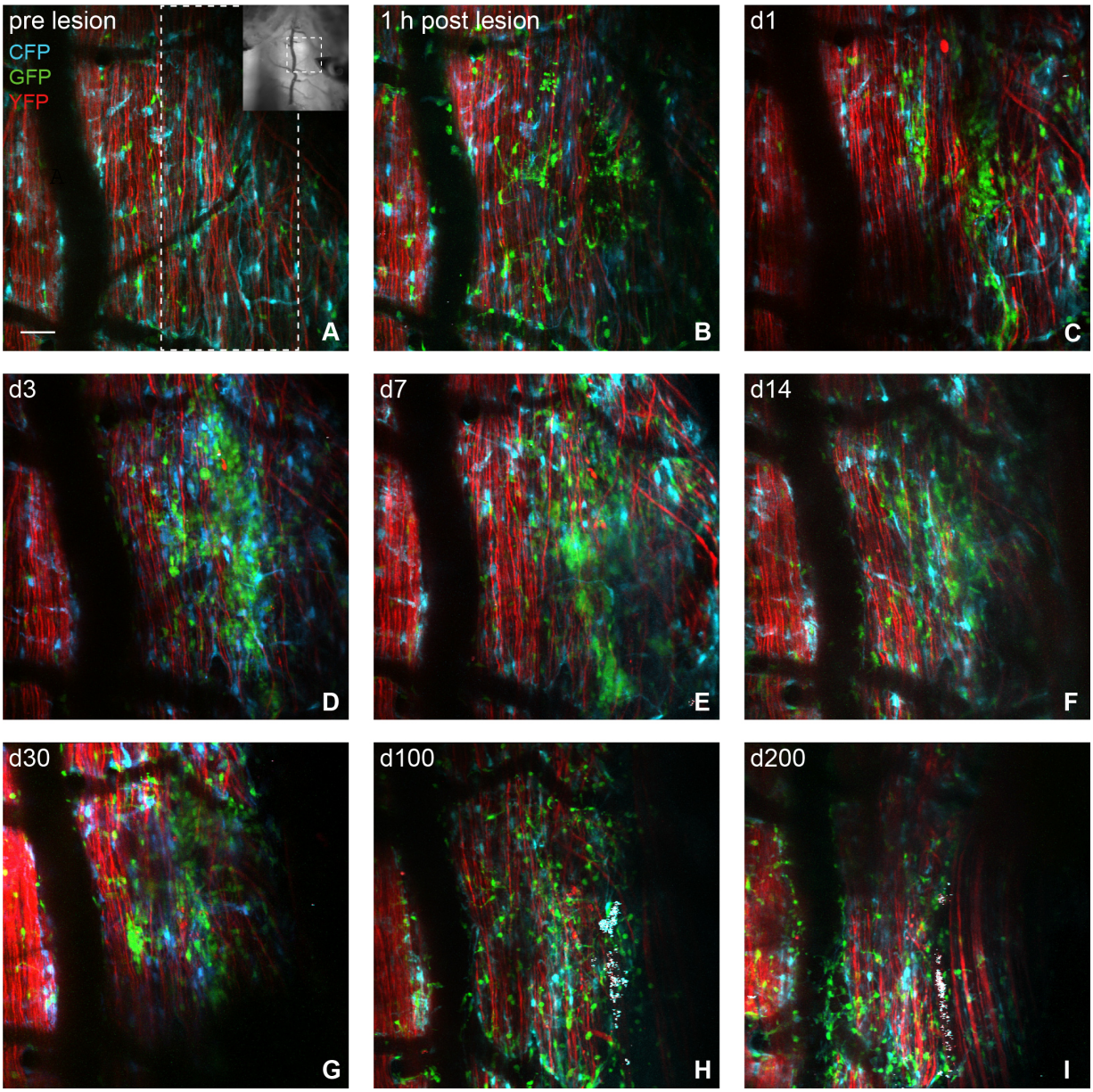

Fig. 2. Long-term repetitive two-photon laser-scanning microscopy (2P-LSM) of the dorsal spinal cord. Repetitive images of the same region in dorsal white matter within the lumbar spinal cord over 200 days after a laser-induced injury (in the center of the images from image B) in a triple transgenic mouse expressing ECFP (enhanced cyan fluorescent protein, in blue) in astrocytes, EGFP (enhanced green fluorescent protein, in green) in microglia, and EYFP (enhanced yellow fluorescent protein, in red) in axons (images A-I). Each image is a maximum intensity projection of a 38-µm stack. The central vein is on the left side. The veins are stable structures used as landmarks for repetitive imaging. All images are arranged such that rostral is to the upper side. Notice the accumulation of green microglia beginning within the first hour after the injury (from image B) followed by the accumulation of blue astrocytes beginning within a few days after the injury (from image D). The inset in the image A shows an epifluorescence overview of the surgically exposed anatomic region. The area in the box within the epifluorescence overview was recorded by 2P-LSM. Scale bar in image A, 50 µm.

sible for the reduced efficacy of spinal reflexes is a decrease in the excitability of spinal α-MNs. Another factor is a decrease in the activity of most spinal interneurons, including PLR-related interneurons. For example, in decerebrate rabbits in which the head, vertebral column, and pelvis were rigidly fixed, anti-phase flexion/extension movements of the hindlimbs caused by roll tilts of a supporting platform elicited PLRs. Neurons in spinal segments L5–L6, which presumably contribute to the generation of PLRs, can be divided into three groups: F-interneurons activated during flexion of the ipsilateral limb, E-interneurons activated during extension of this limb, and a group of non-modulated interneurons. In decerebrate rabbits acutely spinalized at T12, postural functions were lost, including the disappearance

of PLRs in response to roll perturbations of the supporting platform. The three interneuron groups named above reacted differently to spinalization. The proportion of non-modulated interneurons in spinalized rabbits was larger than in controls (33% vs. 18%). This was likely due to the fact that, after elimination of supraspinal drive, part of the modulated interneurons became non-modulated. Spinalization affected the distribution of F- and E-interneurons in segment L5 across the spinal gray matter, causing a significant decrease in their activity, as well as disturbances in processing of posture-related sensory inputs. The decrease in activity (mean frequency, burst frequency, and depth of modulation) of F- and E-interneurons could be caused by three factors: (1) a decrease in excitability of spinal interneurons; (2) a decrease in efficacy of sensory input from limb mechano-receptors; (3) a decrease in the value of sensory input due to a strong reduction in the forces developed by extensor muscles and monitored by load receptors, as well as due to inactivation of γ-MNs, leading to a decrease in signals from muscle spindles.

Spinalization affected the contribution of sensory inputs from the ipsilateral and contralateral limbs that modulate F- and E-interneurons. Thus, there was an almost two-fold increase in the proportion of interneurons modulated by sensory input from the ipsilateral limb and a corresponding decrease in the proportion of interneurons with input from the contralateral limb. This was caused by a significant reduction in the efficacy of tilt-related sensory inputs from the contralateral limb to both F- and E-interneurons across the entire gray matter. Most likely, commissural interneurons (CINs) transmitting signals from the contralateral limb are inactivated by acute spinalization. Spinalization differentially affected the efficacy of sensory inputs from the ipsilateral limb to F- and E-interneurons. These changes in the operation of postural networks underlied the loss of postural control after spinalization and represent a starting point for the development of spasticity [113].

3.2 Chronic Effects of SCI

After the initial spinal shock, locomotor activity and early spinal reflexes reappear in response to appropriate sensory input. In the subsequent 4–8 months, clinical signs of spasticity appear [111], but deficits in excitation of spinal α-MNs by descending pathways remain and conrtibute to weakness. In incomplete SCI (iSCI), sensory afferent inputs may assume a disproportionately larger influence on volitional activation than in healthy adults, such as during volitional upper extremity tasks, standing, or stepping. After iSCI, specific changes contribute to spasticity, including changes in α-MN excitability and sensitivity to serotonin (5-HT) (Sect 4.2.1), decreased reciprocal inhibition (Sect 4.3), recurrent inhibition (Sect 4.4), presynaptic inhibition (Sect 4.5), sprouting of descending (cortico-, bulbo-, and propriospinal) pathways, as well as alterations in interneuronal pattern-generating networks [114]. Beyond these spinal alterations, plasticity in sub-cortical networks and sensory-motor cortices develop, likely to partially compensate for muscle weakness due to loss of whole muscle and muscle fiber size (i.e., atrophy), alterations in fiber phenotype, and increased fatiguability [34].

In patients with iSCI, spinal excitability is increased during the performance of strong voluntary contractions compared to healthy participants with intact spinal cords. In healthy participants, maximal voluntary contractions (MVCs) that fatigue a muscle result in reduced volitional output, but the opposite is observed in SCI patients. In healthy participants, twenty repeated isometric MVCs of the knee extensors resulted in an immediate and sustained decline in peak torque production (~30–35% decrease), while individuals with iSCI produced increased peak torque and electromyographic (EMG) activity by the third contraction (15–20%). In SCI patients, these gains in muscle activation over repeated MVCs were partly due to increased central excitability during maximal contractions, consistent with the presence of PICs (Sect 2.2.1). Thus, in SCI patients, elevated reflex activity typically characterized as spasticity may boost motor performance during both static and dynamic tasks [34].

3.3 Spasticity

Spasticity is a long-term symptom of brain and spinal cord damage. It has tradidionally been defined as an augmented resistance of skeletal muscle at rest to passive stretch in a velocity-dependent manner. However, this definition is based on a fast and simple clinical test and not a comprehensive description of spasticty and its underlying mechanisms. In fact, the term spasticity is now mostly used in a wider sense [115].

Spasticity can occur in response to traumatic brain injury, stroke, cerebral palsy, multiple sclerosis (MS), ALS, and SCI [40,107,111,115–126]. For simplicity, we will focus on SCI-related spasticity, with occasional discussion of stroke-related syndromes. Spasticity goes along with the following chronic symptoms.

Increased muscle tone (hypertonus) with muscle stiffness

Sustained involuntary muscle contractions

Hyperexcitable muscle stretch reflexes associated with velocity-dependent resistance to passive muscle stretch

Increase in short-latency stretch reflexes with enhanced tendon-tap reflexes

Clonus

Clasp-knife reflex

Loss of long-latency reflexes

Synkinesia: co-contraction of normally independently controlled muscles

Long-lasting exaggerated cutaneous reflexes (e.g., flexor or withdrawal reflexes)

Severe uncontrollable muscle spasms

Impaired voluntary activation of multiple muscles

Sensory disturbances such as enhanced abnormal sensation, dysesthesia and pain

Secondary changes in mechanical muscle-fiber properties, collagen tissue, and tendon properties (e.g., loss of sarcomeres, subclinical contractures)

Autonomic and immune dysfunctions

The specific syndromes differ depending on the cause. For example, unilateral stroke in the forebrain may leave various tracts descending to the spinal cord intact. In contrast, a SCI can damage one tract (in iSCI) or all tracts (in complete SCI), and can thus produce primary anatomical and pathophysiological changes and associated secondary changes including neurotoxicity, vascular dysfunction, glial scarring, neuro-inflammation, apoptosis, and demyelination [127]. The effects of SCI also depend on the species, completeness, extent and site of the lesion, and the clinical condition of the animal [33,122,128,129]. One problem elucidating these processes is that they differ considerably between rodents, non-human primates, and humans [130].

Prominent chronic features after SCI are excessive spasms in extensor and flexor muscles with lesser expression of increased muscle tone [120]. This is the opposite pattern than what is observed following a stroke, indicating different underlying mechanisms [33,107]. Some of these changes have formerly been considered maladaptive, particularly those leading to involuntary motor behaviors, such as spasticity, spasms, and clonus (Sect 4.1.1.2). However, animal models of iSCI and human studies suggest that increased spinal excitability underlying hyperexcitable reflexes may facilitate motor function, particularly when utilized during voluntary tasks [34].

It should be emphasised that the disruption of descending tracts also causes a number of autonomic abnormalities, including compromised cardiovascular, respiratory, urinary, gastro-intestinal, thermo-regulatory, and sexual activity. In brief, high thoracic or cervical SCI often causes life-threatening hemodynamics and respiratory dysfunction due to dysregulated sympathetic outflow, while parasympathetic (vagal) control remains intact. With injuries below the 5th thoracic segment, both sympathetic and parasympathetic control of the heart and broncho-pulmonary tree are intact [107,119,131,132]. Moreover, SCI disrupts the neural and humoral control of immune cells. Autonomic dysfunction and impaired neuro-endocrine signalling are instrumental in determining 'SCI-induced immune deficiency syndrome', in which mature leukocyte dysfunction plays a sigificant role and the development and mobilization of immune cell precursors in bone marrow are impaired [133].

3.4 Quiet Standing and Sitting in Humans with SCI and Stroke

Without sensory feedback, there can be no upright stance or its maintenance. The important sensory inputs derive from a number of peripheral receptor systems. Here we concentrate on inputs processed at spinal level and their change after SCI. Covarrubias-Escudero *et al*. [134] used body-worn accelerometers positioned at L5 to measure characteristics of body sway, such as the amplitude, frequency, and smoothness, during quiet upright stance in patients with an iSCI. These patients presented with increased postural sway as measured by altered initial values of jerk (time derivative of acceleration) compared to healthy subjects. Although they were able to generate postural adaptations to environmental challenges, patients with iSCI could not fully compensate for the postural control changes caused by their sensory and motor impairments. It has been argued that iSCI patients might have increased postural sway consequent to deficient motor responses related to timing muscle contractions, which in turn would be the consequence of the diminished motor pathways, thus being insufficient to react and generate appropriate postural adjustments. Postural sway could also increase due to damaged somato-sensory pathways, which are often compromised following a SCI and subsequently reflect noisy somato-sensory feedback from foot pressure, muscle proprioceptors, and joint receptors. Damaged somato-sensory pathways could thus provide inaccurate information about body position in space. Together, these possible consequences of iSCI could generate frequent, abrupt corrections of postural sway direction and might be responsible for higher jerk values as compared to healthy subjects [134].

Due to partial muscle paralysis, iSCI patients tend to have atrophy and weakness in the ankle pantar-flexor muscles and consequently reduced standing balance. A potential compensatory strategy to reduce instability during quiet upright stance is to co-contract ankle plantar-flexor and dorsi-flexor muscles, which increases the ankle-joint stiffness and postural sway. These co-contractions may be a strategy used by older adults as well as subjects with iSCI to compensate for muscle weakness at the ankle joint and their upright posture. Indeed, an iSCI group exhibited more co-contractions than an able-bodied group, and postural sway was larger during ankle muscle co-contractions than during no co-contraction in the SCI-group. It has been hypothesized that the increased co-contraction in the SCI-group may be due to a switch from reciprocal inhibition (Sect 4.3) to facilitation. Both recurrent inhibition (Sect 4.4) and presynaptic inhibition (Sect 4.5) operate incorrectly after SCI which influences reciprocal inhibition. After SCI, reciprocal inhibition has been shown to be replaced with facilitation, which could increase co-contractions of ankle plantar- and flexor muscles [135].

During quiet standing, subjects with iSCI showed larger postural sway than healthy subjects, primarily due to larger ankle-joint acceleration. Also, while in healthy subjects the ankle- and hip-joint accelerations were in antiphase to minimize the postural sway, this interjoint coordination was not affected in SCI patients, which could therefore not reduce the large center-of-mass (COM) accelerations [136].

In one study, patients with spasticity of different etiologies and degrees of severity, stood quietly upright on a force platform. The body sway measured was not correlated with muscle tone, muscle strength, tendon reflexes, plantar responses, or duration of the disease. On average, compared to healthy subjects, all patient groups showed a forward shift of the center of pressure (COP) under the feet. Moreover, paraparetic, and to a much larger extent hemiparetic patients, showed a lateral shift of COP. Sudden rotations of a supporting platform, in a toe-up or toe-down direction to stretch the soleus muscle or the tibialis anterior (TA) muscle, respectively, evoked short-latency (SLR) and medium-latency (MLR) reflex responses. Evoked SLR responses were assumed to be mediated by muscle-spindle group Ia afferents and MLR responses by group II afferents [137]. Compared to healthy controls, soleus SLR was increased in all patients. TA SLR was observed in both patients with ALS and paraparetic patients, but only rarely in healthy subjects and hemiparetic patients. By contrast, the MLRs of soleus and TA in the affected leg were diminished in hemiparetic patients, which could have contributed to increased body sway. These responses were decreased in size and not modulated by background EMG in the affected leg of hemiparetic patients, suggesting a disturbed control of spinal reflexes fed by spindle group II afferent fibers [138].

In post-stroke patients with spastic hemiparesis standing upright on a force platform, the COP under the feet was shifted toward the unaffected limb. This stance asymmetry could predict deficits in gait resulting from increased time and effort required to shift body weight toward the affected limb [139].

Thoracic SCI can negatively affect the ability to maintain unsupported sitting. Subjects with high- and low-thoracic SCI swayed more than did able-bodied controls regardless of upper-limb support. The level of injury was correlated with postural performance insofar as those with higher injuries swayed more and faster. Unsupported sitting was more unstable in comparison to supported sitting posture, especially in the anterior-posterior direction. The way subjects with high-thoracic SCI achieved stability was different from that of subjects with low-thoracic SCI, suggesting different postural regulation strategies [140]. Similar reductions in postural stabilty have been observed in subjects with motor-complete thoracic SCI who showed a trunk postural sway constraint to maintain suboptimal unsupported sitting balance [141]. In another study on seated subjects, the SCI group had greater COP sway than the controls, with no difference in the postural sway between the SCI subgroups, suggesting that the impairment in individuals with SCI resulted from disturbed supraspinal and peripheral mechanisms [142].

3.5 Quiet Stance and Responses to Stance Perturbations in Spinalized Animals

Many aspects of the specific pathophysiology of spasticity remain unclear. To elucidate the underlying mechanisms, various experimental animal models of spasticity have been developed. These animal models are categorized based on the mechanism of injury into contusion, compression, distraction, dislocation, transection or chemical models [143].

3.5.1 Quiet Stance in Spinalized Cats

The extent to which spinal circuits contribute to the maintenance of upright stance has been studied in cats after spinalization. Adult cats chronically spinalized at the mid-thoracic level could be trained to stand for a short period of time, with the body parallel to the support surface and the hip held at normal height [144–146]. This demonstrates that the spinal cord can define set points regarding limb geometry, and in so doing, regulate extensor muscle lengths at the knee, ankle, and metatarsal-phalangeal joints [144]. However, although this mechanism may contribute significantly to weight support, it is not sufficient for balance [145], as the direction-specific muscle synergies were absent [147].

3.5.2 Postural Responses to Surface Motions in Spinalized Cats

Intact cats can maintain balance during unexpected stance perturbations through automatic, stereotyped, and rapid postural responses. Responses were elicited to 16 directions of linear translation in the horizontal plane and various variables measured before and after spinalization at the T(6) level. After spinalization, four cats were trained to stand on a force platform. All cats were able to support their full body weight. However, the cats required assistance for balance in the horizontal plane, provided by gentle lateral force at hips. Perturbations were delivered during the periods of independent stance in three cats and during assisted stance in the fourth. A response to translation occurred only in those muscles that were tonically active to maintain stance and never in the flexors. Latencies were increased and the amplitude of EMG activation were diminished compared to healthy intact cats. Hence, the spinalized cat can achieve good weight support, but cannot maintain balance during stance except for brief periods within narrow limits, with centers above the lumbosacral cord being required for full automatic postural responses. This limited stability is likely provided by the stiffness of tonically active extensor muscles and spinal reflex mechanisms [145].

3.5.3 Interneurons Mediating Postural Reflexes

In decerebrate rabbits, in which the head and the vertebral column and pelvis were rigidly fixed, anti-phase flexion/extension movements of the hindlimbs, caused by roll tilts of a supporting platform, elicited PLRs. Neurons in spinal segments L5-L6, which presumably contributed to the generation of PLRs, could be divided into two groups: F-neurons activated during flexion of the ipsilateral limb and E-neurons activated during extension of this limb. There was also a group of non-modulated neu-

rons. F- and E-interneurons were intermingled and scattered across the whole cross-section of gray matter. The phase of modulation of a neuron was determined mainly by sensory input from the ipsilateral limb. The majority of neurons received mono- and polysynaptic sensory inputs from both limbs, with the inputs being linearly summated. Sensory inputs from the receptive field of a neuron (determined at rest) can be responsible for tilt-related modulation only in some of the neurons [148].

Over time, spinalization in rabbits triggers two kinds of plastic changes: (1) rapid restoration of normal activity levels in interneurons, in days following injury, (2) slow recovery of α-MN excitability, in months following injury. Most likely, recovery of interneuron activity underlies reappearance of α-MN responses to postural stimuli. However, the absence of recovery of normal processing of postural sensory signals and the enhancement of oscillatory activity of interneurons, result in abnormal PLRs and loss of postural functions. The relative number of F- and E-interneurons activated from receptive fields from skin/fur receptors increased up to 60% vs. 7% in controls and 4% after acute spinalization. Chronic spinalized rabbits often show spasms of long duration appearing spontaneously or caused by unspecific sensory stimuli, for which multiple mechanisms have been suggested, inlcuding changes in biophysical properties of α-MNs, reduced presynaptic inhibition (Sect 4.5) of afferents, and changes in inhibition efficacy. Furthermore, excitatory (glutamatergic) interneurons may be important in triggering and sustaining spasms; in particular, V3 interneurons may initiate spasms [113]. The changes are likley due in part to loss of supraspinal inputs, but also to plastic processes whose cellular and molecular underpinnings are not yet well understood.

3.6 Locomotion

Locomotor rhythms can be generated by spinal central pattern generators (CPGs), which are autogenous in the sense that they do not depend on afferent sensory feedback (fictive locomotion) or spinally descending signals for their basic rhythm-generating function [149]. However, autonomy of the isolated spinal cord for generating locomotor rhythms is far greater in the spinalized rat or cat than in primates, including humans.

Spinal rhythm generation by CPGs require the coordinated activity of many neuron groups that organize the basic rhythmic spinal outputs as well as the spatio-temporal patterns of muscle activities, which must be capable of answering the varying demands of internal goals and the environment. The spatio-temporal patterns include flexion–extension alternation in intra-limb coordination and left–right coordination of different limbs. The underlying neuronal mechanisms have begun to be studied over the past few decades using anatomical, developmental, genetic, molecular, anatomical, and electrophysiological methods, particularly in mice [150–157] and cats. CPGs most likely occur in humans but are much less undrstood than in mice and other mammals [158–160].

Sensory inputs have diverse roles in locomotion. Proprioceptive feedback reinforces ongoing motor output, shapes muscle activity, and contributes to timing the transitions between different locomotor step phases. They also play an important role in adjusting basic locomotor rhythm to environmental conditions and compensating for unexpected perturbations. Various sources of sensory feedback change throughout the gait cycle, and all known spinal reflex pathways are modulated during locomotion. These include stretch reflexes, H-reflexes (Sect 4.1), and presynaptic inhibition (Sect 4.5). Sensory information most appropriate for each step phase is gated by CPGs [149,161–165]. Presynaptic inhibition is modulated by supraspinal centers and primary afferents in order to filter sensory information, adjust spinal reflex excitability, and ensure smooth movement [166–169] (Sect 4.5). In SCI animal models and humans with SCI, sensory afferent feedback is important, if not critical, to the locomotor output. The influence of spastic motor behaviors on MN discharge and on different muscles suggests that the altered sensory input-motor output relationships could either facilitate or antagonize the intended motor command [34].

3.6.1 Locomotion in Spinal Cord Injured Humans

In patients with an iSCI, the ability to walk is compromised by lower limb paresis, increased spasticity, poor coordination, and impaired postural control. Body-weight support during treadmill training (BWSTT) increases muscle strength, kinematics, and spatio-temporal gait parameters [134,170–173]. Locomotor training promotes the plasticity of neural spinal circuits. The mechanisms contributing to functional recovery overlap with those underlying spasticity. Specific changes that contribute to spasticity include decreased reciprocal inhibition (Sect 4.3.), presynaptic inhibition (Sect 4.5), muscle afferent and interneuron collateral sprouting, partially resulting from the loss of competition from CST terminals, and changes in MN excitability and sensitivity, particularly in response to residual serotonergic (5-HT) inputs [34,114].

3.6.2 Locomotion in Spinalized Cats

Cats with partial low-thoracic spinal transections recovered voluntary quadrupedal locomotion with treadmill training (3-5 days/wk) over several weeks. The locomotor pattern showed left/right asymmetries in various kinematic parameters, such as homolateral and homologous interlimb coupling, cycle duration, and swing/stance durations. When partial recovery was stationary, cats were spinalized. Thereafter, the hindlimb locomotor pattern rapidly re-appeared within hours, but left/right asymmetries in swing/stance durations could disappear or reverse. Hence, after a partial spinal lesion, the hindlimb locomotor pattern was actively maintained by new dynamic inter-

actions between spinal and supraspinal levels but also by intrinsic changes within the spinal cord [174].

Spinalized and decerebrate cats while walking on treadmills adjust their hindlimb stepping rate to a considerable speed range between 0.1 and 1 m/s. At higher speeds, walking/trotting sometimes gives way to galloping. Increased step rate is achieved primarily by shortening the stance phase, while the flexion phase remains nearly constant. These adjustments indicate a substantial role for sensory feedback in switching between different locomotor phases, especially in regulating the stance phase duration [164].

In cats with a complete SCI, hindlimb locomotion is inhibited by inputs from the lumbar region but facilitated by inputs from the perineal region. In cats with a complete SCI, these inputs also exert opposite effects on cutaneous reflexes from the foot in that lumbar inputs increase the reflex gain while those from the perineal region decrease reflex gain. Moreover, SCI can lead to a loss of functional specificity through the abnormal activation by somato-sensory feedback, such as the concurrent activation of locomotion and micturition [175].

3.7 Reach-and-Grasp Movements

Reach-to-grasp movements to obtain or manipulate objects are synchronous and composed of several observable components, including limb lifting, aiming, and advancing the limb, followed by opening the digits, pronating the wrist, grasping the object, and supinating to orient the object for release. After incomplete or complete SCI at cervical level, this delicately organized sequence is disrupted or impossible, respectively. The consequences of iSCI depend on the site and degree of damage.

In humans, fine motor control of the digits is largely controlled by the descending lateral CST, which decussates and crosses midline at the pyramids in the brainstem, and then continues through the spinal dorso-lateral white matter. These lateral CST fibers synapse in cervical MN pools to control proximal and distal muscles of limbs and digits. The MN pools for the shoulder and arm are located at levels C4-6, and the MN pools of the forearm and digits are located at C7-T1. In addition to CST control in non-human primates, there is evidence of the involvement of descending rubro-spinal and reticulo-spinal tract (RST) fibers in controlling which upper extremity muscles execute the reach and grasp of a target object. Also, direct excitatory projections from the deep cerebellar nuclei to the ipsilateral cervical spinal cord appear to be involved in the control of the reach-to-grasp movement. Mice with silenced ipsilateral cerebello-spinal projection neurons took longer to touch the food pellet and failed to successfully grasp it. After SCI, recovery or compensatory reaching and grasping is mediated by several spared systems that respond after injury. Plasticity of primary sesosry afferent fibers also contribute to improved function post-injury [110].

4. Neuromuscular Changes in Spasticity

The neural control of muscles is heavily compromised during spasticity and depends on the etiology (stroke, SCI, MS), experimental paradigm, condition (rest, static muscle contraction, sitting, standing, locomotion, voluntary movement), and methods used. Here we will focus on SCI, with some discussion of other conditions.

Loss of supraspinal signals leads to an abundance of changes Patientbelow the SCI site. They include changes in the number of neurons, adult neurogenesis, dendritic spine growth, re-distribution of sensory and descending inputs to α-MNs and interneurons, augmented sprouting of descending (cortico-, bulbo-, and propriospinal) pathways, aberrant rewiring of spinal circuits, changes in the use of afferent sensory input, dysfunctions of short- and long-latency reflexes, alterations in interneuron pattern-generating networks, increase of α-MN excitability and sensitivity to serotonin (5-HT), synaptic plasticity, and changes in skeletal muscle, tendon, and ligament properties.

Patients with Chronic spinal diseases often show spasms that are long in duration and appear spontaneously or are caused by unspecific sensory stimuli. A number of mechanisms have been suggested to underlie spasms, including changes in biophysical properties of α-MNs, reduced presynaptic inhibition of sensory afferents, and changes in inhibition efficacy. Furthermore, excitatory (glutamatergic) interneurons, in particular V3 interneurons, may be involved in triggering and sustaining the spasms [34,113,118,128,129,176–180]. Although a number of potential causes for the neuromuscular changes after SCI have been suggested, it is still not clear how these plastic and/or compensatory changes arise.

Clinically, spasticity is often defined as an increased velocity-dependent resistance to passive muscle stretch. This reflex is elicited by sensory receptors excited by muscle stretch, processed by spinal networks as the interface and ends in muscle contraction. In the following, we will discuss the various elements leading to the development of spasms.

4.1 Changes in Muscle Stretch Reflexes

Muscle stretch reflexes are more complicated than relatively simple tendon-tap responses of manually exerted stretches used by neurologists. They are also more complicated than the phasic H-reflex, which generates a short-latency EMG wave in response to electrical stimulation of group Ia muscle spindle afferents in the parent muscle nerve. After complete SCI, the amplitude of H-reflexes in hindlimb muscles is greatly increased but can be reduced by locomotor training [181].

Augmented stretch reflexes require the consideration of various neuronal networks. Several mechano-receptors and their afferents are involved (Fig. 3, Ref. [120]). For example, group Ia and II afferents from muscle spindles modulated by fusimotor control by γ-MNs and group Ib af-

ferents from Golgi tendon organs (GTOs) responding particularly to active muscle contraction. Additionally, group III and IV muscle afferents responding in part to mechanical events in muscles (Sect 4.1.2), as well as their complex central connections to α-MNs. Important special networks include reciprocal Ia inhibition (Sect 4.3), recurrent inhibition (Sect 4.4), presynaptic inhibition (Sect 4.5), group Ib connections (Sects 4.1.1.3, 4.1.2), and connections from group III and IV afferents (Sect 4.1.1.4; review: Windhorst 2021 [182]).

These spinal interneuronal networks are under modulatory influence from various, differentially connected descending tracts [182]. So, any impairment of these descending signals could be expected to derange and shift spinal network functions, including the muscle stretch reflex (Fig. 3). When discussing muscle stretch reflexes, it is important to note that the total mechanical response of a contracting muscle to a stretch is the sum of the response from the passive tissue, the response from the properties of the muscle fibers contracting prior to the stretch (intrinsic properties), and the response from the stretch reflex-mediated contraction of the muscle fibers [183].

4.1.1 Human Work

Resistance to the stretch of a muscle is determined by three mechanisms: passive and intrinsic properties of the intact and active muscle system around the joint ('non-reflex component'), force generated by the stretch reflex ('reflex component'), and supraspinal control of the stretch reflex.

4.1.1.1 Length Feedback. Compared with healthy control participants, the ankle mechanics and stretch reflexes of spastic hemiparetic stroke patients showed various changes, as determined by a nonlinear delay differential equation. Mechanically, stiffness in spastic ankle joints was higher across plantar-flexion and dorsi-flexion torque levels, and the more spastic plantar-flexor muscles were stiffer than dorsi-flexors at comparable torques. Increased stiffness in spastic ankle joints was mainly due to an increase in passive stiffness, indicating increased connective tissue or shortened fascicles. Viscous damping in spastic ankle joints was increased across plantar-flexion torque levels and at lower dorsi-flexion torques, reflecting increased passive viscous damping. The more spastic plantar-flexor muscles showed higher viscous damping than dorsi-flexors at comparable torque levels. Spasticity was associated with decreased threshold and increased gain of tendon reflexes. The gain of the phasic component of the stretch reflex in spastic plantar-flexor muscles was higher and increased faster with plantar-flexor contraction. The gain of the tonic stretch reflex was increased in spastic ankle muscles at rest [184].

In healthy subjects, muscle stretch and H-reflexes are modulated in a manner that is dependent on the walking task and step phase. Evidence for task-dependency was seen through the reduction of soleus H-reflex gain from standing to walking to running. This was thought to be due

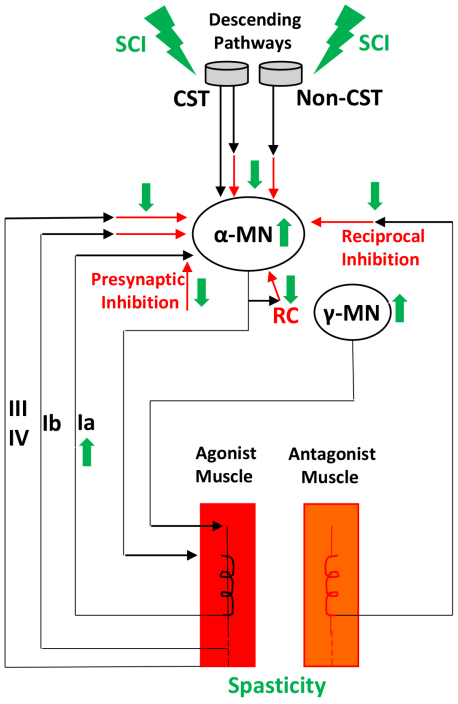

Fig. 3. A schematic diagram to illustrate spinal neuronal networks involved in motoneuron (MN) excitability changes following spinal cord injury (SCI). There are several mechanoreceptors and their glutametrgic afferents involved, including group Ia afferents from muscle spindles modulated by fusimotor control by γ-MNs and group Ib afferents from Golgi tendon organs responding particularly to active muscle contraction. Additionally, group III and IV muscle afferents responding in part to mechanical events in muscles are also involved. The inhibitory spinal networks include (inhibitory glycinergic or GABAergic interneurons marked by red arrows): reciprocal Ia inhibition, recurrent inhibition by Renshaw cells (which by themselves are innervated by cholinergic MN axon collaterals), presynaptic inhibition, group Ib connections, and connections of group III and IV afferents. These spinal interneuronal networks are under supraspinal influences from various, partly inhibitory, descending tracts (Descending pathways are shown in the upper part of the figure: CST: cortico-spinal tract; Non-CST: extrapyramidal tracts from the brain stem). Spasticity resulting from impairments in these descending influences from a SCI is due to a shift of spinal network functions (marked by green arrows). A plethora of neurotransmitters are also involved. While group Ia afferents monosynaptically release glutamate onto α-MNs, the effects of other afferents are oligo- to polysynaptic, implying that interneuronal neurotransmitters are responsible for the effect on α-MNs. Moreover, interneurons may contain various co-transmitters, further complicating their effects. For example, Renshaw cells release glycin and GABA onto α-MNs, however these details are beyond the scope of this review. Reproduced with permission from Ganguly J, Muscle Tone Physiology and Abnormalities. 2021. [120].

to increased presynaptic inhibition (Sect 4.5; references in Thompson *et al*. [185]) caused by supraspinal (including CST) control, and so is phase-dependent modulation of the H-reflex. Another study had patients with spasticity of different etiologies and degrees stand quietly upright on a supporting force platform. Sudden rotations of the platform, in a toe-up or toe-down direction to stretch the soleus muscle or the TA muscle, respectively, evoked short-latency (M1) and medium-latency (M2) reflex responses. Compared to healthy controls, soleus SLR was increased in all patients in the study. TA SLR was often seen in both patients with ALS and paraparetic patients, but rarely in normal healthy subjects and hemiparetic patients. These responses were decreased in size and not modulated by background EMG in the affected leg of hemiparetic patients, suggesting disturbed control of spinal reflexes fed by spindle group II afferent fibers [138].

In standing human subjects, foot dorsi-flexion evoked a short-latency and a medium-latency EMG response in the soleus muscle. SLRs are thought to be mediated by spindle group Ia afferents, while group II fibers contribute to MLRs through an oligosynaptic circuit. Achilles tendon vibration had different effects on both SLR and MLR responses in spastic hemiparetic patients and normals subjects. While there were no differences between controls and spastic hemiparetic patients in term of size of control SLR or MLR, vibration decreased SLR to 70% in control subjects, but increased it to 110% in spastic hemiparetic patients, in both affected and unaffected leg. Vibration did not affect MLR amongst controls but increased it to 165% on the affected and 120% on the unaffected side of spastic hemiparetic patients. Therefore, in spastic hemiparetic patients the lack of inhibition from vibration on SLR indicated that inhibition of the monosynaptic reflex was reduced, while the increased MLR indicated a disinhibition of group II pathway, connected to the loss of descending control on group II interneurones. Spastic hypertonia depends on release of group II rather than group Ia reflex pathways [186].

Phase-dependent modulation of the H-reflex during locomotion in healthy subjects is likely generated by presynaptic inhibition (Sect 4.5; references in Thompson *et al*. [185]). In spastic stroke patients, the input-output properties of the soleus stretch reflex during sitting and walking was different from healthy subjects. In the early swing phase, the threshold of the input-output relation was significantly lower in the spastic stroke patient group. There was a significant correlation between the stretch reflex threshold in the early swing phase and the clinical spasticity score. It has been suggested that in the early swing phase, the reduced soleus stretch reflex threshold prevents stroke patients from making fast foot dorsi-flexion and thereby impairs walking speed [187]. In chronic iSCI patients, the swing-phase H-reflex, which was absent or very small in neurologically normal subjects, is abnormally large, but can be down-regulated by operant conditioning [188].

In another study, spastic patients with hemiparetic stroke and age-matched healthy volunteers had three types of ankle perturbations during treadmill walking applied. Fast dorsi-flexion perturbations elicited a short-latency stretch reflex in the soleus muscle, which were facilitated in the patients compared to the control subjects. Fast plantar-flexion perturbations, applied during the stance phase to unload the plantar flexor muscles and remove the afferent input to soleus α-MNs, decreased soleus activity that was significantly smaller among stroke patients compared to the healthy volunteers. Slow-velocity, small-amplitude ankle trajectory modifications, which mimicked small deviations in the walking surface, generated gradual increments and decrements in the soleus EMG in the healthy volunteers, but significantly depressed modulation in the stroke patients. This was taken to indicate that, although the stretch reflex response was facilitated during spastic gait, the contribution of afferent feedback to the ongoing locomotor soleus activity was depressed in patients with spastic stroke [189].

In healthy subjects and patients with spasticity due to chronic iSCI, unexpected ankle dorsi-flexion perturbations and soleus H-reflex were elicited throughout the gait cycle. In healthy subjects, spinal short-latency M1 (mainly elicited by group Ia muscle spindle afferents), spinal medium-latency M2 (presumably mediated mainly by group II muscle spindle afferents), and long-latency M3 reflexes (probably mediated via transcortical or sub-cortical pathways) were modulated throughout the step cycle. The responses were largest in mid-stance and almost completely suppressed during the stance-swing transition and swing phases. In SCI patients, M1 and M2 responses were abnormally large in the mid–late-swing phase, while M3 modulation was similar to that seen in healthy subjects. The H-reflex was also large in the mid–late-swing phase. Elicitation of H-reflex and stretch reflexes in the late swing often triggered clonus (Sect 4.1.1.2) and affected the soleus activity in the following stance phase. The large M1 enhancement in SCI patients has been suggested to result from reduced inhibition of group Ia excitatory pathways, while the enhancement of the M2 component could be due to increased oligo- or polysynaptic group Ia excitation, reduced inhibition of excitation from group II spindle pathways, changes in pathways containing excitatory and inhibitory interneurons that receive inputs from group Ib afferents (Sects 4.1.1.3, 4.1.2), and/or increased excitation of interneuronal pathways fed by other afferents. It has also been suggested that, at least partly, the firing of group II and Ib afferents and an altered modulation or excitability of Ib/II interneurons (Sect 4.1.2) may explain abnormal swing-phase bursts in the soleus EMG or abnormally large M2 responses in the late-swing phase. Group Ib feedback interacts with other reflex pathways (Sect 4.1.2) and cutaneous reflexes, which are also altered after SCI. Other interneuronal networks are also likely involved. Reduced CST activation of the TA muscle results in weak dorsi-flexion and foot drop and would reduce reciprocal inhibition (Sect 4.3)

of the soleus even if reciprocal inhibition itself were normal. Yet in SCI patients, reciprocal inhibition between the plantar-flexors and dorsi-flexors is often abnormal (Sect 4.3) and would further reduce the suppression of the soleus α-MN excitability in the stance-swing transition through the late-swing phase. Recurrent inhibition (Sect 4.4) inhibits α-MNs, γ-MNs, and reciprocal inhibitory interneurons and is modulated by sensory afferents (not well investigated; [182]) and signals descending from supraspinal sources. Thus, it is probable that multiple inhibitory mechanisms are altered during walking, resulting in disorganized and ineffective activation of multiple muscles in SCI patients [185]. These suggestions emphasize the potential involvement of complex interneuron networks, which are almost all influenced by descending fiber tracts [182] (Sect 4.1.2).

In hemispheric stroke patients, increased drives via the vestibulo-spinal tracts (VeST) and/or reticulo-spinal tracts (ReST) contribute to spasticity on both sides [190]. After hemispheric stroke, alterations in the activity of the reticular nuclei affect both sides of the spinal cord, and thereby should contribute to increased α-MN excitability on both paretic/spastic and contralateral sides, compared to neurologically intact subjects. Experiments measuring stretch reflex threshold showed that both contralateral and affected sides exhibited increased α-MN excitability as compared to intact subjects, including a reduction in stretch reflex thresholds in the contralateral limb. This would be in line with ReST activation, which has bilateral descending influences. Thus, spasticity may be due to a different strongly lateralized pathway, such as the vestibulo-spinal tract. There may also be changes in neuromodulation (Sect 4.2.1) at the spinal level [191].

4.1.1.2 Clonus. Ankle clonus is an involuntary 5- to 7-Hz joint oscillation [120,192] and commonly occurs at the ankle in patients with motor-incomplete SCI and other forms of CNS pathology. Clonus may be promoted by increased soleus α-MN excitability, reduced post-activation depression of repeated stretch activations, and antagonist co-activation. Clonic soleus activity may impede walking progression and compromise independent walking. Ankle clonus likely results from the loss of descending inhibition of soleus stretch reflexes and maladaptive re-organization of spinal reflex pathways. The latter comes with other abnormalities, such as co-activation and reciprocal facilitation of TA and soleus MNs (S) (Sect 4.3). Operant conditioning can increase muscle TA activation and decrease H-reflexes in patients with SCI [193].

Computer simulations of the reflex circuit involving the ankle muscles and monosynaptic spinal connections between spindle afferents and α-MNs showed that oscillations such as clonus occur when the α-MN excitability increases in a reflex pathway containing long delays. This change in excitability is mediated by a reduction in α-MN firing threshold, rather than by an increase in feedback gain [194].

4.1.1.3 Force Feedback. In stroke patients, constant velocity stretches elicit, after movement onset, progressively increasing active reflex force with increasing joint angle. However, after the reflex force magnitude exceeds a particular level, it begins rolling off until maintaining a steady-state value. The magnitude of these force plateaus are correlated with the speed of stretch, such that higher movement speeds result in higher steady-state forces. These force plateaus could result from a force-feedback inhibitory pathway.

A simple model representing the elbow-reflex contains two separate feedback pathways, one representing the monosynaptic stretch reflex originating from muscle spindle excitation, and another representing force-feedback inhibition arising from force sensitive receptors. The force-feedback inhibition altered the stretch-reflex response, resulting in a force response that followed a sigmoidal shape, similar to that observed experimentally. Moreover, simulated reflex responses were highly dependent on force-feedback gain, such that increases in this gain predicted that reflex force plateauing would begin at decreasing force levels. The parameters from the model indicate that the force threshold for force-sensitive receptors is relatively high, suggesting that the inhibition may arise from muscle free nerve endings rather than GTOs. The experimental results together with the simulations of elbow-reflex responses suggest that after stroke, the effectiveness of force-feedback inhibition may increase to a level that has functional significance [195].

4.1.1.4 A Special Stretch-Reflex Component: Clasp-Knife Reflex. The clasp-knife reflex is one sign of spasticity. It can be evoked in decerebrate and spinalized (T12) cats by muscle stretches or contractions. Sudden relaxation can be induced by continued passive bending or straightening of a limb. Stretch of a hindlimb extensor muscle can evoke inhibition in homonymous and synergistic extensor muscles, but only if the stretch is of large amplitude and produces large force. The reflex effects also extended to other muscles. Extensor muscles were inhibited and flexor muscles were excited throughout the hindlimb. Stretch of the tibialis anterior muscle generated the same spatial pattern and time course of reflex action as stretch of an extensor muscle - inhibition of extensor muscles and excitation of flexor muscles throughout the hindlimb [196]. The receptors responsible for the reflex are group III and IV muscle afferents from free nerve endings. In decerebrate and spinalized (T12) cats, group III and IV muscle afferents are sentivive to muscle stretches of large amplitude that produce considerable passive force. In response to ramp stretches, their discharge began after a brief latency, attained its maximum at the ramp end and then showed a rapid and complete decay during static stretch, and the discharge adapted to repeated stretches. Isometric muscle contraction also excited the afferents. Thus, the afferents responded to both length and force. Stimulation of free nerve endings by

squeezing the Achilles tendon in cats exhibiting the clasp-knife reflex evoked strong homonymous inhibition and a flexion/withdrawal pattern of reflex action, i.e., inhibition of extensor and excitation of flexor muscles throughout the hindlimb, which parallels the spatial divergence of the clasp-knife reflex [197]. Muscular free nerve endings activated interneurons in laminae V-VII of the cat L5-S1 spinal segment. These interneurons were suggested to be responsible for mediating the clasp-knife reflex as the time course and magnitude of their responses to stretch and contraction paralleled the time course and magnitude of the clasp-knife reflex [198].These simulations suggest that GTOs play no great role in force feedback in spasticity, but that muscle group III and IV afferents from free nerve endings assume the role. This leaves the question as to what the role of GTOs might be.

4.1.2 Intricacies of Spinal Networks in Cats

Stretch of active muscles activates muscle receptors other than muscle spindles, such as GTOs. It is therefore important to estimate what the contribution of GTO afferents to the reflex might be, in healthy and diseased states. Unfortunately, this is difficult as a result of group Ib afferents from GTOs having complex spinal effects via interneurons, and these effects being state-dependent (review: Windhorst 2021 [182]).

In cats, group Ib afferents from flexor and/or extensor muscles provide the dominant excitatory monosynaptic or both mono- and disynaptic effects on so-called 'Ib-Ins'. Inhibitory Ib-interneurons exert widespread oligosynaptic actions that reach almost all α-MN pools of the ipsilateral hindlimb. Most intermediate-zone 'Ib-interneurons' receive convergent inputs from sensory afferents in groups I-IV and from descending tracts [199]. Conversely, α-MNs receive oligosynaptic inhibitory inputs from group Ib fibers originating in various muscles, implying that group Ib input from one muscle diverges to different α-MN pools. 'Ib-interneuron' terminals producing inhibitory postsynaptic potentials (IPSPs) in homonymous and synergistic α-MNs are subject to presynaptic inhibition (Sect 4.5), which gates autogenetic Ib inhibition of active homonymous α-MNs and is rhythmically modulated by CPGs during locomotion [151,199,200].

In cats, group Ia and group Ib afferents converge on 30–50% of intermediate-zone interneurons (so-called 'Ia/Ib interneurons'; below), on which they exert co-excitatory, co-inhibitory, or mixed effects. Convergence occurs on afferents from the same muscle, different muscles acting at the same joint, or at different joints. Interneurons with Ia/Ib convergence may project to all α-MN pools in the hindlimb and to contralateral pools. Excitatory intermediate-zone interneurons project ipsilaterally, bilaterally, or contralaterally, while all inhibitory neurons project only ipsilaterally [201].

At rest, e.g., in reduced immobile preparations, group Ib afferents exert di- or trisynaptic inhibition on homonymous α-MNs and closely related synergistic α-MNs (autogenetic inhibition) as well as di- or trisynaptic excitation on antagonist α-MNs. During locomotion, extensor group Ib and Ia afferents activate ipsilateral extensor α-MNs and inhibit flexor α-MNs, thus switching to positive force feedback to extensors widely distributed in the cat hindlimb (for a review, please see Windhorst 2021 [182]). Excitatory force feedback is active and predominant during both locomotion and quiet standing in cats [202]. However, inhibitory and excitatory force feedback coexist during locomotion, with inhibition being re-distributed towards more distal muscles [203].

Group III and IV Afferents originate from free nerve endings and their activation reflexly elicits, for example, nocifensive flexor and withdrawal reflexes. Group III and IV afferents of muscle origin are in part nociceptive and in part ergoceptive, with wide-ranging central effects and diverse functions. They exert modulatory effects on most spinal interneurons and reflexes, which may work to adjust muscle contractions during muscle fatigue [165,204,205] and ventilation, heart rate, blood pressure, and vascular resistance during physical exercise [205–207].

Group III muscle afferents are more mechanosensitive than group IV afferents during skeletal muscle contraction, force production, dynamic/static muscle stretch, and local intramuscular pressure. Muscle group IV afferents are more sensitive to metabolites released into the interstitium by muscle activity as their activation usually starts after a delay during prolonged muscle contraction and continues to discharge until the withdrawal of muscle metabolites [205]. In particular, group III and IV muscle afferents appear to elicit the clasp-knife reflex (Sect 4.1.1.4).

All the interneurons intercalated in the above connections receive modulating inputs from various descending tracts and sensory afferents [182]. The partial or complete interruption of descending tracts should thus have complex effects on the operation of these interneurons. In humans, such intracate spinal connections are more difficult to investigate and would require indirect methods.

4.1.3 Stretch Reflexes in Animal Models of Spasticity

In adult decerebrate spinalized cats, reflexes elicited by ramp-hold-return stretches of the triceps surae muscles were abolished in the acute spinal state. In chronic spinalized cats (4 weeks after spinalization), reflex force partly recovered. However, soleus and lateral-gastrocnemius activity remained fairly depressed, despite the fact that injecting clonidine, a α_2-adrenoceptor agonist, could activate these muscles during locomotor-like activity. In contrast, other ankle extensor muscles not activated in the intact state, such as medial gastrocnemius (MG), plantaris, flexor hallucis longus, and the peroneal muscles as well as muscles that cross other joints, such as semimembranosus and biceps

femoris, were strongly activated by stretching the triceps surae muscles in chronic spinalized cats [208]. This suggests that the reflex pattern is re-organized after spinalization.

Several types of sensory receptors contribute to stretch reflexes. First, muscle stretch activates group Ia and group II muscle spindle afferents. Electrically stimulating tricep surae muscle afferents at group I (i.e., Ia and Ib) strength evokes similar or larger homonymous and heteronymous excitatory postsynaptic potentials (EPSPs) in chronic spinalized cats (>6 wk) than in cats with intact spinal cords. Immediately after spinalization, group I-evoked EPSPs are increased in tricep surae α-MNs. Second, group II inputs from secondary muscle spindle endings involved stretch reflexes in cats and humans could contribute to the observed stretch reflex changes, but their effects are complicated due to their mediation by complex interneuron networks [182,208]. Contributions from group II, III, and/or IV muscle afferents from free nerve endings can be excited by muscle stretch and could also contribute. Finally, the clasp-knife reflex (Sect 4.1.1.4) could play a role. Stretching triceps surae muscles after an acute dorsal hemisection in decerebrate cats evoked inhibition in ankle and knee extensors, i.e., the clasp-knife response, while eliciting activity in muscles such as semitendinosus, tibialis anterior, and iliopsoas. Hence, triceps surae muscle stretch activates muscles throughout the hindlimb, particularly in chronically spinalized animals [208].

Functional re-organization of stretch reflex pathways after spinalization likely occurs at the pre-motoneuronal level. That is, within a complex interneuron network [182,208]. For example, in the intact state, triceps surae group II inputs readily excite interneurons and transmit signals to ankle extensor α-MNs, whereas those that project to semitendinosus and sartorius α-MNs are tonically inhibited. After spinalization, the excitability of interneurons reverses such that interneurons receiving group II inputs from triceps surae and projecting to ankle extensor α-MNs are inhibited, while those projecting to semitendinosus and sartorius α-MNs are disinhibited [208].

Finally, inhibitory mechanisms within the spinal cord are particularly affected by SCI. Disynaptic reciprocal inhibition (Sect 4.3) between ankle flexors and ankle extensors can be altered following SCI in humans. Spinalization also changes presynaptic inhibition (Sect 4.5). After spinalization, collaterals from the same muscle afferent can be differentially regulated by other segmental inputs. Changes in presynaptic regulation of tricep surae muscle afferents could explain why the same muscle stretch fails to activate some muscles after spinalization, which were strongly activated in the intact state (e.g., soleus and lateral gastrocnemius) while activating muscles that were inactive before spinalization (e.g., semitendinosus and sartorius).

Descending monoaminergic influences likely participate in the re-organization of stretch reflexes. Depressed stretch reflexes after acute spinalization may be due to the loss of serotonergic drive because selective activation of 5-HT_2 receptors restores triceps surae excitability, as does clonidine [208].

In summary, stretch reflex pathways from triceps surae muscles to multiple hindlimb muscles undergo functional re-organization after spinalization. Altered activation patterns by stretch reflex pathways could explain some sensory-motor deficits observed during locomotion and postural corrections after SCI [208].

It has been hypothesized that length- and force-dependent reflexes have integrated functions. A rapid ramp-and-hold stretch elicits a fast muscle force response with an initial overshoot that subsides into a maintained steady-state phase. The overshoot is probably due to excitation of group Ia afferent fibers, shortly afterwards complemented by excitation of group II afferents and group Ib afferents from GTOs during the length and force hold phases. The composite reflex response is thus a complex response elicited by the different afferents filtered by the distributed spinal interneuronalnetwork possibly including recurrent pathways and integrated premotor INs with distributed convergence [203,209–211].

Inhibitory force feedback is predominantly intermuscular and distributed. It may promote proportional coordination of the knee and ankle during locomotion and manage inertial interactions between joints, particularly at higher forces and velocities. Together with length feedback, it may manage limb mechanics at a higher, more global level. Collectively, all sources of force feedback as well as length feedback determine the mechanical properties of the limb as a whole [203,212].

4.2 Changes in α-Motoneuron Excitabiliy

α-MNs receive multifarious direct or indirect inputs via excitatory recurrent axon collaterals (recurrent facilitation), recurrent inhibition via Renshaw cells (Sect 4.4), reciprocal Ia inhibitory interneurons (Sect 4.3), other spinal interneurons, proprio-spinal neurons, diverse sensory afferents, and several supraspinal structures (Fig. 3). The distribution patterns depend on the species, the muscles innervated (e.g., extensors vs. flexors), and their roles in posture and movement. The supraspinal structures include the cerebral cortex, cerebellum, vestibular nuclei, nucleus ruber, reticular formation, and neuromodulatory structures such as the locus coeruleus and raphé nuclei [182,213]. Brain lesions may damage different combinations of descending tracts and thus create different pathological pictures.

In human spasticity, α-MNs are hyper-excitable. This is indicated by various measures. For example, the latency of the reflex response of single motor unit discharge in the biceps brachii of stroke patients was systematically shorter in the spastic muscle compared to the contralateral muscle [214]. Also, motor units in the resting spastic-paretic biceps brachii muscle showed sustained spontaneous discharges,

which increased after voluntary activation on the impaired side [215]. It was suggested that this could be attributed, at least in part, to low-level excitatory synaptic inputs to the resting α-MN pool, possibly from regional or supraspinal centers, while less likely to an increase in PIC activation [216]. Nonetheless, in spastic-paretic biceps brachii muscles, the firing rates of motor units during voluntary contractions were abnormally low and their rate modulation was impaired by running into saturation despite increasing force [217].

Such changes may have anatomical causes. For example, after a SCI, the α-MN somata and dendritic arbors are reduced, which may explain increases in cell input resistance and decreases in rheobase current, alterations in the input/output relationship and hyper-reflexia. Resting membrane potential and spike threshold may or may not depolarize. Voltage-gated ion channels dramatically change and so does α-MN firing after SCI [122]. In part, these changes result from the reduction or complete loss of descending neuromodulation.

4.2.1 Changes in Neuromodulation

As mentioned before, PICs in α-MNs are greatly facilitated by serotonin and noradrenaline released by axons descending from monoaminergic brainstem nuclei [32]. Damage to serotonergic descending axons by SCI changes spinal neuronal activity and has been implicated in paralysis, spasticity, sensory disturbances, and pain. Moreover, loss of 5-HT innervation leads to a disinhibition of sensory transmission. Serotonin denervation supersensitivity is one of the key mechanisms underlying increased α-MN excitability [178].

After SCI, PICs increase in amplitude, which restores α-MN excitability. This recovery may be mediated by hypersensitivity to monoamines in α-MN populations; serotonin (5-HT) receptors become constitutively active following SCI [178]. The increased PIC strength thus enables synaptic inputs to evoke prolonged firing activity in α-MNs. These prolonged excitatory postsynaptic potentials can re-activate the PICs and trigger long-lasting reflexes and muscle spasms. Long-lasting reflexes and self-sustained firing during muscle spasms are associated with the activation of the Ca^{2+} PICs, whereas the slow and regular firing of motor units after muscle spasms are associated with Na^{+} PIC activation [33,122].

4.2.2 Changes in Repetitive Discharge

A characteristic feature of α-MNs is the ability to fire repetitively during sustained current injection. After SCI, changes in repetitive firing appear to be modest, with some reductions in the frequency-current (F-I) relationship, which can be partially reversed if the SCI group is exposed to daily exercise. Spike-frequency adaptation (SFA) is particularly prominent in α-MNs that innervate fast-twitch muscle fibers. After SCI, muscle-fiber types, and the α-MNs that innervate them, revert from diverse slow and fast phenotypes to a more homogeneous fast type [122].

4.2.3 Synaptic Plasticity and Axonal Sprouting

SCI interrupts at least some descending motor and neuromodulatory pathway connections and causes a loss of down-stream activity-dependent processes. This activity loss produces spinal interneuron degeneration and several activity-dependent maladaptive changes that underlie hyperreflexia, spasticity, and spasms [114].

In complete SCI, the loss of long descending connections makes volitional control of movement impossible. Depending on the type and location of incomplete injury, damaged and undamaged neurons show some spontaneous plasticity of the spared axons by sprouting, new synapse formation, and changes in electrophysiological properties. Synaptic connections become stronger and more efficient following short high-frequency bursts and repetitive input (short-term facilitation or LTP, which stands for long-term potentiation, respectively). On a molecular level, single bouts of high-frequency input result in increased neurotransmitter release, while repetitive bouts increase synaptogenesis and synaptic efficiency by modulating post-synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). Conversely, synaptic connections can become weaker and less efficient after low-frequency input. A burst of low-frequency input results in short-term depression and is associated with decreased presynaptic neurotransmitter release and desensitization of AMPA receptors. Repetitive low-frequency input results in long-term depression (LTD), which results in weakened, less efficient synapses, changes in N-methyl-D-aspartate (NMDA) receptor composition, and pruning of unused synapses. In contrast to LTP, LTD diminishes and prunes unnecessary, redundant, and inefficient connections. Hence, LTP involves receptor-mediated plasticity and synaptogenesis of either intact sprouting axons or the regeneration of damaged axons, and LTD does the opposite. Thus, synaptic sprouting and pruning result from LTP and LTD, both may promote recovery and functional improvement. On the other hand, injury-induced plasticity can also be maladaptive, by aberrant sprouting and synaptogenesis as neurons try either to compensate for lost connections or to regenerate through the injury site as they respond to inflammation. Hyperexcitability and inefficiency can result from these new connections, making restoration of normal function difficult [110].

In rats, lesions of the cortico-spinal tract at high cervical level led to significant sprouting of the contralateral ventral CST across the midline into the ipsilesional medial MN column of lamina IX The anatomical plasticity of the medial MN column was critical to post-injury gains in function [218]. Similarly, non-human primates with unilateral cervical SCI showed some improvement in reaching and

grasping over time and this corresponded with changes in the distribution of CST terminals in the spinal gray matter compared to intact macaques [219]. These CST axons rostral and caudal to the injury site terminate in lamina VII, whereas the sprouting fibers synapse near MN pools in lamina IX [110].

Brain-derived Neutrophic Factor (BDNF) is an important regulator of neuronal development, axon growth, synaptic transmission, and cellular and synaptic plasticity. BDNF is also important for the formation and maintenance of certain forms of memory. BDNF is intricately involved in spinal plasticity, including plasticity in response to a SCI, but BDNF actions are multifaceted as it can mediate both adaptive plasticity and maladaptive plasticity. The effects of BDNF relate to nociceptive processes [2,3,220]. While BDNF is pro-nociceptive in the healthy state, it is not after injury, at least acutely. Increases in BDNF after SCI promote adaptive plasticity and functional recovery [221].

One potential mechanism for the hyperexcitability of α-MNs in spastic muscles of stroke patients may be the prolongation of EPSPs produced by group Ia afferents, which would facilitate the temporal summation of successive group Ia EPSPs and make action-potential initiation easier [222].

Plasticity of Postsynaptic Membrane Properties occurs, in part, by altering receptor densities and respective ionic concentration gradients across the cell membrane. Intracellular recordings of α-MNs in the adult rodent sacral spinal cord are sensitive to N-methyl-D-aspartate (NMDA), causing spontaneous bursts of rhythmic activity. After SCI, postsynaptic receptor expression favors excitation over inhibition with increased gene expression for NMDA receptors and down-regulation of GABA receptors and AMPA receptors. Both NMDA and non-NMDA receptor blockade probably prevent excitotoxicity following SCI. Since intracellular Cl^- increases following spinal cord trauma, postsynaptic inhibitory drive onto α-MNs is reduced, leading to a hyperexcitable state [122].

Dorsal root injury caused collateral sprouting of adjacent dorsal root axons into the dorsal horn in cats [223]. Later studies showed that collateral sprouting of primary afferent fibers resulted in recovery of motor function after either dorsal root or SCI. Sprouting of intact propriospinal interneurons following spinal hemisection occurred as a neural mechanism of locomotor recovery. Altered primary afferent input may be transmitted to MNs through deep dorsal horninterneurons, and membrane properties of these interneurons rostral and caudal to SCI demonstrated decreased input resistance and rheobase, indicating a hyperexcitable state [110].

Plasticity of Nociceptive Afferents exert widespread influences on many types of spinal interneurons [182], and their dysfunction could therefore play various roles in pain sensation and motor control. After experimental SCI, nociceptive fibers display maladaptive increases in terminal arborization in the dorsal horn, and exhibit hyperexcitability, and increased spontaneous activity. In patients with SCI, findings suggest that morphological and intrinsic changes in these sensory afferents could, in part, mediate the return of functional sensation, as well as maladaptive allodynia and hyperalgesia, and the development of neuropathic pain. But nociceptive signals are also supplied for tissue and joint protection via reflex arcs to modulate normal motor circuit function and motor output. Therefore, aberrant plasticity of nociceptive afferents may be detrimental to functional recovery following SCI [110].

4.2.4 Changes in Muscle Spindle Afferent Inputs

It has been suggested that increased excitability of the muscle stretch reflex could be due to increased activity of muscle spindle afferents caused by an increased fusimotor bias by γ-MNs, which are under the influence of inhibitory and facilitatory descending pathways. However, augmented spindle afferent discharge and stretch sensitivity, and hence γ-MN activity, has not been confirmed in stroke [224,225] or SCI patients [226]. It is also worth mentioning that muscle spindles issue two types of sensory afferents, group Ia and group II, and these types have some shared monosynaptic connections to α-MNs, but otherwise different effects on spinal neurons [182].

4.3 Changes in Reciprocal Inhibition

It has been shown extensively that spinal networks, such as reciprocal inhibition, recurrent inhibition (Sect 4.4), and presynaptic inhibition (Sect 4.5), are modulated by many descending and sensory inputs [182,213,227]. It is evident, therefore, that the operation of these networks are bound to change after the disruption of descending inputs following SCI and probably also by the modification of sensory inputs, for which there is experimental evidence (Fig. 3).

Reciprocal inhibition is important for regulating the actions of antagonist muscles at a joint. It is mediated by reciprocal Ia inhibitory interneurons which inhibit antagonist α-MNs and receive their (partial) proprioceptive inputs from group Ia fibers whose inputs they share with agonist α-MNs. Moreover, with their corresponding α-MNs, these interneurons share many inputs from descending tracts and various sensory afferents [213].

Inhibition of hindlimb α-MNs from the CST, rubrospinal (RuST), reticulo-spinal (ReST), and vestibulo-spinal (VeST) tracts is largely mediated by reciprocal Ia inhibitory interneurons [199,200,213,228,229]. For example, activation of an extensor α-MN pool by the VeST coincides with inhibition of the antagonist flexor α-MNs by collaterals of extensor-activating tracts.

Reciprocal inhibition may contribute to adjust ankle-joint stiffness. For instance, when the soleus muscle is stretched, its autogenetic stretch reflex increases its stiffness. At the same time, the antagonist TA α-MNs receive increased reciprocal inhibition and their muscle shortens,

which reduces the reciprocal inhibition onto soleus and further increases its stiffness, and vice versa [182,203,210,211, 230]. It is more complicated for co-contractions of antagonists. During co-contractions of TA and soleus, reciprocal Ia inhibition is modulated depending on the soleus/TA activity ratio [231].

Changes in reciprocal inhibition after SCI, mostly tested from TA α-MNs to soleus α-MNs, have been determined many times, and results depend on the site (caudal to rostral), type (contusion, rupture, tumor, section), and extent (complete, incomplete, to what degree) of the lesion. They have been reported as depression or elimination [124,232,233] or replacement with facilitation [234–236].

But if, after iSCI, reciprocal inhibition is replaced with facilitation [135,235], how then does it change to precisely tune co-contraction for ankle stiffness? In other words: What are the mechanisms to adapt it to the new conditions?

During voluntary ankle dorsi-flexion movements in MS patients, reciprocal inhibition and presynaptic inhibition do not increase at movement onset, as is the case in healthy subjects, which may be responsible for the tendency to elicit unwanted stretch reflex activity and co-contraction of antagonistic muscles [237].

In healthy subjects, the stretch reflex increases during voluntary muscle contraction, which is attributed in part to the depression of inhibitory mechanisms. In spastic patients, these inhibitory mechanisms are depressed at rest and cannot be depressed any further. This depression may in part explain the occurrence of co-contraction in antagonist muscles. In most normal movements, antagonist muscles should remain silent and maximally relaxed. This is ensured by increasing transmission in several spinal inhibitory pathways. In spastic patients, this control is inadequate, and therefore stretch reflexes in antagonist muscles are easily evoked at the beginning of voluntary movements or in the transition from flexor to extensor muscle activity [238].

In healthy human subjects, the strength of reciprocal Ia inhibition between ankle flexor and extensor muscles can be temporarily increased by electrically stimulating, for 30 min, the common peroneal (CP) nerve with a patterned input (10 pulses at 100 pulses/s every 1.5 s; mimicking Ia afferent discharge during stepping), but not regular pattern at the same average rate (1 pulse every 150 ms). However, this effect is short-lived. Thus, the patterned stimulation induced, but did not maintain, plasticity. Various mechanisms have been suggested to underlie these observations. The glutamatergic group Ia afferent synapses on the reciprocal Ia inhibitory interneurons could be potentiated. Or the inhibitory synapses on α-MNs could be potentiated. Alternatively, greater excitability of the reciprocal Ia inhibitory interneuron pool could recruit subliminal interneurons or 'latent' inhibitory connections [239].

4.4 Changes in Recurrent Inhibition

In cats, spinal recurrent inhibition is mediated by Renshaw cells (RCs), which receive their most important excitatory input from α-MNs (and some rarer and weaker effects from γ-MNs) and in turn inhibit α-MNs, reciprocal Ia inhibitory interneurons, γ-MNs (weaker and rarer effects), other RCs and cells of origin of the ventral spino-cerebellar tract (VSCT) [165,213,240–247].

Recurrent inhibition is further influenced by sensory afferents and signals descending from supraspinal sources, however it is still not well understood [182]. In cats, RCs receive modulating inputs from the motor cortex, cerebellum, nucleus ruber, reticular formation, and vestibular nuclei. These are in part independent of inputs of the same origin to α-MNs [182].

Descending influences have also been investigated in humans. In healthy subjects, recurrent inhibition is modulated in various conditions, including stance, locomotion, and voluntary movements. For example, compared to upright stance supported by a wall, recurrent inhibition is enhanced in soleus muscle during unsupported free stance. This has been interpreted as a mechanism to diminish the reciprocal inhibition between antagonistic α-MN pools to insure rapid alternating contractions of flexors and extensors for fast stance corrections. Recurrent inhibition is decreased during isolated voluntary plantar ankle flexion carried out by ankle extensor muscles, probably by descending inhibition of RCs. By contrast, recurrent inhibition is increased during co-contraction of plantar- and dorsi-flexors, which might diminish the gain of the stretch reflex and prevent it from falling into oscillations and clonus [227].

In about half of spastic patients, recurrent inhibition is not abnormal, irrespective of lesion site and origin, while in the rest, these factors influence changes in recurrent inhibition. In hemiplegic patients, recurrent inhibition at rest was increased compared to the unaffected side and to healthy subjects. In patients with progressive paraparesis (hereditary spastic paraparesis, ALS), recurrent inhibition was decreased when abnormal. In SCI patients, recurrent inhibition was often increased [227,248]. In other studies, recurrent inhibition has been reported to change after SCI, but in different ways: increase [249], normal, reduced, or absent [248].

Changes of recurrent inhibition in spasticity are complicated, probably reflecting the different kinds of lesions. If the above results somewhat represent the operations of recurrent inhibition under natural conditions, their effects would not simply be mirrored by changes in reciprocal inhibition because the latter would be additionally determined by inputs other than recurrent inhibition.

Siembab *et al.* [250] argue that the competition of α-MN axon synapses and group Ia afferent synapses on RCs is subtle and specific to VGLUT1 synapses (at central group Ia afferent terminals) and cholinergic VAChT synapses (at α-MN axon terminals), but not VGLUT2 synapses (at other

glutamatergic afferents). "One intriguing possibility is that the synaptic formation and maintenance of VGLUT1 and motor synapses involve competition for some critical, limited, RC-derived factor (that could be related to electrical activity or not) on which VGLUT2 synapses do not depend". For example neuregulin-1, neuroligin-1 or gephyrin [250]. The functional rationale for these maturation processes and their underlying mechanisms need to be more fully explored, but they suggest that RCs might play a strong role in ontogenetic plasticity.

In neonatal mice, RCs receive monosynaptic proprioceptive inputs, likely group Ia, which subsequently lose weight because of increasing Renshaw cell dendritic growth [122,250–253]. One reason could be that different synaptic inputs on RCs compete. Strengthening of proprioceptive inputs reduces α-MN axon synaptic density on RCs. Absent or diminished sensory afferent inputs correlate with increased densities of α-MN axon synapses. In contrast, the normal developmental retraction of afferent inputs to RCs and α-MNs does not occur after complete SCI, which leaves RCs with few collateral fibers from α-MNs [254]. Also, increasing sensory activity with electrical stimulation induces axonal withdrawal and decreases connections of the CST onto α-MNs and interneurons. Conversely, a decrease of sensory afferent activity by rhizotomy increases CST connections [255]. Hence, afferent stimulation affects the CST development, and CST stimulation affects the development of sensory afferent inputs [256], indicating that proprioceptive afferents and descending fibers compete for contribution to normal spinal circuitry formation [114,122].

One hypothesis regarding the potential role of α-MNs, their proprioceptive inputs, and interneurons including RCs in spinal motor learning has recently been put forward by Brownstone *et al*. [257]. They suggest that α-MNs are controllers effecting muscle contractions and thus posture and movement. Group Ia afferents originating in muscle spindles and contacting α-MNs monosynaptically provide 'instructive' feedback about the ongoing motor actions. RCs, fed by an efference copy of the α-MNs' outputs, generate a 'predictive' feedforward signal reflecting the expected sensory consequences. The instructive and predictive feedback signals are then compared at the level of α-MNs that have a hybrid role in being the controllers as well as the comparators that compute a 'sensory prediction error' used to adapt system parameters. This arrangement could be regarded as a 'fundamental learning module', which "offer(s) the flexibility for both short-term adjustments, and a circuit in which plasticity can lead to long-term changes" [257]. An important point is the balance between the two types of α-MN input, group Ia afferents and RCs. If this balance is disturbed, plastic processes should restore it. The model suggested by Brownstone *et al*. [257] employs supervised learning, as proposed by the authors in reference to cerebellar learning. This hypothesis is important in that it defines an instructive signal initiating the learning process, but the detailed mechanisms are not yet known.

Important progress has been made by targeting RCs by genetic modification. In mice, Enjin *et al*. [258] used the selective expression of the nicotinic cholinergic receptor2 (Chrna2) to genetically target the vesicular inhibitory amino acid transporter (VIAAT) in RCs. Loss of VIAAT from Chrna2Cre-expressing RCs had the following consequences. In adult mice, the loss of VIAAT had no effect on grip strength, change in gait, or motor coordination. In neonatal mice, the loss of VIAAT did not alter drug-induced fictive locomotion. However, α-MNs developed a lower input resistance and an increased number of proprioceptive glutamatergic and calbindin-labeled putative Renshaw cell synapses on their soma and proximal dendrites. Additionally, α-MNs received spontaneous inhibitory synaptic input at a reduced frequency and RCs exhibited increased excitability despite receiving a normal number of cholinergic α-MN synapses [258].

The above results suggest plastic compensation within the proprioceptive-α-MN-Renshaw cell circuit. Surprisingly, the elimination of RCs output elicited distributed plastic changes in proprioceptive-α-MN-Renshaw cell function. The precise mechanisms leading to the coordinated plastic changes have yet to be elucidated.

4.5 Changes in Presynaptic Inhibition

Spinal presynaptic inhibition provides a mechanism by which signal flow from segmental sensory afferents into the CNS may be modulated and regulated at the first central synapse. Presynaptic inhibition is produced predominantly by GABAergic interneurons acting on $GABA_A$ receptors on primary sensory terminals [166–168]. GABAergic interneurons depolarize primary sensory afferents of all classes, which can be recorded in the dorsal root as primary afferent depolarizeation (PAD). Presynaptic inhibition shows complicated input-output patterns with a fair degree of functional differentiation that suggests the existence of several interneuronal sub-populations, in part with different locations. Presynaptic inhibition is modulated by a variety of descending and sensory systems. Proprioceptive afferents also regulate the level of their presynaptic GABAergic inhibitory input in an activity-dependent manner. This retrograde influence thus constitutes a feedback mechanism by which excitatory sensory activity drives GABAergic inhibition to maintain circuit homeostasis [259].

Animal and human studies have shown that presynaptic inhibition can be set to different mean levels and modulated dynamically during rest, locomotion, and voluntary movement [149,162]. For example, inhibition becomes weaker during voluntary contraction [260]. Also, synaptic transmission from group Ia muscle spindle afferents to α-MNs is presynaptically inhibited more strongly during stance than rest, more strongly during locomotion than rest, and more strongly during running than walking [169,261]. In humans, presynaptic inhibition of group Ia afferent terminals on α-MNs of voluntarily contracting mus-

cles is decreased, while presynaptic inhibition of group Ia fibers to α-MNs of muscles not involved in the contraction is increased. Hence, the control of presynaptic inhibition of group la fibers at the onset of movement may be organized to help achieve selectivity of muscle activation [262].

The disruption of descending tracts should change the operation of presynaptic inhibition. It should be noted that, in humans, presynaptic inhibition suppresses different reflexes differently, where H-reflexes are suppressed strongly and stretch reflexes undergo little supression [263]. SCI has been suggested to lead to hyporeflexia during the 'spinal shock' because of an initial increase in the efficacy of presynaptic inhibition. Afterwards, over the time of chronification, presynaptic inhibition of ankle extensor group Ia input declines to levels less than those of control subjects, thereby contributing to enhance spinal reflexes, consistent with the clinical state of 'spasticity' [264]. Evidence for this comes from data obtained in paraplegics with bilateral spinal cord lesion sugesting that presynaptic inhibition of soleus group Ia terminals was decreased [1,265]. More direct evidence for decreased presynaptic inhibition was found in decerebrate rats, in which chronic SCI decreased presynaptic inhibition of the plantar H-reflex through a reduction in primary afferent depolarization (PAD) evoked by stimulation of the posterior biceps-semitendinosus (PBSt) muscle group I afferents [266]. Thus, after SCI, the supraspinal control of interneurons mediating PAD is disengaged, which suggests an augmented role for sensory afferents.

5. Final Comments

The musculo-skeletal system is multi-variate, nonlinear, time-varying and complex. It is difficult to "understand how these structures define the control problems that are solved by the nervous system" [165,267]. The upper CNS echelons appear to be heavily involved in solving these problems, but "the spinal cord circuitry is in fact capable of solving some of the most complex problems in motor control and, in that sense, spinal mechanisms are much more sophisticated than many neuroscientists give them credit for" [268]. Specifically, the vertebrate spinal cord can solve, at least to some degree, e.g., the degrees-of-freedom problem, the problem of complex spatial sensory-motor transformations, and the inverse-dynamics problem [268].

Among the many challenges that organisms face are perturbations that originate externally or internally and are either harmless or deleterious in nature. Here we have reviewed damage to the nervous system to which mammals must react. These reactions may be direct or indirect consequences of the original lesions or attempts to adapt to the circumstances so as to make the best of the situation and potentially come up with a solution to keep going.

Despite the variability of symptoms and anatomical/functional alterations depending on species and lesion sites, one symptom appears to be ubiquitous: spasticity. It may be speculated, therefore, that spasticity has developed trans-individually as a common adaptation with a beneficial effect, namely stabilization of stance and locomotion against weakening muscles. It may be regarded as an outcome of trying to find a solution to changed circumstances. Other learning processes may be taylored to provide individual solutions for particular problems.

"There is a third solution that is based on trial-and-error learning, recall and interpolation of sensorimotor programs that are good-enough rather than limited or optimal. The solution set acquired by an individual during the protracted development of motor skills starting in infancy forms the basis of motor habits, which are inherently low-dimensional" [5].

Thus, after lesions and the loss of substantial descending inputs, the CNS has to learn new sensory-motor programs that are sufficient to restore some motor capacity. Since favorable programs depend on the precise site and extent of the lesions, they must be taylored to individual circumstances, using trial-and-error learning supported by inputs that mirror the sensory feedback occurring during natural movements such as locomotion. In so doing, the re-designed spinal circuits must be able to cope with old problems. Important roles in doing so are played by interneuronal networks.

"Engineers use neural networks to control systems too complex for conventional engineering solutions. To examine the behavior of individual hidden units would defeat the purpose of this approach because it would be largely uninterpretable. Yet neurophysiologists spend their careers doing just that! Hidden units contain bits and scraps of signals that yield only arcane hints about network function and no information about how its individual units process signals. Most literature on single-unit recordings attests to this grim fact" [269].

The workings of spinal neuronal networks on the backstage will never be figured out. An important characteristic of these networks is the wide and often semi-random connectivity between several descending systems, sensory inputs from diverse muscles, joints and cutaneous sources to α-MNs, and among interneurons themselves. Contributors to these extended networks may also be the diffuse, but modest, effects of group Ia afferent fibers, which include reciprocal inhibition and recurrent inhibition, that contrast the more concentrated and stronger effects at individual joints. The convergence of group Ia, group II, and group Ib afferents in conjunction with other mechano-receptor afferents onto common neurons and the wide distribution of related reflex effects from many muscles throughout the limb would enable the handling of the complex peripheral biomechanics, regulating both more local and individual muscle properties such as stiffness and non-linearities as well as transjoint limb mechanics [182].

The impenetrability of the backstage network has advanced experimentally more accesible networks like reciprocal Ia inhibition, recurrent inhibition and presynaptic in-

hibition onto the frontstage. But it should not be forgotten that the latter are complex networks in their own right [182].

Abbreviations

ALS, amyotrophic lateral sclerosis; α-MN, α-motoneuron; AMPA, α-amino-3-hydroxy-5-methylisoxazol-4-propionic acid; BDNF, brain-derived neutrophic factor; 5HT, 5-hydroxytryptamine, serotonin; C1-C8, cervical spinal segments; Chrna2, nicotinic cholinergic receptor2; CIN, commissural interneuron; CNS, central nervous system; COM, center of mass; COP, center of pressure; CP, common peroneal; CPG, central pattern generator; CST, cortico-spinal tract; DOF, degree of freedom; DSCT, dorsal spino-cerebellar tract; EMG, electromyogram, electromyography; EPSP, excitatory post-synaptic potential; GABA, gamma-aminobutyric acid; H-reflex, Hoffmann reflex, elicited by electrical stimulation of group Ia fibers from muscle spindles in a muscle nerve and measured as short EMG wave in the related muscle; γ-MN, γ-motoneuron; IN, interneuron; IPSP, inhibitory post-synaptic potential; L1-L7, lumbar spinal segments; LMC, lateral motoneuron column; LPN, long proprio-spinal neurons; MAG, myelin-associated glycoprotein; MG, medial gastrocnemius; MLR, medium-latency reflex, also M2; MMC, medial motoneuron column; MN, motoneuron; MND, motoneuron diseases; MS, multiple sclerosis; *mSOD1-G93A*, mouse model of ALS; MVC, maximal voluntary contraction; NMDA, N-methyl-D-aspartate; NMDAR, N-methyl-D-aspartate receptor; OMgp or Omg, oligodendrocyte myelin glycoprotein; pTDP-43, phosphorylated protein TDP-43; PIC, persistent inward current; PSI, presynaptic inhibition; PLR, postural limb reflex; PSP, post-synaptic potential; RCs, Renshaw cells; recIaIN, reciprocal Ia inhibitory interneuron; RF, brainstem reticular formation; ReST, reticulo-spinal tract; RuST, rubro-spinal tract; SC, spinal cord; SCI, spinal cord injury; SLR, short-latency reflex, also M1; SMA, spinal muscular atrophy; *SMN1*, motor neuron 1 gene; *SMN2,* motor neuron 2 gene; *SMN*Δ*7*, mouse model of spinal muscular atrophy; *SOD1*, mouse model of ALS; SOD-93, mouse model of ALS; TA, tibial anterior; TNF, tumor necrosis factor; VAChT, vesicular acetylcholine transporter; VGAT, vesicular GABA transporter; VGLUT, vesicular glutamate transporter; VIAAT, vesicular inhibitory amino acid transporter; VOR, vestibulo-ocular reflex; VSCT, ventral spino-cerebellar tract; VST, vestibulo-spinal tract.

Author Contributions

UW: Coceptualized and designed the review, conducted literature search, writing of the main part of the text; PD: Contribution of some parts of the text, designed the figures, revision and editing of the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

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