

# Modulation of motor function and cortical plasticity in health and disease

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**Abstract.** Basic science studies demonstrated mechanisms of plasticity and metaplasticity. More recent human studies identified some of these mechanisms as operating in multiple areas of human cognition, such as learning and memory, and in functional recovery from lesions in the CNS, as in stroke. One of the goals of neurorehabilitation is the translation of these principles into rational strategies to promote recovery of function. Understanding the mechanisms and functional role of human plasticity could lead to the development of therapeutic options in situations in which there is virtually no treatment alternative, as in chronic stroke. We review some of the work performed to better understand the substrates and mechanisms underlying cortical plasticity and discuss some experimental approaches to enhance cortical plasticity and recovery of function, like cortical stimulation.

Keywords: Plasticity, motor, somatosensory, rehabilitation, TMS

## 1. Introduction

For many years, the central nervous system (CNS) has been viewed as a rigid structure with little capacity for modification and adaptation. In the last two decades, however, there has been a paradigm shift characterized by the understanding of the CNS as a plastic organ, capable of adaptation or modification when confronted with environmental challenges or lesions. This property of the brain has been termed neuroplasticity. In this review, we discuss strategies geared to influence motor function and cortical plasticity in the human CNS.

## 2. Techniques to study cortical reorganization

Cortical reorganization in humans can be studied noninvasively using a variety of techniques. Positron

emission tomography (PET) and functional magnetic resonance imaging (fMRI) permit the identification of brain regions activated in association with performance of different tasks [79]. These methods provide good anatomical resolution but relatively poor definition in the temporal domain. On the other hand, physiological techniques, such as EEG and MEG, have excellent temporal resolution [37,89]. When combined, these tools provide the investigator with useful strategies to evaluate changes in brain organization associated with learning or lesions (see chapter by Dal Forno et al in this volume). Transcranial magnetic stimulation (TMS) allows the study of plastic changes in cortical representations of motor and sensory functions [32], mechanisms of plasticity [118], and the behavioral consequences of noninvasive transient inactivation of specific cortical sites [103].

In TMS, a brief, strong electric current is passed through a copper coil, inducing a large, rapidly changing magnetic field with different shapes, depending on the coil configuration [17,38,39,67,91–94,96]. The 8-shaped coil induces the largest and most localized currents under the intersection of both wings of the magnetic coil, where the circumferences of the two compo-

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nents come together [31]. The magnetic field readily passes into the brain and elicits currents that flow in a plane parallel to the coil [94]. These currents depolarize the exposed neurons. Thus, two general types of effects can be observed with cortical stimulation. First, a response that resembles normal function can be seen in the area stimulated, such as a muscle twitch with stimulation over the motor cortex [9] or phosphenes with stimulation over the occipital cortex [12–14,56,62]. Second, single pulses of TMS can have disruptive effects on ongoing regional cortical activity in motor [71], visual [62], or somatosensory [29] domains. Using TMS trains, cortical activity under the stimulating coil is disrupted for longer periods of time and, therefore, allows the evaluation of more complex behaviors [26,30,46,47,73]. Trains of stimuli are more effective than single stimuli in inducing disruption of cortical activity [70]. Disrupted behaviors resulting from the application of TMS trains to specific brain regions are usually interpreted as indicative of the participation of these cortical sites as a substrate of the specific behavior.

Plastic changes in the intact and lesioned CNS can be induced by a variety of experimental manipulations and daily life events. This chapter discusses the influence of somatosensory input, motor training, and cortical stimulation on motor function and cortical plasticity.

### 3. Somatosensory input and motor function

Somatosensory input is required for motor learning [10,76]. For example, reduction of somatosensory input by local anesthesia impairs motor control in healthy human subjects [8,36]. Similarly, patients with large-fiber sensory neuropathy and poor somatosensory function exhibit characteristically abnormal motor behavior [48,95]. Patients with stroke and poor somatosensory function experience slower and often incomplete functional recovery relative to those with intact somatosensory function [82]. These clinical findings have led to a renewed interest in the investigation of the influence of somatosensory input on motor function.

#### 3.1. Somatosensory stimulation modulates motor function of the stimulated body part

In animal models, peripheral nerve stimulation [54,81] and acute [22] and chronic [42] deafferentation all result in changes in receptive fields in the primary so-

matosensory cortex. Moreover, given the strong connections between somatosensory and motor cortices, it is not surprising that peripheral nerve stimulation results in reorganizational changes in the motor cortex across species in human and non-human primates, cats, and rodents [2–4,6,7,52,57,75,87,107,115]. For example, a 2-hour period of peripheral nerve stimulation (PNS) in rodents results in characteristic increases in corticomotor excitability, as tested with TMS [60,61]. In humans, somatosensory stimulation elicits clear reorganizational and excitability changes in the contralateral somatosensory cortex [78]. A period of 2 hours of PNS applied to the ulnar nerve results in an increase in excitability of the stimulated body part representation in the human motor cortex as tested with TMS [55]. These excitability changes exhibit topographic specificity because they do not occur in motor representations other than the one corresponding to the stimulated body part [49,55,83,84]. These changes last for minutes to an hour depending on the experimental paradigm. Consistent with basic science studies that looked at the mechanisms underlying rapid plastic changes in the somatosensory and motor cortices [45,53], human studies demonstrated that this process is influenced by GABAergic inhibition. Specifically, GABAergic agents, such as lorazepam, block the PNS-dependent increase in motor cortical excitability [55]. GABAergic function appears to be involved in deafferentation-induced plasticity in the human motor cortex as well [24,59]. Acute deafferentation in the form of ischemic nerve block is associated with a significant decrease in cortical GABA, as identified by magnetic resonance spectroscopy [59] and physiological techniques [117,118,121].

Stefan et al. used these principles to implement a novel interventional approach to influence motor function [104]. In healthy volunteers, a single pulse stimulus was delivered to the median nerve 20 ms preceding a TMS pulse to the contralateral motor cortex. In this way, the researchers theorized, somatosensory input originating in the median nerve stimulus would reach the contralateral motor cortex synchronously with the TMS pulse. This paired stimulation technique, described as *paired associative stimulation* (PAS), was applied for 30 min. PAS resulted in an increase in motor cortical excitability that developed rapidly over minutes and persisted for up to an hour with topographic specificity [104]. This form of plasticity, highly dependent on the accuracy of synchronization between peripheral nerve and cortical stimulation, had features reminiscent of associative long-term potentiation, a form of

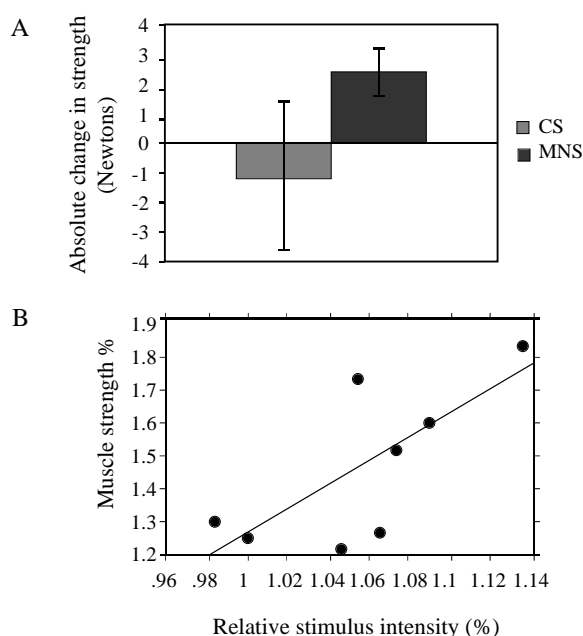


Fig. 1. Changes in pinch force (Newtons) following application of 2-hour median nerve stimulation (MNS) or sham stimulation (CS) in different sessions in a group of patients with chronic stroke (A). Error bars represent standard errors of the mean. (B) The magnitude of improvement in pinch force correlated with the relative intensity of peripheral nerve stimulation. Modified from Conforto et al. [33].

learning that follows Hebbian rules [51]. The subsequent finding that NMDA receptor function is one of the mechanisms operating in this form of plasticity further supports the link with associative long-term potentiation [112].

These results in intact human and animal brains led to the proposal that somatosensory input could be used to influence motor function in patients with weakness secondary to lesions of the CNS, such as in stroke. In one of these studies, Conforto et al. evaluated the effects on muscle strength of a 2-hour period of PNS applied to the median nerve in a group of patients with chronic stroke [33]. The authors documented an improvement in pinch muscle strength of  $2.41 \pm 0.74$  N after median nerve stimulation, compared to a non-significant decrease of  $1.07 \pm 2.4$  N in the control session, which consisted of stimulation with intensity below that required to induce paresthesia (Fig. 1). Interestingly, the magnitude of improvement correlated well with the intensity of PNS, and 2 patients spontaneously reported that they could write better and hold objects and play cards more accurately, a perception that lasted for approximately 24 hours. This preliminary report demonstrated that PNS could, under certain circumstances, play an adjuvant role to other neurorehabilita-

tive techniques and directly influence motor function in patients with stroke. These results are consistent with those of Struppler et al. [105], who documented a rapid decrement of spasticity and an improvement in finger extension mobility after PNS in patients with chronic stroke. The results also correspond with those of Uy et al. [108], who applied PAS in stroke patients with stable gait abnormalities and documented improvements in gait function. While preliminary by nature, all these results are consistent with the view that somatosensory stimulation applied to a weak limb could influence cortical plasticity and motor function in patients with stroke. In addition to the direct effects of stimulation on motor function in patients with stroke, a recent study suggests that somatosensory stimulation can enhance the effects of motor training in patients with chronic stroke. Sawaki et al. reported that motor training performed after 2-hour PNS (using a paradigm similar to Conforto et al. [33]) enhanced training-dependent encoding of an elementary motor memory in the primary motor cortex [101].

### 3.2. Somatosensory input from one hand can influence functions of the other hand

Recent studies indicate that cortical function is influenced not only by somatosensory input originating in the contralateral hand but also by input from the ipsilateral hand. The existence of interactions between homotopic sites within the motor cortical representations in both hemispheres could provide a substrate for such an effect [5,35,40,50]. For example, in primates and flying foxes, acute deafferentation leads to rapid changes of receptive fields in the somatosensory cortex in both hemispheres [23]. In one study, Werhahn et al. [110] showed that acute hand deafferentation by ischemic nerve block (INB) in healthy volunteers led to increased excitability of the cortical representation of (a) the opposite, non-deafferented hand and (b) body parts proximal to the deafferented hand (upper arm), in the absence of excitability changes in other body part representations, such as thorax or leg muscles. This effect persisted throughout the period of deafferentation and returned to baseline values afterward. Motor responses to brainstem electrical stimulation remained unchanged during INB, indicating that the effect is likely of cortical origin. Lorazepam, a GABA A receptor agonist, blocked this increased excitability, suggesting that this form of plasticity is influenced by GABAergic function. Additionally, it was found that interhemispheric inhibition between hand muscles

decreased during INB. Altogether, these results indicate that acute hand deafferentation can elicit a focal increase in excitability in the hand motor representation contralateral to the deafferented cortex that is influenced by transcallosal interactions and GABAergic transmission [110].

To what extent these physiological changes impact behaviour was not known. To address this question, Werhahn et al. [111] studied the behavioral impact of acute deafferentation of one hand on performance abilities of the other hand in a group of healthy volunteers. The authors identified rapid improvements in tactile spatial acuity in the left hand, accompanied by changes in cortical processing during cutaneous anesthesia of the right hand. The gain in tactile spatial acuity (approximately 19%) was identified shortly after the onset of deafferentation, suggesting unmasking of existing neural substrates. Enhancement of the cortical somatosensory-evoked potentials originating in S1 in the absence of overt changes in subcortical generators pointed to a modulation of excitability in the primary somatosensory cortex. This view is consistent with previous reports of neurophysiological [23] and cerebral blood flow [97] changes in the primary somatosensory cortex ipsilateral to an acutely deafferented hand. It is possible that unmasked intracortical horizontal connections in the primary somatosensory cortex contributed to these behavioral gains in a way similar to that proposed for their role as mediators of improvements in the visual [34] and motor cortices. These results are consistent with the proposal that deafferentation of a hand representation in the somatosensory cortex by INB influences the homotopic representation in the opposite hemisphere [23,110]. The anatomical and functional substrates for such interactions do exist and are thought to be predominantly inhibitory [11]. In humans, unilateral brain lesions result in a relative increase in function of homonymous areas in the opposite hemisphere [63]. It is possible that deafferentation of one hand representation enhances processing in the opposite representation. Such increase could support the remaining hand's need to tackle enhanced environmental requirements, consistent with interhemispheric competition models of sensory processing [111].

### *3.3. Somatosensory input from the upper arm can influence hand motor function.*

Basic science studies have demonstrated that deafferentation leads to cortical reorganization in which body part representations proximal to the deafferented

one expand over the deafferented representation [113, 114]. In humans, amputations lead to expansion of nearby representations over the deafferented one [28]. These cortical changes [24,44,86] involved a GABA-related disinhibition mechanism and changes in neuronal membrane excitability [25]. A similar effect has been documented after acute limb deafferentation using INB. In these studies, INB applied to the wrist increased motor cortical excitability, targeting muscles proximal to the wrist [15,16,85,116–118,120].

These studies raised the hypothesis that performance of a weak hand could be improved by manipulation of somatosensory input originating in a nearby body part (upper arm). Muellbacher et al. explored this hypothesis by applying a local anesthetic to the upper trunk of the brachial plexus of the paretic arm of chronic stroke patients, inducing anesthesia of the proximal arm but sparing the distal limb [64]. The authors obtained preliminary evidence that anesthesia of the upper arm elicits transient improvements in performance in the nearby paretic hand, accompanied by an increase in motor cortical excitability.

### *3.4. Somatosensory input from one body part representation can influence the same representation in the motor cortex*

Acute limb anesthesia leads to rapid changes in motor cortical function. Ischemic nerve block of one hand results in well demonstrated reorganization in the same representation of the adjacent human motor cortex [15, 16,110,111,117,119,120], that can be associated with behavioral gains [120]. Anesthesia of the median and radial nerve results in reduction of motor cortical representation of ulnar nerve-innervated muscle enveloped in the area of cutaneous anesthesia [88,90]. This type of information could possibly be useful to develop novel interventional strategies based on principles of neuroplasticity.

## **4. Motor training and motor function**

Motor training leads to reorganizational changes in the motor cortex in animals and humans and represents a pillar of rehabilitative treatments [27,58,65,68,74]. One form of training, performance of simple, repetitive finger movements, leads to encoding of the kinematic details of the practiced movements as an elementary motor memory in the primary motor cortex [27]. Follow-up studies identified NMDA receptor activation

and GABAergic inhibition as mechanisms operating in use-dependent plasticity in the intact human motor cortex and pointed to similarities in the mechanisms underlying this form of plasticity and long-term potentiation (LTP) [21]. The development of this model of human plasticity allowed the investigation of issues relevant to neurorehabilitation, like the influence of various drugs. It was demonstrated that drugs that act as agonistic to the GABAergic function and those that act as antagonistic to NMDA and muscarinic receptor function exert a deleterious effect on human plasticity [21, 98]. Additionally, drugs with adrenergic or dopaminergic function, such as D-amphetamine, when used in combination with training, can enhance use-dependent plasticity [20,99,100]. One study determined that the magnitude of this particular form of plasticity decays significantly with age [102], an important finding given that the majority of strokes occur after 55 years old.

## 5. Cortical stimulation and motor function

Basic science studies have reported that cortical stimulation can modify representations in the motor cortex [69], while human studies have shown that TMS could alter motor cortical excitability [72]. Based on this evidence, studies in our lab focused on the hypothesis that cortical stimulation could exert a modulatory effect on cortical plasticity. In an initial report, Ziemann et al. demonstrated for the first time that cortical stimulation in the form of TMS applied to a reorganized motor cortex enhanced deafferentation-induced plasticity [117]. Candidate mechanisms proposed included strengthening (e.g., LTP) of pre-existent synaptic connections, since the observed time course of excitability changes was too rapid to allow for such structural reorganization mechanisms as sprouting. This study demonstrated as a proof of principle that cortical stimulation could modulate cortical plasticity in intact humans [117], as has been recently shown in a different brain region [80].

In a subsequent study, Ziemann et al. characterized the topographic specificity of this effect [116]. The authors found that the long-lasting (>60 min) stimulation-induced increase in deafferentation-induced plasticity was input specific because it required TMS of that representation (i.e., the arm), whereas it did not occur with stimulation of nearby representations (i.e., the face, hand, or leg). Therefore, input specificity, in addition to cooperativity that describes a threshold phenomenon for induction [117] and NMDA receptor de-

pendence [118], characterizes this form of plasticity in the human motor cortex. While these studies demonstrated the principle that TMS can modulate human cortical plasticity, it remained to be determined if cortical stimulation could specifically influence use-dependent plasticity.

In a recent study, Butefisch et al. demonstrated that TMS synchronously applied to a motor cortex engaged in a motor training task enhances use-dependent plasticity [19]. Healthy volunteers were studied in different sessions: training alone, training with synchronous application of TMS to the contralateral or ipsilateral motor cortex, and training with TMS delivered asynchronous to the training movement to the motor cortex contralateral to the training hand. This study found that the longevity of use-dependent plasticity was significantly enhanced by TMS applied in synchrony to the cortex contralateral to the training hand. These results demonstrated for the first time that use-dependent encoding of a motor memory can be enhanced by synchronous Hebbian stimulation of the motor cortex that drives the training task [51]. Overall, these findings have important implications for neurorehabilitation and suggest that cortical stimulation could represent an adjuvant to motor training in efforts to recover lost function after cortical lesions like stroke [77].

## 6. Conclusions

Overall, basic science studies have substantially advanced our understanding of the mechanisms of plasticity and metaplasticity [1,41]. These mechanisms are thought to operate in multiple areas of human cognition, such as learning and memory, and in functional recovery from lesions in the CNS, as in stroke [18,43, 66]. While these findings may have direct implications in the way human disease is treated, relatively few efforts have been invested in research that translates these advances in the basic science domain to the formulation of new, rational strategies for promoting recovery of function in humans [106]. To accomplish this goal, it would be important to demonstrate that similar principles to those described in animal models apply to the human cerebral cortex in relevant behavioral settings (for example deafferentation, learning, or during stroke recovery) [109].

Over the last decade, emphasis has been placed on studies of human plasticity because of the obvious implications for clinical neurorehabilitation [68]. Understanding the mechanisms and functional role of human

plasticity could lead to the development of therapeutic options in situations in which there is virtually no treatment alternative or only empirical approaches are used, as in chronic stroke. This chapter has reviewed work performed to better understand the substrates and mechanisms underlying cortical plasticity and evaluated some experimental approaches to testing novel strategies to enhance cortical plasticity and recovery of function, like cortical stimulation [19,116,117].

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