Neurotherapeutics (2018) 15:588–603
https://doi.org/10.1007/s13311-018-0638-z

REVIEW

Cortical Reorganization of Sensorimotor Systems and the Role of Intracortical Circuits After Spinal Cord Injury

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Published online: 7 June 2018

Abstract

The plasticity of sensorimotor systems in mammals underlies the capacity for motor learning as well as the ability to relearn following injury. Spinal cord injury, which both deprives afferent input and interrupts efferent output, results in a disruption of cortical somatotopy. While changes in corticospinal axons proximal to the lesion are proposed to support the reorganization of cortical motor maps after spinal cord injury, intracortical horizontal connections are also likely to be critical substrates for rehabilitation-mediated recovery. Intrinsic connections have been shown to dictate the reorganization of cortical maps that occurs in response to skilled motor learning as well as after peripheral injury. Cortical networks incorporate changes in motor and sensory circuits at subcortical or spinal levels to induce map remodeling in the neocortex. This review focuses on the reorganization of cortical networks observed after injury and posits a role of intracortical circuits in recovery.

Keywords Motor cortex · Somatosensory cortex · Cortical reorganization · Plasticity · Spinal cord injury · Intracortical circuits · Rodents · Primates

Introduction

The primary motor cortex is a critical center for the planning, initiation, and execution of movements [1, 2]. The appropriate topographic organization of the motor cortex is essential for mediating these functions, and it is during development that this body map arises [3]. Cortical motor maps are shaped through the anatomical refinement of cortical output [4] as well as the strengthening of intrinsic connectivity [5]. The primary motor cortex (M1) exhibits extensive intrinsic connectivity [6–8] in addition to topographic connections with a myriad of cortical and subcortical targets [9–14].

Importantly, cortical motor maps are plastic and reorganize in response to skilled learning, altered sensory experience, amputation, peripheral nerve and spinal cord injuries, as well as cortical injuries such as stroke. Motor skill training results in reorganization of movement representations across mammalian models [15–17]. In primates, motor training on specific tasks that engage the distal muscles of the hand results in differential expansion of digits or forearm representations in the motor cortex [15]. Similarly, rodents exhibit cortical reorganization during dexterous motor learning. Training on a skilled reach task, but not an unskilled one, drives an increase in the movement representations of the distal forelimb at the expense of more proximal representations [17]. The correlation between forelimb behavior and the expansion of motor representations indicates that the neurophysiological substrate for skilled motor learning resides in the motor cortex.

In addition to motor learning, cortical representations are shaped, in part, by somatosensory feedback. Early somatosensory experience shapes movement representations in the motor cortex. In rodents, this is evident as unilateral whisker trimming at birth, but not in adulthood, results in a smaller whisker representation in the contralateral motor cortex [18]. Physiologically, this results in lower thresholds for evoking bilateral or ipsilateral whisker movements. The mature motor cortex is more resistant to the altered tactile experience than neonatal M1, indicating that the motor cortex undergoes an experience-dependent critical period during development.

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While the cortex is less plastic in the adult than in the neonate, injury can still dramatically alter cortical motor and sensory maps. Peripheral nerve injuries and amputation in the adult can both silence large sections of de-afferented cortex and result in the generation of new topographic representations of the body regions spared by injury [19, 20]. Spinal cord injuries in both humans and animal models result in varied extents of cortical reorganization over periods ranging from weeks to years. Rehabilitation after injury further shapes cortical reorganization, likely leveraging the same circuit mechanisms as those used during motor learning, albeit now on top of an altered neural architecture. A mechanistic understanding of this plasticity will drive the refinement of rehabilitation strategies and provide targets for therapeutic intervention.

Motor Cortex in Mammals

In the latter part of the nineteenth century, Fritsch and Hitzig found that stimulation of the frontal cortex in dogs evokes body movements and that the type of movement evoked varied with cortical location. They also found that surgical lesions of the frontal motor sites did not abolish movements [21]. Ferrier identified a similar cortical topographic motor map in primates [22]. Similar to these animal models, the somatotopic cortical map was confirmed by cortical mapping experiments in awake humans [23]. The first evidence of the plasticity of this topography arose from the studies of Sherrington, who described the instability of cortical representations in primates and concluded that "the motor cortex is a labile organ" [24]. These topographic maps are not simple point-to-point representations of individual motor units, but complex networks representing functional motor movements. This is apparent as long-duration microstimulation of the motor cortex recruits large regions of the motor network and elicits ethologically relevant complex movements [25, 26].

The primate neocortex has many different motor cortical areas, which play specific roles in planning, initiation, coordination, and control of movements. For example, neurons in the primary motor cortex have been proposed to control the muscles directly via spinal motor neurons, whereas the more upstream areas such as the premotor and supplementary motor areas play a role in planning and coordination of movements [1, 2, 27, 28]. More primitive mammals, such as opossums, lack distinct sensory and motor representations in their cortex, instead consisting of a "sensorimotor amalgam" [29]. Both rats and mice do have a true motor cortex located rostral to the somatosensory representation, with movements evoked at relatively low microstimulation thresholds and containing a rough mirror image of the primary somatosensory cortex (S1) representation [30–33]. The separation of S1 and M1 is not complete in rodents, however, as some overlap occurs over most of the hindlimb and part of the forelimb representations [9, 31, 33, 34]. The sensorimotor overlap may reflect the remnants of evolutionary segregation of the sensorimotor systems or perhaps a specialization for immediate proprioceptive feedback within the motor cortex of rodents [35].

In rodents, the primary motor cortex has been completely delineated with a musculotopic representation of different body parts [30, 31, 33, 36, 37]. The body motor maps include the whisker, forelimb, hindlimb, trunk, neck, and jaw. Two distinct forelimb representations exist in the rodent motor cortex, the caudal forelimb area (CFA) and rostral forelimb area (RFA). CFA and RFA are suggested to be either part of a fractured M1 forelimb representation [30] or as two distinct motor areas [38]. Details of evoked movements are markedly different in these two forelimb motor areas in rats and mice. In rats, CFA has representations of elbow and wrist whereas RFA has additional representations of digits [17]. Excitatory and inhibitory neurons in both RFA and CFA are active during the skilled movements of a reaching task in rats [39, 40]. Additionally, activity of RFA neurons is greater during the preparatory phase of forelimb movements, indicating that this forelimb region may integrate motor information with internal state information to adapt to specific motor behaviors [40].

In mice, however, electrophysiological mapping of CFA shows representations mostly of digits whereas RFA shows representations of elbow and wrist [33]. Optogenetic mapping of mouse motor cortex shows evoked distal and proximal muscle movements in RFA and anteromedial CFA, with posterolateral regions of CFA preferentially activating more proximal muscles [14]. The corticospinal neurons active prior to grasping during a skilled reach task are clustered in more rostral forelimb cortical areas [14]. The structure and organization of the sensorimotor cortex support both the execution of highly coordinated, skilled movements, and the plasticity to adapt to new motor skills. In the case of injury, this plasticity will be required for relearning previously acquired motor skills during rehabilitation.

Cortical Reorganization After Peripheral and Central Injuries

In some of the earliest studies on cortical plasticity, the brain was deprived of afferent input by cutting the median nerve to hand in owl and squirrel monkeys [19]. The median nerve innervates the radial half of the glabrous hand. If the somatosensory cortex is mapped immediately after such a deprivation, parts of the median nerve territory are activated by expanded representations of the radial nerve inputs from the hairy skin on the back of the hand. If both median and ulnar nerves are transected, the entire hand representation in the

cortex is deprived of its glabrous inputs and, over a period of several months, becomes responsive to stimulation of the back of the hand. When radial nerve transection is performed in combination with that of the median or ulnar nerve, the cortex remains silent permanently. Thus, the extent of cortical reactivation following nerve transection seems to depend on the innervation pattern of nerves rather than on the extent of deprived skin or the central cortical territory [19].

Similar to the changes observed in somatosensory maps, motor maps reorganize in response to peripheral injury, in both neonatal and adult animals [20, 41, 42]. Forelimb amputation results in expansion of the shoulder and stump representations into the de-efferented forelimb motor cortex in rodents and primates [20, 43–45]. In primates, stimulation in de-efferented M1 elicits movements of the remaining proximal muscles as well as movements from adjacent body representations [44, 45]. Similarly, rats with neonatal forelimb amputation exhibit enlarged evoked shoulder and vibrissa representations [20, 46]. This plasticity is reciprocal, as facial nerve transection results in the enlargement of forelimb and eye/eyelid motor representations into the de-efferented vibrissa area [20]. Cortical reorganization occurs within hours of the facial nerve transection and is dependent upon horizontal projections from the converted whisker cortex [5, 41, 42]. These latent intracortical connections are unmasked immediately following injury and provide a substrate for further cortical remodeling following de-efferentation.

In the case of central injuries such as stroke, the movement representations or cortical areas adjacent to the cortical lesion have been shown to support the relearning of motor skills through reorganization [15, 47–49]. In primates, focal ischemic infarcts result in the reduction of digit representations adjacent to the lesion and the enlargement of adjacent proximal representations with a corresponding impairment of skilled digit use [48]. Retraining of skilled hand use after similar infarcts results in the reestablishment of hand territory adjacent to the infarct [50]. This expansion of hand representations into regions formerly occupied by elbow and shoulder occurs coincident with the rehabilitation of skilled hand function [50]. Following ischemic infarcts in the primate hand representation of M1, there is also an increase in the hand representation in remotely located ventral premotor cortex [49]. In rats that recover motor function after bilateral ablations of the forelimb motor cortex, stimulation of the adjacent cortical area evokes forelimb movements [47]. A second ablation of this reorganized cortical area results in further behavioral impairment [47]. These results suggest that, after local damage to the motor cortex, rehabilitative training engages mechanisms of motor learning in the spared, adjacent cortex.

Neonatal animals exhibit an even more robust capacity for cortical reorganization after injury than adults. In rats with neonatal hemidecortication, the sensorimotor network in one hemisphere is disrupted. However, these animals exhibit a marked ability in reaching and grasping movements in the contralesional side of the forelimb when tested as adults. Secondary lesion of the remaining contralesional sensorimotor cortex results in a severe impairment of both forelimbs, suggesting that the sensorimotor cortex on the contralesional side supports the formation of a novel, ipsilateral motor network to control the movement of both forelimbs [51, 52]. The remaining hemisphere exhibits aberrant projections to the different subcortical motor structures as well as ipsilateral and contralateral spinal cord, a result of the lack of competition-based, activity-dependent refinement from the absent cortex [51, 53–55]. Ascending sensory pathways also reorganize following neonatal hemidecortications with the formation of bilateral thalamic projections from the dorsal column nuclei [56]. Leveraging the robust plasticity of the immature nervous system is one potential approach to supporting functional cortical reorganization in the adult after injury.

Reorganization of Motor Cortex After Spinal Cord Injury

Unlike stroke, after spinal cord injury, the cortical substrate remains intact, while the input and output of large cortical areas may be interrupted. Therefore, for meaningful functional recovery after injury to occur, mechanisms of cortical plasticity will be required for the cortex to relearn previous motor patterns using an altered motor pathway. Humans, primates, and rodents all show changes in cortical motor maps after spinal cord injury [57–72]. In humans with spinal cord injury, there is increased activity in existing and novel areas within motor, somatosensory, and parietal cortex, as well as in the thalamus, basal ganglia, and cerebellum during movement execution, in comparison to controls [73–77]. This is characterized by distinct shifts towards the de-efferented motor regions, secondary motor areas, and somatosensory cortex [73, 77–84]. Activation of novel secondary motor areas immediately after injury could reflect their involvement in the development of new motor strategies. The resting-state functional connectivity between brain regions also seems to change after spinal cord injury in humans [85–87].

Evidence from primates indicates that cortical plasticity occurs alongside compensatory functional recovery from spinal cord injury. After an incomplete, low cervical injury, reorganization of the hand/digit motor regions parallels recovery of manual dexterity [60]. In digit regions that do not recover or become unresponsive after injury, representations of the face or more proximal arm arise [60, 61]. The ipsilateral motor cortex and callosal projections may contribute to compensatory recovery after injury as well. Compensatory mechanisms at the cortical level have been shown to mediate behavioral recovery of finger dexterity after cervical (C4–C5) spinal cord injury. After mid-cervical injury, the bilateral motor cortex is

active during the early stages (first 6–7 weeks) of behavioral recovery while more extensive reorganization of the contralesional primary motor cortex occurs during later stages (3–5 months) [59]. The early involvement of ipsilateral motor areas may be due to latent ipsilateral corticofugal projections, such as those observed in rodents that contribute to ipsilateral motor maps after unilateral transection of the corticospinal tract [88].

As in primates, rodents show a significant alteration in cortical motor maps after spinal cord injury. In the rat, thoracic dorsal column injury of the descending corticospinal tract and ascending sensory fibers results in a loss of hindlimb-evoked movements and the expansion of forelimb, whisker, and trunk movements into the de-efferented hindlimb motor cortex 4 weeks later [64]. Mid-cervical spinal hemisection affects the sensorimotor performance and electrophysiological maps in rat motor cortex in a similar manner. At 1–2 months after hemisection, spared shoulder and elbow movements are over-represented in the M1 map, consistent with recovered proximal forelimb movements in rats [67] (Fig. 1). These disrupted cortical motor maps persist in a long term in rats after cervical spinal cord injury, with an enduring expansion of whisker and neck representations and an emergence of ipsilateral forelimb movements when measured between 5 and 15 months post injury [68] (Fig. 1).

Just as in motor learning, these altered maps respond to training in the form of rehabilitation. Robotic rehabilitation that promotes hindlimb weight support, or rehabilitation coupled with pharmacological treatment with serotonergic agonists, drives the reorganization of trunk representations in rats after a low thoracic spinal cord injury [69–71]. A similar reorganization of the motor cortex after mid-cervical dorsal column injury has been observed with rehabilitation in mice. The de-efferented hindlimb cortical representation is recruited to control forelimb motor function [65]. The reorganized motor cortex provides the substrate by which rehabilitation supports recovery, as lesioning the areas recruited through rehabilitation reverses the gains in behavioral recovery [71].

Studies have largely attributed cortical reorganization in rodents to remodeling of the corticospinal tract or other descending tracts [64, 89–93]. This is due, in part, to the observation that injured, and intact, axons departing the cerebral cortex (corticofugal axons) have been found to elicit new growth coincident with the changes in cortical motor maps. After thoracic injury, large-scale structural changes of corticospinal axons occur rostral to the injury concomitant with shifts of forelimb, trunk, and vibrissae movements into de-efferented hindlimb motor areas [64]. Anterograde tracing of the corticospinal axons originating from hindlimb regions revealed an increase in collateral sprouts into the cervical spinal cord [64]. This increase in axonal sprouting has also been confirmed by retrograde tracing of corticospinal neurons located in the rostral part of the former hindlimb motor cortex [94]. Similar changes occur in the corticospinal projection of the intact ipsilesional cortex of adult rats after cervical spinal cord lateral hemisection [95]. The minor dorsolateral and ventral corticospinal tracts may also support cortical reorganization in the rodent. Sprouting of the spared, ventral corticospinal tract after injury supports recovery of skilled forelimb reaching [96], a behavior dependent on cortical reorganization. Additionally, the dorsolateral corticospinal axons in the mouse appear to support both the behavioral recovery from high cervical spinal cord injury and the return of impaired cortical maps, though with little displacement from

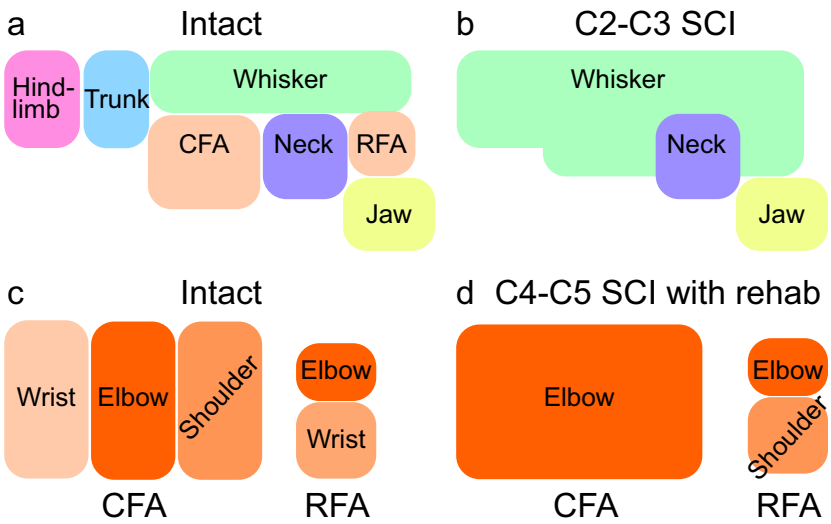

Fig. 1 Cortical motor map changes after cervical spinal cord injury in rodents. Representative changes in maps of evoked output in rodents after high (C2–C3) or mid (C4–C5) spinal cord injury. **a** Topographic organization of the motor cortex in intact rats (adapted from [31]). **b** High cervical injury results in an aberrant motor map at chronic time points. Intact whisker representations expand into de-efferented areas (adapted from [68]). **c** Topographic representation of proximal and distal forelimb muscles in CFA and RFA. **d** After mid-cervical injury and rehabilitation, proximal elbow and shoulder movements expand in both CFA and RFA (adapted from [67])

the intact positions [66]. The extent of spontaneous remodeling of the corticospinal tract in primates is greater than that in rodents and has been proposed to support the recovery of function after spinal cord injury [97–100].

Whether or not novel corticospinal circuits underlie motor map reorganization during rehabilitation from injury is unclear. Alternative pathways for cortical input to the spinal cord exist and even arise as collateral projections from corticospinal neurons. After bilateral transection at the level of the medullary pyramids (pyramidotomy), injured corticospinal axons sprout into the red nucleus, supporting recovery of skilled forelimb function [91]. Chemogenetic silencing of the injured corticospinal neurons, or forelimb motor cortex stroke, disrupts this behavioral recovery [91]. Additional corticofugal pathways likely contribute to the recovery of skilled function. Reticular nuclei are critical mediators of skilled motor control [101], and axonal plasticity of reticulospinal projections can contribute to locomotor recovery [92, 93].

Regardless of the specific corticofugal pathway involved, widespread changes in descending motor circuits after spinal cord injury will require remodeling of intracortical connections in order to generate functional motor networks. Spinal cord injury disrupts cortical networks with effects on corticospinal dendrites. Both injured and non-injured layer 5b neurons in hindlimb cortical areas begin to show a reduction in dendritic spines within the first week after thoracic spinal cord injury [102–105]. This reduction in spines proceeds over a time scale ranging from days to months, with continuous remodeling of the dendritic spines in the hindlimb representation after thoracic injury. Injury reduces the number of stable spines, increasing spine elimination and the formation of immature, filopodia-like spines [105, 106]. Spine loss may contribute to the altered cortical maps observed in the days following spinal cord injury, disconnecting injured corticospinal neurons from cortical motor networks. In this case, rehabilitation and remodeling of intrinsic axons would require a commensurate dendritic and synaptic remodeling of corticospinal neurons to support functional recovery. Additionally, spinal cord injuries, specifically those that disrupt the ascending dorsal column-medial lemniscal system, will also alter the nature of sensory input to the motor cortex.

In primates, it has been shown that lesions of the dorsal column-medial lemniscal pathway affect the organization of the motor cortex. Sensory inputs occupy a significant role in the development and retention of hand motor control. In juvenile primates, the functional organization of the motor cortex is altered by mid-cervical dorsal column injury of the ascending dorsal column-medial lemniscal sensory pathway. Digit representations are reduced, and the lowest stimulation thresholds are found for wrist or elbow movements, rather than for movement of the digits [62]. In adult primates, mid-cervical dorsal column injuries result in permanent deficits in the use of digits for precision grip and a loss of fractionated digit movement and reorganization of the motor cortex [63]. Electrophysiological mapping has revealed that extension-flexion movements of the thumb decrease and adduction-abduction movements increase after cervical dorsal column injury. Additionally, threshold currents required to evoke movements of the digits increase following the loss of ascending sensory input [63].

Reorganization of Somatosensory Cortex After Spinal Cord Injury

In contrast to the conserved motor network remodeling after spinal cord injury, there is less consensus on sensory network reorganization across animal models. Sensory reorganization in humans shows medial shifts in sensory regions with spared input into the de-afferented primary sensory cortex [107]. Similarly, in primate models, primary somatosensory cortex area 3b shows disrupted sensory maps after spinal cord injury and depends on thalamic input of mechanoreceptive information from the dorsal column-medial lemniscal system. Mid-cervical dorsal column lesions result in the interruption of ascending afferents and an initial loss of responsiveness of area 3b hand representations, followed by an eventual shift to responsiveness to tactile face stimulation [108]. Incomplete dorsal column injury results in an eventual recovery of hand representations at several months after injury [109]. This recovery is attributed to a few spared axons and a second-order spinal cord pathway arising from lamina IV below the level of the lesion that projects to the cuneate nucleus through the lateral funiculus [109, 110].

Unlike the motor cortex, reorganization of sensory maps appears to occur earlier in the circuit, as evidenced from the expansion of face representations in the ventroposterior nucleus of the thalamus [111]. Rather than a cortical mechanism supporting plasticity in somatosensory area 3b, the expansion of face representations is owed to changes at the level of the brainstem [112, 113]. Face afferents from the trigeminal nucleus of the brainstem sprout and grow into the cuneate nucleus in adult monkeys after lesions of the dorsal columns (Fig. 2) [114]. However, with a full de-afferentation of the cuneate nucleus following a C1 lesion, no responses to face stimulation are observed in the dorsal column nuclei at 2 years after injury [115]. The absence of facial responses may owe to the loss of cuneate input from the transverse cutaneous nerve of the neck, with receptive fields overlapping with the mandibular branch of the trigeminal nerve. Furthermore, the loss of input to the cuneate nucleus results in a trans-synaptic degeneration of both medial lemniscal and thalamocortical projections, potentially unmasking latent intracortical connections between somatosensory representations [115].

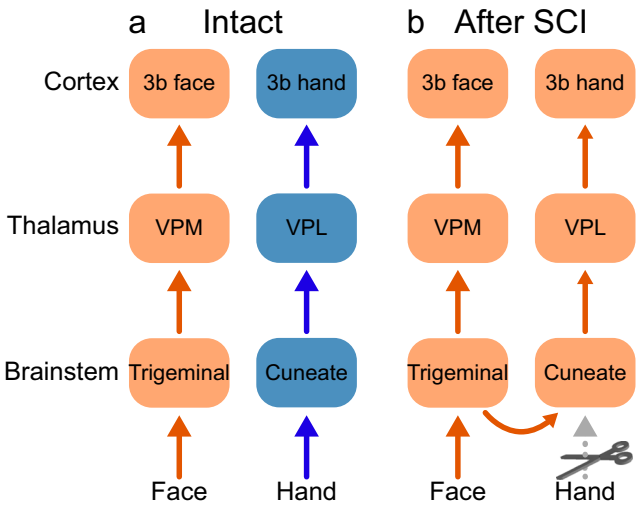

Fig. 2 Sprouting in brainstem nuclei mediates cortical reorganization after spinal cord injury in primates. **a** Mechanoreceptive sensory information from the hand and face ascend through the brainstem and thalamic nuclei into area 3b of the somatosensory cortex through parallel pathways. **b** After cervical spinal cord injury, sprouting occurs within the brainstem as collaterals sprout from trigeminal to cuneate nuclei. This adaptation results in face responses within the de-afferented hand representations in area 3b (adapted from [112, 114])

Brainstem plasticity has been demonstrated in other species after de-afferentation. Cervical transection of dorsal roots (rhizotomy) in the rat has been shown to increase projections from fasciculus gracilis into the cuneate nucleus [116]. Aberrant cortical representations do appear to depend on changes in brainstem circuitry after spinal cord injury, as selective inactivation of the reorganized cuneate nucleus eliminates the face expansion in area 3b [112]. In contrast, inactivating the normal face representation within area 3b does not affect the face expansion, indicating a limited role of intracortical reorganization [112].

The anatomical plasticity of brainstem nuclei is in contrast to that of the somatosensory cortex. Dorsal column lesions in macaque monkeys do not result in large-scale remodeling or significant axonal sprouting across the hand face border in either area 3b of the primary somatosensory cortex or ventroposterior nucleus of the thalamus [117]. Smaller, more limited changes have been observed in intracortical connectivity between hand and face sensory representations after dorsal column injury in primates (Fig. 3) [119]. The reorganization that occurs in lower levels of sensory circuits extends into other higher somatosensory areas as well, including secondary somatosensory cortex (S2) and parietal ventral area (PV) of the lateral sulcus [120]. Following dorsal column lesion, former hand regions in S2 and PV receive inputs from the face, but in a more restricted manner than in area 3b of S1 [120]. The spontaneous reorganization of somatosensory areas may give rise to perceptual abnormalities such as phantom sensations, common in patients with spinal cord injuries or amputations [121, 122]. Remodeling the aberrant somatosensory circuits induced by injury may be a mechanism to limit the adverse effects of somatotopic reorganization.

In rodents, there is conflicting evidence over the extent of sensory cortex remodeling after spinal cord injury. In rats, neonatal cervical over-hemisection results in a more limited reorganization of the resulting adult primary sensory cortex than that observed in primates [123]. Neurons in the forepaw regions do not respond to face stimulation, but rather to stimulation of upper arm afferents that enter the spinal cord rostral to the site of lesion [123]. In adult rats, thoracic dorsal column lesion results in a lack of electrophysiological responses to tactile hindlimb stimuli in the somatosensory cortex and forelimb tactile responses do not spontaneously extend into de-afferented hindlimb areas even after 3 months post injury [124]. In contrast to findings from tactile stimulation, the hindlimb somatosensory cortex appears to be more labile in response to electrical stimulation. Spontaneous activity of the deprived somatosensory cortex decreases, and excitability of the intact cortex increases immediately after spinal cord injury in rats [125]. Thoracic spinal transection eliminates cortical responses to electrical hindpaw stimulation and results in long-latency responses to electrical stimulation of the forepaw within former hindlimb cortical areas [125, 126]. Additionally, sensory responses measured by blood oxygen level-dependent functional magnetic resonance imaging (BOLD-fMRI) and changes in membrane potential via voltage sensitive dyes have shown a progressive expansion of forelimb sensory responses to electrical stimulation into the de-afferented hindlimb cortex after thoracic spinal cord injury [94, 127]. The forelimb sensory responses measured by BOLD-fMRI are variable early after thoracic injury, with some animals showing reduced maps at 1 day post injury, but all expand within the first week [128]. By 1 week after spinal cord injury, the response to forelimb stimulation shifts to the rostral edge of hindlimb sensory areas after injury and activity persists over a much longer timescale as it sweeps through hindlimb regions [94]. Early changes in forelimb sensory maps, at 1 and 3 days post injury, appear to predict the spared functional ability at 1 week after injury [128]. The differences in somatosensory reorganization may arise from the distinct techniques of measurement used, the sensory modality activated by tactile stimulation versus electrical stimulation, the injury models employed (dorsal column injury, dorsal hemisection, full transection), or differences in post-injury training and activity levels.

Post-injury rehabilitative training acts not only on motor networks but also on sensory networks. After cervical hemisection, a loss of forepaw tactile sensitivity is paralleled by abolishment of somatosensory-evoked responses in the deprived forepaw representation [129]. In contrast to the spontaneous, partial recovery of motor skills, tactile responses to an adhesive removal test remain permanently impaired, as do

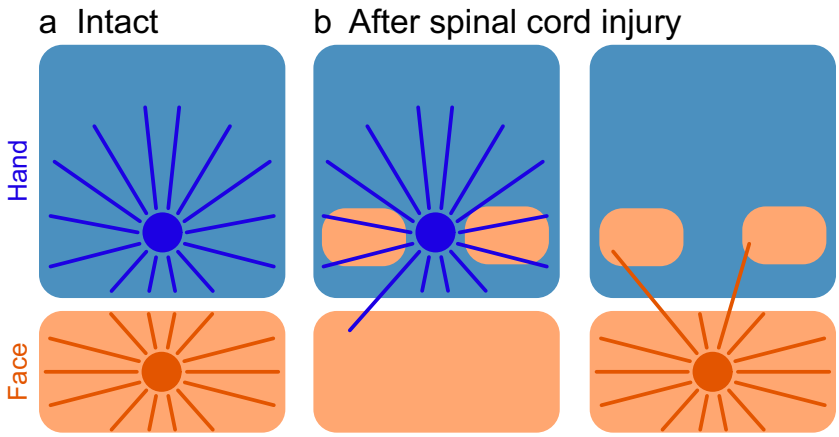

Fig. 3 Intracortical circuits in area 3b of the somatosensory cortex change after spinal cord injury in primates. **a** Intracortical connections within the hand and face representations in area 3b of the primate somatosensory cortex span the respective representations but do not cross the hand-face border (adapted from [118]). **b** After cervical spinal cord injury, face representations expand into parts of the hand representation while sparse, new intracortical connections arise from hand and face regions of area 3b and cross between the two regions (adapted from [119])

electrophysiologically detected forelimb sensory maps to tactile and mechanical stimulation [67, 129]. In rats with a behavioral training paradigm using discrete tactile stimuli, tactile sensory function recovers, as does a limited reactivation of S1 cortex forepaw representations [129].

Intracortical Circuits in the Sensorimotor Cortex

Intracortical connectivity provides a neuroanatomical substrate for the control of functional cortical topography. Motor intrinsic connections dictate the selection of movement-related muscle synergies through functional linking of motor cortical points, lateral inhibition of competing output, and shaping of representational borders [130–134]. Physiological and anatomical studies have illuminated the extensive intrinsic connections within the primary motor cortex [6–8] as well as the intracortical connections to higher motor areas [135–137], somatosensory cortex [10, 138, 139], and other cortical areas involved in motor control and spatial awareness (i.e., posterior parietal cortex, prefrontal cortex, and retrosplenial cortex) [10, 139–142]. Horizontal circuits interconnect neurons in the cortical columns within and across cortical regions, comprising a network of horizontally projecting axons in layers 2/3 and 5 [143, 144]. The intrinsic motor connections that arise in layer 5 project over longer distances (greater than 2 mm in the rat) than those from more superficial layer 2/3 [145]. These are monosynaptic connections with a linear relationship between distance and latency, which become exponentially weaker in amplitude at longer distances. Intracortical projections originating in layer 2/3 exhibit robust horizontal monosynaptic input to dendrites of distant layer 2/3 pyramidal neurons, with weaker monosynaptic input to the dendrites of deeper layer neurons [145]. In contrast, excitatory layer 5 projections form monosynaptic inputs to pyramidal neurons in all layers of neighboring columns by synapsing throughout superficial layer 2/3 as well as within deeper layer 5 [145]. Activation of these discrete intracortical pathways likely provides the substrate for the observed spatiotemporal recruitment of neighboring cortical units during motor movements and the functional plasticity supporting motor learning.

Long-range horizontal connections arise mostly from excitatory pyramidal neurons rather than from inhibitory GABAergic neurons, whose long-range projections are sparse [146–148]. Intracortical circuit specificity, both inter- and intra-laminar, is guided by neuronal activity and experience [149, 150]. Additionally, reciprocal connections exist between the motor cortex and subcortical structures like the thalamus [9, 141, 151–154], basal ganglia [11], cerebellum [12], brainstem [13], and spinal motor networks [14].

Within the rodent motor cortex, there are distinct responses to motor learning as well as differences in the intracortical connections of the rostral and caudal forelimb motor control areas RFA and CFA. CFA, which reorganizes during skilled motor learning [17], exhibits significantly greater input from the primary somatosensory cortex and less from the secondary somatosensory cortex than RFA (Fig. 4) [10]. Physiological studies in the rat also suggest that RFA lacks sensory inputs, in contrast to CFA [155]. Furthermore, the reciprocal connections between RFA and CFA are asymmetrical, with CFA receiving robust inputs to layers 1 and 5b from RFA layer 5b [156]. In contrast, CFA sends primarily horizontal projections from layers 2/3 and 5a to RFA [156]. The corticospinal projections also differ between CFA and RFA, with terminations in the dorsal and intermediate laminae of spinal cord gray matter, respectively [14].

Non-local horizontal connections are a consistent feature of cortical networks and constitute the majority of excitatory

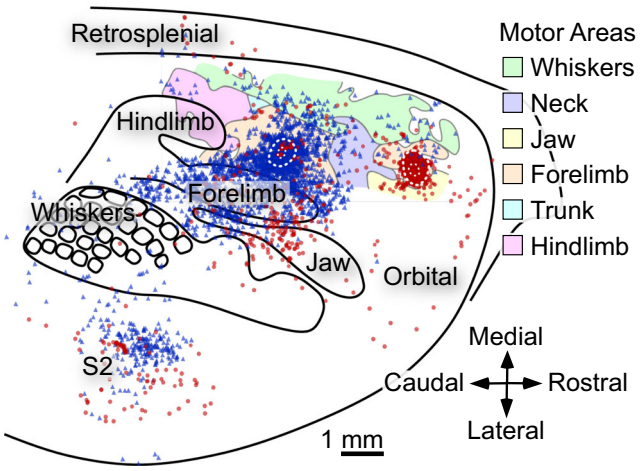

Fig. 4 Cortical inputs to forelimb motor areas RFA and CFA in rats. A representative flattened cortical hemisphere with the somatosensory isomorph (black outline) illustrates the patterns of cortical inputs to rostral and caudal forelimb areas (RFA and CFA). A color-coded topographical motor map of evoked movements is shown medially, while primary somatosensory areas are outlined in more caudal and lateral positions. Red and blue markers correspond to individual neurons retrogradely labeled by tracer injection into RFA or CFA, respectively. Injection sites are indicated by dashed outlines (adapted from [10])

inputs to pyramidal neurons [157, 158]. In the somatosensory cortex, layer 5b pyramidal neurons receive the most robust input from layers 2/3, 5b, and 6a [159, 160]. Though the layer and cell type of target neurons are different, the synaptic physiology of local and long-distance connections retains similar characteristics [159, 160]. In the cat, it has been proposed that horizontal motor cortex connections integrate muscle control into functional groups through recurrent network connectivity [8]. Neural network modeling suggests that non-local, horizontal inputs improve signal detection by reducing noise correlations and response variability [159]. Furthermore, layer 2/3 somatosensory neurons laterally suppress neighboring layer 2/3 neurons through local horizontal connections, while exciting layer 5 neurons oriented directly below and in neighboring regions through feed-forward facilitation [161]. A similar organization in M1 would allow for the strengthening of horizontal connections arising from layer 2/3 to reduce noise in layer 5b and give rise to distinct evoked movements using shared pools of corticofugal output neurons.

Intracortical Circuits and Sensorimotor Plasticity After Injury

Just as changes in cortical motor maps indicate the locus of skilled motor acquisition, the remodeling of impaired cortical maps after neurological injury denotes the extent of compensatory network recovery during rehabilitation. In stroke, the severity of injury is intimately linked with the level at which relearning through rehabilitation plateaus as the substrate for motor learning is compromised [162]. Unlike stroke, however, the limitation on functional recovery after spinal cord injury is owed not to cortical damage, but rather to the interruption of efferent and afferent pathways as well as to the ability for cortical mechanisms to adapt to the altered spinal cord substrate.

The mechanisms of motor learning and, by extension, rehabilitation, require plasticity across multiple levels: pre- and post-synaptic structures, cytoskeletal remodeling, and integration of connections into a functional motor network. During skilled motor learning, rats develop stronger horizontal connections in layer 2/3 as measured by increased amplitudes of extracellular field potentials in the trained hemisphere, relative to the untrained hemisphere [163, 164]. Selective, dynamic synapse changes underlie the electrophysiological changes during motor learning [165–167]. Layer 5 pyramidal neurons undergo a rapid induction of spine formation during skilled behavior [165]. Many of these spines persist throughout the life of the animal, indicating a role in the persistence of motor memory [166]. Furthermore, over the course of training to proficiency, subsequently formed dendritic spines cluster, amplifying the post-synaptic response to related task-specific motor input [165]. There is evidence that these training-induced changes are specific to cortical neurons that are engaged in the trained reaching task. Corticospinal neurons that project to low cervical spinal levels and control distal forelimb dexterity exhibit significant spine and dendrite remodeling, while those neurons not engaged in task-specific training do not [168]. Furthermore, the elimination of newly potentiated spines disrupts performance on a recently learned task, but not on an independent, previously established motor task [169].

Remodeling of intrinsic motor networks is required to restructure inputs to corticospinal neurons during motor learning. Layer 2/3 neurons show a remarkable transformation of activity patterns during motor learning. During the initial phase of a lever press task, different activity patterns of layer 2/3 excitatory neurons can give rise to similar forelimb movements [170]. With repeated training, the variability of motor cortex activity patterns decreases and reproducible, spatiotemporal activity patterns gradually emerge. These changes in population activity coincide with a transient increase in dendritic spine turnover in layer 2/3, demonstrating that changes in intracortical connectivity occur during the acquisition of novel motor learning [170]. These structural changes in layer 2/3 are required as intra-level refinement of corticospinal axons does not occur with motor learning [168].

The immediate reorganization of cortical motor maps after injury can be attributed to extensive intrinsic connections and inhibitory GABAergic influences. While the underlying anatomical projections of intrinsic connections support the plasticity of cortical networks, topographic borders are enforced by intracortical inhibition. Infusion of the GABA antagonist

bicuculline in the rat primary motor cortex reduces intracortical inhibition and modifies the output of vibrissae only areas to elicit both vibrissae and forelimb responses [130]. The unmasking of excitatory horizontal connections is responsible for this rapid and reversible change in topography as evidenced by the immediate reorganization of vibrissa areas following facial nerve injury [5]. Facial nerve transection results in the expansion of forelimb representations medially into fragments of the former vibrissae cortex. This novel, expanded forelimb region extends axons with bouton-like structures across the vibrissae/forelimb border. In contrast, regions of the vibrissae cortex that remain silent after injury have axonal projections that are restricted to the original vibrissae representation, with only sparse projections that cross into forelimb areas (Fig. 5) [5].

If large-scale cortical remodeling is the mechanism that supports functional rehabilitation from spinal cord injury, it will remain limited by the underlying architecture of intrinsic, horizontal connections in the absence of new intracortical axon growth. There is limited evidence of horizontal axon remodeling after spinal cord injury; however, several examples of intracortical axon remodeling have been observed following cortical stroke in both rodents and primates [171–175]. After stroke, cortical neurons within the peri-infarct region undergo axonal sprouting and restore connections to discrete targets throughout the brain [171, 176]. Focal strokes in the rodent somatosensory cortex result in the formation of novel intracortical axons projecting in aberrant orientations away from the peri-infarct cortex [171]. The plasticity of inputs to peri-infarct regions is also increased after stroke, with sprouts arising from the contralateral motor cortex [172]. In addition to changes in the peri-infarct cortex, distant cortical targets also undergo remodeling after cortical stroke in rodents. As animals recover from forelimb cortical stroke, sensory-evoked responses shift significantly into the peri-infarct motor and hindlimb somatosensory areas as well as distal retrosplenial cortex [173]. These functional changes are coupled with increased anatomical connectivity with the retrosplenial cortex and striatum, indicating large-scale circuit remodeling [173].

In primates, circuit changes occur within the sensorimotor cortex after lesions of the motor cortex [174, 175]. Positron emission tomography (PET) imaging studies after focal lesions of the M1 digit area show enhanced activation during post-lesion precision grip training early in the ventral premotor cortex and later in the perilesional primary motor cortex [175]. Pharmacological silencing illustrates the requirement for the reorganized cortical areas in the recovery of precision grip as the behavior is disrupted by infusion of the GABA agonist muscimol [175]. The ventral premotor cortex gives rise to novel connections with primary somatosensory area 1/2 after ischemic injury to M1 hand area [174]. This remodeling of intracortical connections likely supports the cortical reorganization and functional recovery observed after M1 stroke. Sensory and motor impairments correlate with the location of M1 lesion, and recovery of each follows similar time courses [177]. Novel intracortical connections to S1 may support the recovery of motor function through an adaptive response of the injured cortex. The sensory cortex is activated in patients with recovery from hemiparesis [178].

Although cortical stroke can spare a significant amount of cortical tissue and facilitate remodeling within the perilesional cortex, subcortical remodeling also plays a role in functional recovery after stroke, potentially drawing parallels with axonal plasticity after spinal cord injury. Following ischemic injury to the rat forelimb motor cortex, the degree of recovery in skilled reaching correlates with the sprouting of new connections from the peri-infarct hindlimb motor areas into the cervical spinal cord [179]. Intracortical microstimulation mapping confirmed that a greater recruitment of the peri-infarct hindlimb cortex to forelimb movements correlated with improved functional recovery. The capacity for sprouting from intact, peri-infarct, hindlimb corticospinal neurons to restore skilled forelimb function is similar to the capacity of injured

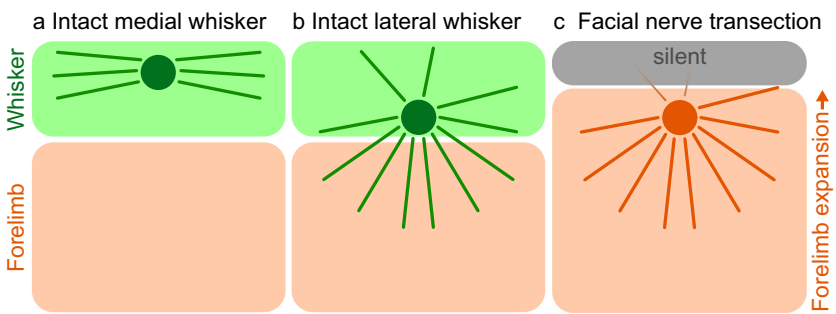

Fig. 5 Latent intracortical circuits underlie motor map changes after facial nerve transection in rats. **a** Intracortical projections arising from the medial part of the whisker representation are restricted to the whisker representation. **b** Whereas, intracortical projections of the lateral part are more widespread and cross the whisker-forelimb border into the forelimb representation (adapted from [6]). **c** After facial nerve transection, latent intracortical connections from the lateral whisker area support the medial shift of evoked forelimb motor maps. More medial whisker cortex becomes unresponsive as intrinsic connections are restricted to whisker regions (adapted from [5])

corticospinal axons to sprout and drive changes in cortical motor map topography after spinal cord injury [64, 94]. Rehabilitative training and forced limb use after stroke result in the enlargement of ipsilesional cortical forelimb motor area and recovery of skilled forelimb functions after internal capsule lesions with intracerebral hemorrhage [180]. Recovery is mediated by increased axonal sprouting from the forelimb motor cortex to the red nucleus [180]. Similar corticorubral projections arise from corticospinal neurons axotomized at the level of the medullary pyramids [91]. Subcortical changes in descending corticofugal motor pathways observed after cortical stroke are likely to act in concert with remodeling of intracortical connections.

Peripheral injury also alters intracortical connections, with reorganization apparent after amputations in rodents and primates [181–183]. In rodents, the capacity for sensory circuit reorganization decreases with age, with greater plasticity of primary sensory neurons and their brainstem targets in rats with perinatal forelimb amputation, compared to adults [184]. Intracortical reorganization is also decreased with age, as sensory representations of the forelimb stump contain a greater level of latent hindlimb connectivity when forelimb amputation is performed perinatally [185]. Within the cortex, a direct, polysynaptic connection arises in S1 from the hindlimb to the forelimb stump with projections through the dysgranular cortex [181].

Novel horizontal axons that cross representation borders following peripheral injury are dynamic and undergo rapid remodeling, with an initial growth phase followed by pruning and establishment of a remodeled intracortical network. This is observed in S1 following partial peripheral denervation of the rodent forelimb (radial and median nerve transection) [182], and in the primary visual cortex after retinal lesions in primates [186]. These changes in intracortical projections persist for years after injury in primates. Long-term peripheral injury or amputation in adult macaque monkeys results in the establishment of large-scale remodeling between somatosensory areas 1 and 3b, with normal patterns of thalamocortical projections [183].

Barrel cortex presents a unique structure in which to observe cortical plasticity in response to the loss of sensory input. Whisker trimming or removal interrupts afferent input to only a local region of the sensory cortex and is followed by somatotopic reorganization driven by rapid and robust plasticity of both excitatory and inhibitory axons [187]. The experience-dependent plasticity is principally driven by remodeling of local axons, with limited dendritic structural remodeling [188]. Excitatory neurons in non-deprived barrels with intact afferent input extend new axonal projections into deprived barrel columns. Conversely, inhibitory neurons in deprived barrels retract proximal axons and sprout long-range projections to non-deprived barrels [187]. Thus, not only does afferent input shape horizontal connections in the somatosensory cortex, but it also alters the balance of excitation and inhibition within the cortex to drive cortical plasticity.

Although spinal cord injury disrupts the sensory and motor networks within the spinal cord, the cortical sensorimotor networks are intact and could underlie the map changes occurring at the cortical level. There is evidence of reorganization of callosal networks and intracortical circuits of the motor and somatosensory cortex after spinal cord injury, in addition to the dendritic spine changes that likely alter cortical motor maps [104, 105]. In primates, the bilateral compensatory mechanisms that support recovery of finger dexterity after mid-cervical spinal cord injury appear to depend on both callosal projections and a remodeling of connections intrinsic to the affected M1 [189]. Intracortical connections in the somatosensory cortex are altered following spinal cord injury in rodents and primates [119, 190]. In adult rats that have been subjected to neonatal cervical C3 over-hemi-sections, callosal connections to forepaw S1 areas are widely distributed, while those with incomplete injury and unilateral dorsal column sparing have a normal distribution of callosal projections [190]. This suggests that dorsal column sensory inputs are required for the proper refinement of a mature pattern of callosal connections. In adult primates, there is limited remodeling of intracortical connections of the hand and face representations in S1 area 3b following spinal cord injury [119]. Sparsely traced intracortical connections have been observed bridging the hand and face representations (Fig. 3). These connections were more substantial in monkeys with incomplete injury, suggesting that spared afferent input can shape a limited intracortical remodeling after spinal cord injury [119].

Conclusion

Cortical motor and somatosensory representations exhibit spontaneous reorganization following spinal cord injury. Alterations in cortical neurophysiology and neuronal structure appear to underlie these changes. While spontaneous plasticity of motor and sensory systems occurs with time after injury, functional recovery and remodeling require the engagement of activity-dependent mechanisms. Rehabilitation has been shown to elicit remodeling of cortical motor maps concomitant with behavioral recovery, likely engaging the intracortical mechanisms of motor learning. However, motor recovery does not occur in isolation and learned movements require the recovery of both descending motor and ascending sensory systems. Plasticity of both motor and sensory networks after injury has been observed in other loci (e.g., brainstem, spinal cord), though it is the refinement of intracortical connectivity that is of particular interest in the recovery of skilled and dexterous movements. Latent intracortical connections shape the aberrant motor maps after injury, and it is probable that refinement of these connections as well as synaptic

remodeling on corticofugal output neurons are critical mechanisms supporting rehabilitation-mediated recovery. Rehabilitative strategies after spinal cord injury should therefore take into consideration the intracortical substrates available for mediating beneficial cortical remodeling and limiting maladaptive plasticity. The parallels in cortical plasticity between animal models and human spinal cord injury indicate that a better understanding of the intracortical circuits that support cortical reorganization will lead to improved therapeutic and rehabilitation strategies.

Acknowledgements Hisham Mohammed would like to acknowledge Prof. Neeraj Jain for the doctoral training.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

Funding Information Financial support was provided by the Winifred Masterson Burke Foundation and the NIH Common Fund (1DP2NS106663).

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