

The importance of neuronal stimulation in central nervous system plasticity and neurorehabilitation strategies

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Summary

Basic neuroscience has demonstrated new mechanisms of neuroplasticity in the healthy and the lesioned brain. Post injury, behavioral experience and neuronal stimulation-based therapy seem to play an adaptive role in the injured brain, modifying the functional organization of remaining cortical tissue and leading to clinical improvements. A better understanding of the cellular and molecular mechanisms underlying human neuroplasticity might benefit neurorehabilitation strategies designed to promote recovery of function. We review some of the main results from animal experimental and human clinical studies focusing on mechanisms of reorganization of the motor cortex in response to injury and highlight different available approaches used to modulate and to evaluate motor cortical plasticity. Finally, we discuss how knowledge on neuroplasticity might be applied to neurorehabilitation strategies in neurologically impaired patients.

KEY WORDS: brain, neuroplasticity, recovery of function, rehabilitation, stimulation.

Introduction

During the past two decades, experimental animal investigations and neurophysiological/neuroimaging studies in humans have demonstrated that the healthy adult brain maintains the ability to reorganize connections and functions throughout life (1). Cortical reorganization, or plasticity, was defined by Bütefisch (2) as “any enduring change in the cortical brain properties either morphological or functional”. Since Donald Hebb’s original demonstration (3), in which laboratory rats allowed to move freely had better memory and learning capacities than

animals kept in laboratory cages, further studies have shown that neuronal cortical connections can be remodeled by experience or injury in order to improve neurological functions and abilities (4). These responses are best conceptualized as spanning various levels: brain level (microvasculature function, brain barriers, nutritional support), neuronal network level (dynamics of neuronal interconnection and synaptic features), inter-cellular level (regulation of glial-neuronal events), intracellular level (downstream signals), biochemical level (protein conformation, enzyme mobilization), and genetic level (transcriptional regulation) (5). With regard to neurological impairments, the wide range of events related to neuroplasticity play a very important role and may correlate with improvements but also with apparent deteriorations of neurological function.

Thus, cortical reorganization after neurological injury was classified, in clinical terms, as *function-enabling* or *function-disabling plasticity*. The first leads to a behavioral improvement, for instance, changes in cortical representation and functional gain with the use of an affected extremity. The second may result in an apparent deterioration of function, for instance, the appearance of epileptic seizures after brain injury or of progressive hyperreflexia, clonus, dystonias and phantom limb after amputation or spinal cord injury (6). In this context, functional gains can be conceptualized as adaptive behaviors, offering opportunities that may be addressed in order to minimize disabilities.

Neurorehabilitation seeks to overcome the disabilities of neurologically impaired patients by looking for strategies to bring about functional improvement and amelioration of neurological deficits. The possibility of driving cortical plasticity with a view to neurofunctional gain has opened up a new dimension in the care of neurologically impaired patients and provides a creative new set of tools for the rehabilitation team.

This review focuses on mechanisms of reorganization of the motor cortex in response to injury and considers experiments in laboratory animals and clinical evidence. Different approaches intended to modulate and stimulate motor cortical plasticity are discussed from the perspective of their clinical application in the rehabilitation of neurologically impaired patients.

Evidence of cortical plasticity after injury in experimental and human studies

The concept of neuroplasticity dates back to 1928 and Cajal’s observation (7) on the responses of the peripheral nervous system to injury. Cajal showed initially morphological changes in axotomized motor neurons. Over the many decades since then, animal and human studies have provided evidence of neuronal responses in

cortical regions after peripheral or central nervous system (CNS) injuries (8).

Morphological and physiological analyses have shown a loss of rat motor cortical representation of the respective innervated musculature with specific cortical areas taken over by adjacent regions after nerve transection (9). Moreover, a similar cortical reorganization response was also described, following facial tactile stimulation, in monkeys with somatosensory deafferentation of an entire forelimb (10). Peripheral stimuli gave rise to evoked responses in the facial projection areas of the animal cortex but also triggered signals in the adjacent cortical zones representing the now deafferented arm. Thus, the somatosensory cortico-facial area overlapped the cortical zone representing the deafferented arm.

More recently, Stroemer and collaborators, by means of modern immunolabeling techniques, showed increases in the growth-associated protein 43 (GAP-43) and synaptophysin protein in the rat neocortex after unilateral ischemia (11), providing further evidence of the occurrence of neurite growth and synaptogenesis in the injured neocortex. These events are considered morphological features of cortical plasticity after injury.

We have indeed learned a lot from experimental models. However, the time course of lesion progression, the influence of surrounding tissue, and the regenerative capacity of nervous tissue may differ among species, influencing interpretation of the cortical responses related to neurofunctional recovery. Investigators have studied cortical neuroplasticity in rodent brain lesion models of ischemia/stroke because of its clinical relevance to humans (12,13). These models include transient or permanent vascular occlusion by means of arterial vessel manipulation as well as thrombotic lesions, which trigger different types of blood-brain barrier breakdown (14). Despite methodological limitations, cortical plasticity appears to play a beneficial or adaptive role in general behavioral responses after brain lesions. It should be pointed out that various factors, genetic, gender, and hormonal, for example, as well as animal age, might also influence lesion-induced brain plasticity (15).

The development of brain imaging, especially methods using motor activation, opened up the possibility of looking at the functional organization of the human motor system, and of analyzing recovery mechanisms in human beings. Among others, Rossini and Dal Forno (16) have discussed the strengths and limitations of the available non-invasive brain imaging tools. For instance, positron emission tomography, functional magnetic resonance imaging (fMRI), high-resolution electroencephalography, magnetoencephalography (MEG), and transcranial magnetic stimulation (TMS) have been employed in several neurological services around the world. In the case of stroke, the combination of imaging techniques has allowed a detailed description of cortical plasticity events (16).

A variable expansion of the cortical region can be recruited in functional reorganization after brain lesions or other disease. It is likely that functional changes of the motor cortex after brain lesions depend on the influence of other functionally connected brain regions. One report suggested that the decreased intracortical inhibition pattern found in patients with cortical or thalamic stroke might follow the opposite direction when the cerebellum is included in the infarct area (17). Furthermore, an ab-

normally high interhemispheric cortical inhibition from the contralateral hemisphere to the ipsilesional lesioned M1 (primary motor cortex) was demonstrated (18) to impair rather than facilitate motor performance in stroke patients. Moreover, other events, like ipsilateral recruitment of activity within the corresponding sensorimotor area in the non-involved hemisphere, may occur in neurofunctional recovery after stroke injuries (19). These responses are part of a compensatory cortico-cortical process, and they seem to be related to the severity and location of the cortical lesion.

Moreover, longitudinal studies have shown that the motor activity improvement after a brain injury is accompanied by a cortical activation pattern on fMRI and TMS in many motor-related regions, such as the bilateral sensorimotor cortex, premotor cortex, cingulate motor areas and cerebellum (20,21). Furthermore, MEG showed a significant reduction of the cortical hand representation for the affected side of patients with a chronic pain syndrome (22). Moreover, the center of the hand was shifted toward the cortical representation of the lip. Additionally, activation in the primary sensory cortex following tactile stimulation was significantly increased on the chronic painful side compared to the unaffected limb.

Finally, cortical reorganization events may persist following chronic deafferentation. In limb amputees, the motor-evoked potentials of muscles proximal to the stump level were elicited by TMS at a lower intensity and from more distant scalp positions, indicating a facilitation of cortical efferent output to the periphery (8,23).

Taken together, current knowledge on the mechanisms of neuroplasticity of the brain cortex and subcortical regions after nervous system injury could favor new strategies to improve neuronal responses necessary for behavioral rehabilitation.

Role of neuronal stimulation in neuroplasticity in human and animal studies

There is exciting evidence in both animal and human studies that brain plasticity can be driven by a number of factors triggering neuronal stimulation, such as physical activity, motor and cognitive learning, reading, and environmental enrichment (2,4,23-26).

A certain degree of neurofunctional recovery can occur in a variable time span following a neurological injury, a span that can range from seconds to years. The neurobiology behind this evidence has recently become better understood. Prompt restoration of the original substrate after a stroke is of course desirable and may include immediate reperfusion of ischemic areas, elimination of edema, restitution of non-infarcted penumbral areas and resolution of diaschisis. In many circumstances, adequate initial clinical management of the acute phase post stroke can allow partial or total recovery of function. Tissue protection is an objective in the neuroscience and neurorehabilitation fields, too (5).

Mechanisms for functional recovery also include mobilization of new or existing neural substrate to achieve function, possibly both at anatomical and molecular level. As mentioned above, the large number of brain events involved in neurofunctional adaptation are known as neuroplasticity, and neuroplasticity occurs during normal neural processing and after neuronal injury. Cellular

and molecular mechanisms related to stimulation of neuronal sprouting, functional enforcement of existing neural circuits and development of fresh polysynaptic connections have been extensively investigated. The time-window for inducible neuroplasticity is wide and may be unrestricted (27).

Important events in cerebral cortical reorganization post injury include, for instance, the unmasking of existing, but latent, horizontal connections and the modulation of synaptic efficacy through mechanisms of long-term potentiation (LTP) and long-term depression (LTD). Both mechanisms can occur within milliseconds to hours, and in some cases might be prolonged for weeks after injury, and they are based on the concept that the motor cortex contains multiple overlapping motor representations which are functionally connected (28). LTP and LTD may lead to changes in the strength of connections among motor neurons, and different functional neuronal assemblies can form, thereby providing a substrate for the construction of dynamic motor output zones. Many recent publications have focused on the involvement of γ aminobutyric acid (GABA)ergic and glutamatergic systems, paying particular attention to the role of the activated N-methyl-D-aspartate (NMDA) subtype of glutamate receptor (29).

Recent analyses have shown the effect of motor practice and intensive training on motor system reorganization in the healthy and injured primate brain (30), including the human brain (31). Sustained performance of a specific motor task, for instance playing string instruments, is able to induce a motor cortical reorganization, providing data about the neural mechanisms for skill acquisition (32). Moreover, imaging studies in humans indicated that motor recovery after stroke, as promoted by training, is correlated with changes in the sensorimotor pattern of cortical activation (33), highlighting the importance of specific functional demands such as more carefully performed visuomotor, sensorimotor and/or cognitive tasks (34).

Learning-dependent synaptogenesis has been shown at cellular level in rats trained to perform a skilled reaching task, accompanied furthermore by FOS expression (a marker for neuronal activation) and increases of synaptic density within motor cortical layer II/III (35).

Moreover, the complex nature of sensorimotor integration as a possible substrate for functional motor cortical adaptations after brain damage and training has been underlined (24,34).

The voluntary efferent output as well as afferent input may assist in the organization of altered signals arising from a damaged brain area. Proprioceptive feedback seems to play a critical role in motor planning by updating an internal model of the state and properties of motor activity. On the basis of the proposed model of the sensorimotor cycle (Fig. 1), strategies like peripheral sensory stimulation, pharmacological stimulation of brain receptors and direct cortical stimulation, have been tested in order to achieve neuroplasticity-induced motor system responses (24,36).

Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) are methods applied to humans in order to modulate excitability in specific cortical areas. Indeed, low-frequency rTMS (about 1 Hz) usually results in inhibitory effects which may be related to LTD mechanisms. High-frequency

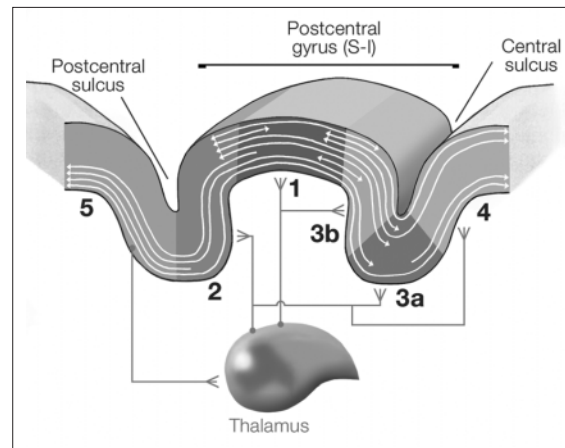


Figure 1 - Anatomical connections between somatosensory cortex and primary motor cortex. Connections are shown in the somatosensory cortex of Brodmann area 1, 2, 3 and 5, and primary motor cortex area 4. Note that somatosensory and motor cortices are highly interconnected. The thalamus acts as a relay station for peripheral somatosensory input into the cortex.

rTMS (more than 5 Hz), on the other hand, leads to LTP-related excitability responses. Interestingly, TMS is able to trigger a predominantly transsynaptic activation of pyramidal neurons through their cortical connections, and is a potential method to stimulate motor plasticity following motor functional impairment (37).

Peripherally or centrally applied electrical stimulation is another valuable tool to promote functional improvement related to modulation of specific cortical areas and the underlying mechanisms have been investigated. Recent analyses with fMRI have revealed areas of brain activation induced by peripheral neuromuscular electrical stimulation in healthy and stroke subjects (38, 39), a method of stimulation that has been combined with TMS in order to evaluate neuroplasticity changes in the CNS during training.

An exciting finding involving central neuroplasticity was the effect of environmental enrichment. This refers to the paradigm of behavioral modeling wherein the animal is kept in an open, stimulus-rich environment or in a closed, unstimulating one. Although implications for rehabilitation in humans have been suggested, well-designed studies in environmental enrichment have been conducted only in animals. In the context of an enriched environment, neuroplasticity events such as dendritic arborization, synaptogenesis and neurogenesis, have been found to be enhanced in the dentate gyrus of rodent hippocampus (40,41).

Physical exercise in a wheel, an important component of such an enriched environment, is also able to trigger neuronal growth, proliferation and survival in healthy mouse hippocampus (Fig. 2) (25,42). Moreover, wheel running prior to experimental transient global cerebral ischemia is capable of reducing animal mortality and hippocampal neuronal damage (43). Studies demonstrate, as described below, the mechanisms by which the neuronal activation promoted by physical activity are able to trigger the neuroplasticity responses necessary for post-ischemic neurofunctional recovery (25).

More recently, it has been shown that drugs with adren-

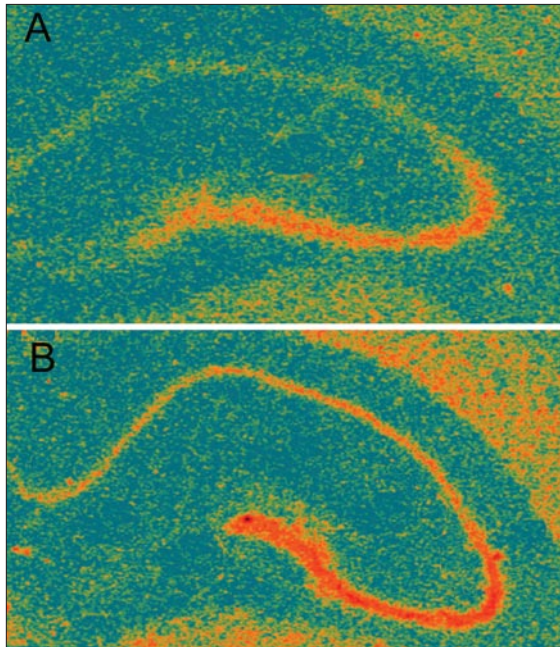


Figure 2 - An example of neuronal stimulation promoted by physical activity inducing molecular plasticity in the brain. Digital color image of a film radioautogram showing growth associated protein 43 (GAP-43) mRNA signal from a hybridized section of the hippocampus of rats kept in a control cage (A) or in a cage provided with an exercise wheel (B). GAP-43 expression has been associated with morphological neuronal changes in the brain. Exercised rats were allowed spontaneous physical activity in the wheel for 14 days. GAP-43 mRNA signals were massively increased in all sub-regions of the hippocampal formation of the trained animals. Several research groups have associated an enriched environment, including exercise wheel training, with better cognitive performance and reduced anxiety.

ergic or dopaminergic function administered in combination with training might modulate neuroplasticity in cortical areas. Indeed, drugs inducing functional modulation of GABA, glutamate or muscarine cholinergic receptors might trigger or impair cortical plasticity. For example, it was shown that the GABA receptor agonist lorazepam is able to block LTP responses. Moreover, the antagonist action induced by dextromethorphan on NMDA receptors also blocks LTP and experience-dependent plasticity in the motor and somatosensory cortices (29). These descriptions emphasize the role of neuronal activity, physiological and/or drug-induced, on cortical neuroplasticity in the brain.

Several reports have shown the involvement of neurotrophic factors, particularly the members of the neurotrophin family, in the brain mechanisms related to neuroplasticity during normal conditions or after injury (44). Their actions are seen in a wide range of neuronal events, including development, proliferation, differentiation, myelination, maintenance and apoptosis. Moreover, neurotrophic molecules are also factors for axonal growth and synaptic plasticity (45).

The history of neurotrophins can be traced back 50 years, to when Levi-Montalcini, Cohen and Hamburger discovered the nerve growth factor (NGF), a prototypical

neurotrophin required for axonal growth from peripheral sympathetic and sensory neurons (46). Other members of the neurotrophin family, such as brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4), were then identified and their contribution to brain neuroplasticity has been the subject of extensive investigation. Indeed, several recent reports have described in detail the importance of BDNF in neuroplasticity, highlighting the molecular mechanisms involved in its ability to modulate synaptic efficacy, including regulation of synapse formation, neurotransmitter release and neuronal excitability (Fig. 3) (47-49). Recent studies have demonstrated the ability of an enriched environment to upregulate neurotrophins in the rat hippocampus, providing a valuable tool for triggering the hippocampal neuroplasticity required for learning and memory (50). Despite the robust knowledge acquired from experimental models on the importance of neurotrophic factors in brain plasticity, data about their effects in humans are still lacking, given the inherent infeasibility of *in vivo* chemical investigations of human brain tissue.

Attention should be drawn to the fact that molecules involved in axon guidance during CNS development may interfere with axonal outgrowth after neuronal injury and may also be important in the process of neurorehabilitation. They include oligodendrocyte myelin proteins (e.g. Nogo-A) as well as astroglial cell surface and extracellular matrix molecules (51). It is worth drawing attention to the analysis of the effects of Nogo-A neutralization on neuronal regeneration and plasticity in experiments conducted *in vitro* and also after CNS lesions, in this latter case leading to functional recovery *in vivo* (52). Moreover, there is a role for regulation of extracellular matrix molecules, like proteoglycans, after CNS injury, given that their expression in the lesioned area changes and

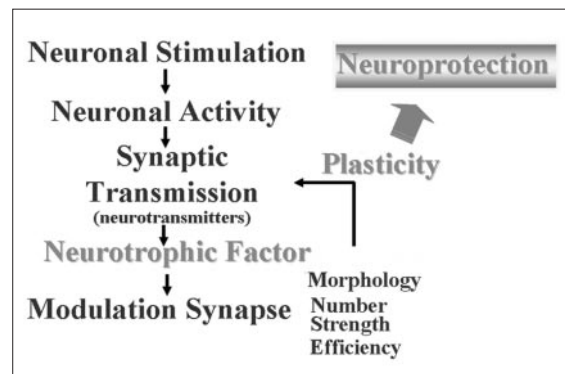


Figure 3 - Scheme showing the relationship between neuronal activity and neuroplasticity in the brain. Neuroplasticity is modulated by neurotrophic factor signaling during neurotransmission. Neuronal stimulation and activity triggering synaptic transmission lead to neurotransmitter and neurotrophic factor signaling between pre- and postsynaptic neurons. BDNF is the most studied neurotrophin in glutamatergic synapses. Morphological and molecular responses take place in the involved synapses leading to increased synapse efficiency. Due to the participation of neurotrophic molecules, the neuronal stimulation-induced neuroplasticity may be able to trigger neuroprotection against secondary neurodegeneration in the subacute phases post injury, favoring subsequent neurorehabilitation.

contributes to the inhibition of axon regrowth and brain repair (53). Despite the potential of these molecules to influence the results of neuroplasticity, analysis of their regulation by neuronal stimulation or neurorehabilitation strategies is still lacking.

The effects of adaptive plasticity on functional recovery after motor cortical damage and its relevance to clinical neurorehabilitation strategies

While many animal experiments and clinical brain imaging studies have attempted to clarify the mechanisms underlying neuroplasticity after brain lesions, only few clinical studies have focused on the benefits of neuroplasticity and rehabilitation intervention in the time course of human neurofunctional recovery. Currently, neurorehabilitation interventions are based on the concept that neuronal stimulation triggers neuroplasticity, however, clinical examination of its effects has been mainly at behavioral level. In spite of the fact that several types of rehabilitation intervention have been employed to achieve functional gain after CNS lesions, much work is still needed in order better to understand the underlying mechanisms. Having, on the basis of experimental evidence, gained enormous knowledge of cellular and molecular mechanisms related to neuroplasticity and cortical reorganization after brain lesions, we now need to understand better the exact role of clinical intervention in these events and vice versa.

In a meta-analysis conducted on a behavioral level, Kwakkel et al. (5) provided evidence of a similar non-linear pattern of arm and leg functional spontaneous recovery, as well as competence in basic activities of daily living, over approximately six months after stroke. Indeed, a powerful predictor of degree of independence at six months was the rate of responses during the phase with fastest recovery, which was the first few weeks post stroke. After reviewing the mechanisms of brain and behavioral reorganization, the authors concluded that the neuroplastic capacity of the CNS is more intense during acute and subacute phases and that early training can favor functional improvements, thus providing support for the value of therapeutic rehabilitation intervention as early as the initial phases post injury.

Another issue in rehabilitation strategies that has been analyzed behaviorally is how to deal with affected body segments. *Constraint-induced movement therapy* for chronic stroke hemiparesis and other disabilities has given some functional results, however it is not yet widely accepted among rehabilitation professionals. Enduring non-use of the affected limb can be observed after stroke and may, in part, be behaviorally conditioned by the experience of uselessness in the acute phase. This kind of non-use learning might persist even after the release of the affected limb in the chronic phase. This notion has provided support for the strategy of *constraint-induced rehabilitation*. This approach uses several techniques, including restraint of the healthy limb, to stimulate the use of the paretic extremity in an attempt to encourage function-enabling plasticity, because non-use of the paretic limb may further contribute to function-disabling plasticity (54).

Like other authors, Deutsch et al. (55) described the use of the virtual reality technology model of neuronal stim-

uli for neurofunctional rehabilitation of individuals post stroke. This system, mimicking the enriched environment studies, creates several virtual simulations which engage the user in a problem-solving task in order to acquire a skill. In addition, virtual simulation is able to address specific impairments, of range of motion, strength and speed for example, to promote intense repetitive practice, and to provide sensory and proprioceptive inputs using cues and feedback in a variety of ways (5). Likewise, many studies using assistive technology in rehabilitation, for instance functional neuroprostheses, peripheral sensorimotor stimulation, anesthesia or brain cortical stimulations, showed clinical evidence of improved motor recovery. Visuomotor coordination, motor learning, skilled finger movements and working memory responses could be seen in healthy volunteers and also in patients with brain lesions (2,24,56,57). Worth highlighting are the results of clinical studies on functional neuromuscular electrical stimulation, which show that local coordination training associated with active stimuli on the impaired upper extremity can promote motor recovery in terms of muscle activation pattern and manual dexterity (58).

All in all, there is much scope for neurorehabilitation therapies based on the concepts of task-specific repetitive training, sensorimotor stimulation and intensive training. These may enhance functional recovery by exploiting brain plasticity, which should be further investigated clinically at cellular and molecular level with the development of appropriate technologies.

Concluding remarks

Recent neurochemical and neuroimaging evidence has highlighted the functional and structural dynamic properties of the nervous system, particularly the cerebral cortex, allowing a non-linear neurological functional recovery after injury. At cellular level, neurochemical and morphological changes in the neuronal contacts and also in non-neuronal cells are observed experimentally. The functional topography of the motor cortex can be modified after brain injury by a variety of experimental manipulations, including neuronal stimulation and behavioral experience. Spontaneous post-injury neuroplasticity or therapeutic stimulation may play an adaptive role in modifying the functional organization of the remaining cortical tissue, leading to clinical improvements. A better understanding of the mechanisms of neuroplasticity is necessary to develop more effective rehabilitation strategies.

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