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Plasticity of the Cortical Motor System

by
Bogdan Sadowski[1]

The involvement of brain plastic mechanisms in the control of motor functions under normal and pathological conditions is described. These mechanisms are based on a similar principle as the neuronal models of neuronal plasticity - long-term potentiation (LTP), and long-term depression (LTD). In the motor cortex, LTP-like phenomena play a role in strengthening synaptic connections between pyramidal neurons. LTD is important for the elimination of unnecessary inputs to the cortex. The dynamic features of the primary motor cortex activity depend on particular neuronal interconnectivity within this area. The pyramidal cells send horizontal collaterals to adjacent subregions of the primary motor cortex, and so can either excite or inhibit remote pyramidal cells. These connections can expand or shrink depending on actual physiological demands, and play a role in skill learning.

Key words: brain plasticity; ischemic brain stroke, motor cortex, transcranial brain stimulation

The brain has two fundamental functional properties – excitability and plasticity. The excitable brain can respond to a variety of stimuli with a short-lasting physiological process, leading to generation and propagation of action potentials (nerve impulses). The plastic brain can undergo biochemical and morphological changes, due to which neurons and brain centers become more (but also less) susceptible to environmental stimuli, or can store relevant information long after the stimulus has already decayed.

Plastic properties of the brain

Two main forms of brain plasticity are distinguished – neuronal and representational. Neuronal plasticity is responsible for the improvement of synaptic transmission between neurons. Due to representational plasticity of the sensory and motor cortex, the representations of body parts are not stable, but expand or shrink depending on physiological demands, or a function of a cortical area can be taken over by an adjacent or a remote region.

Neuronal plasticity

The idea of brain plasticity was introduced into physiology by the Polish neurophysiologist Jerzy Konorski (in 1948) and the Canadian psychologist Donald O. Hebb (1949). The concept of neuronal plasticity, commonly referred to as the Hebbian rule, is briefly summarized by saying: neurons that fire together, wire together.

[1] - *Professor Emeritus from the Polish Academy of Sciences. Lecturer in physiology and neurobiology at the Warsaw Medical University, English Division. Awarded by the Fellowship for Senior Scientists, Foundation for Polish Science (2006)*

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The mechanism of neuronal plasticity was evidenced directly at the synaptic level in two cellular models of learning, one called long-term potentiation (LTP), and the other long-term depression (LTD). LTP consists of an increase, and LTD consists of a decrease in the efficacy of the synapse connecting two simultaneously excited neurons (reviewed by Malenka and Bear 2004).

LTP and LTD are most often studied ex vivo, in brain slices excised from the hippocampus, a structure involved in encoding episodic memory, but also in other structures involving the motor cortex and cerebellum. Parallel studies were made in living animals.

Routinely, two electrodes are introduced into the hippocampal slice: one to stimulate the presynaptic axon, and the other, a microelectrode, to record electric activity of the postsynaptic neuron innervated by this axon. The experiment is done in three steps.

In step 1, the axon is stimulated with a single electric pulse to elicit in the following neuron a postsynaptic synaptic potential (EPSP) of moderate amplitude (1 in Figure 1).

In step 2, to induce LTP, the axon is stimulated by one or several series of high frequency pulses (usually 100 Hz, 2a in figure 1). If LTD is intended, low-frequency (usually 1 Hz) stimulation of the axon is administered for 15 min (2b in figure 1). Thus, depending on the stimulus parameters used to repeatedly excite the presynaptic fiber, either LTP or LTD can be induced in the postsynaptic neuron.

In step 3, the presynaptic axon is stimulated with the same single electric pulse as it was in step 1. When LTP was induced in step 2, the stimulation now produces a far larger EPSP in the postsynaptic neuron, and this effect can be assessed up to 2 weeks later (3a in figure 1). The prolonged augmentation of EPSP is thought to reflect a more efficient synaptic transmission between the two neurons, which is just the essence of LTP. In the case LTD was induced, the stimulation produces a lower EPSP, reflecting a lessened synaptic transmission (3b in figure 1).

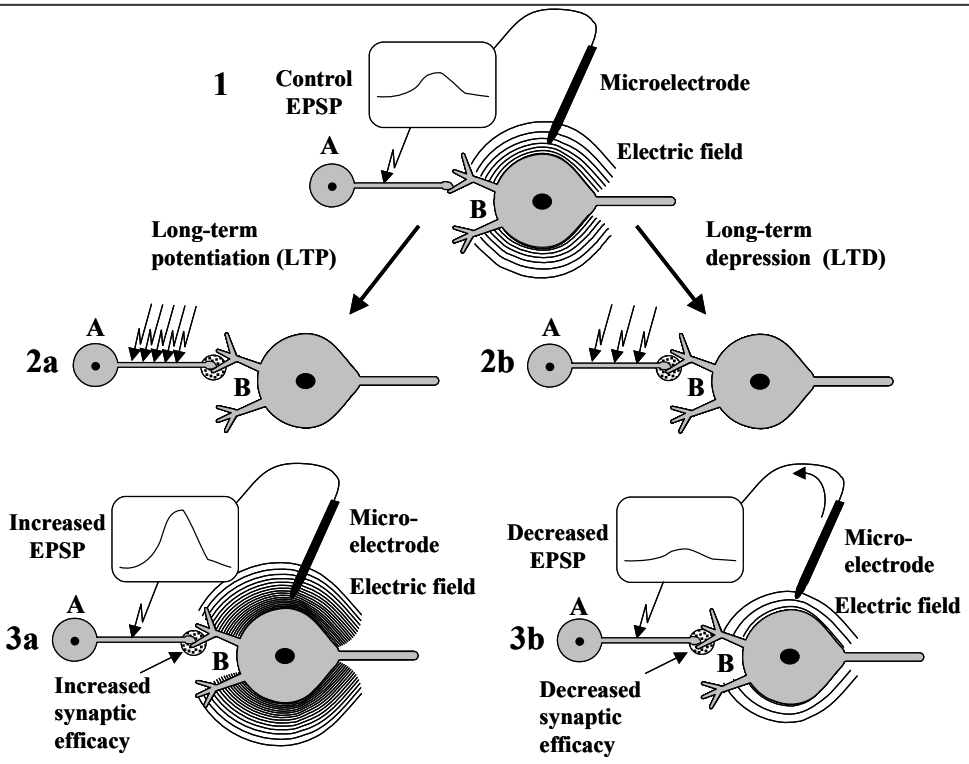

Figure 1

Three stages of inducing and testing long-term potentiation (LTP) and long-term depression (LTD). 1 – stimulating the axon of neuron A (afferent fiber) with a single pulse to evoke in the postsynaptic neuron (B) an excitatory postsynaptic potential (EPSP) of moderate amplitude. 2 – repetitive stimulation of the same afferent fiber with high frequency pulses to induce LTP (2a), or with low frequency pulses to induce LTD. 3 – testing LTP (3a) or LTD (3b) with a singlepulse, as in 1; note a respective increase (3a) and decrease (3b) in EPSP amplitude

LTP and LTD are most often induced in glutamatergic synapses, located on dendritic spines of the postsynaptic neuron. Glutamate, which is released as neurotransmitter from the axon terminal into the synapse, acts on AMPA and NMDA receptors, embedded in the postsynaptic membrane (Figure 2A). These two classes of glutamate receptors are equipped with ion channels that open as glutamate, released into the synapse from the axon terminal, binds to the receptor. The AMPA-receptor channels become then permeable to Na^+ ions, which enter into the cytoplasm. The Na^+ ions, being carriers of positive electric charges, produce depolarization of the neuron (excitatory postsynaptic potential, EPSP). Glutamate also binds to NMDA receptors, whose channels are permeable to Na^+ and Ca^{2+} ions. However, the NMDA-receptor channels, though open, cannot immediately pass the Na^+ and Ca^{2+} ions, because they are blocked by Mg^{2+} ions. They can do so only as the magnesium blockade has been removed by the earlier depolarization produced by the entry of Na^+ ions through the AMPA-receptor channels. Then the unblocked NMDA-receptor channels allow additional massive influx of Na^+ ions, which increase and prolong the existing depolarization. Together with the Na^+ ions, also Ca^{2+} ions enter the neuron through the NMDA-receptor channels. Calcium is a potent activator of many enzymes, which profoundly modify the biochemistry of the cell. In particular, Ca^{2+} ions bind to the protein calmodulin to form the Ca^{2+}/calmodulin complex (CaM).

High-frequency stimulation of the presynaptic axon in step 2 leads to accumulation of large amounts of Ca^{2+} ions and CaM in the postsynaptic neuron. High CaM level activates Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). CaMKII plays a crucial role in the induction of LTP. First, it phosphorylates AMPA-receptor proteins, thereby increasing the recep-

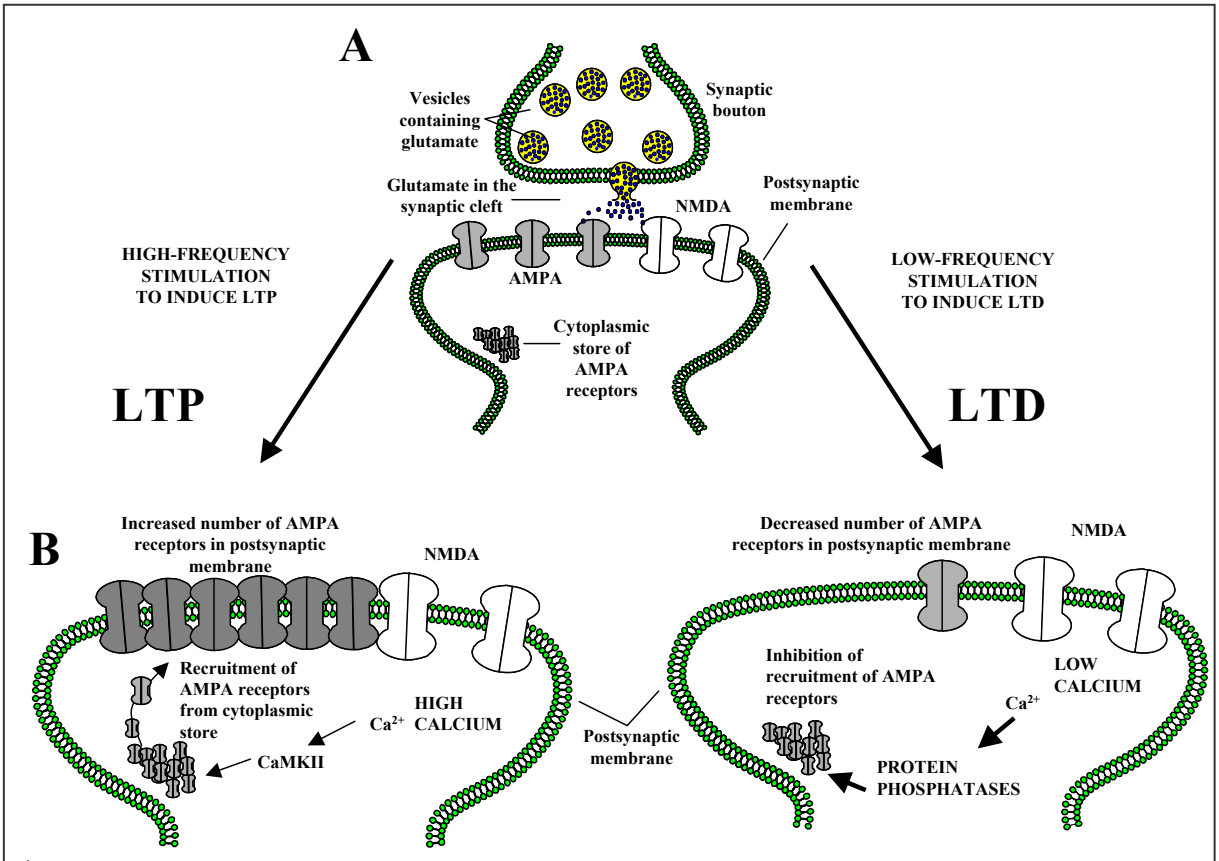

Figure 2

Intraneuronal changes during the induction of long-term potentiation (LTP) and long-term depression (LTD). A – glutamatergic synapse. B – LTP: increase in AMPA receptors density in the postsynaptic membrane in response to high Ca2+ concentration and activation of Ca2+/calmodulin-dependent protein kinase II (CaMKII). C – LTD: increase in AMPA receptors density in the postsynaptic membrane in response to low Ca2+ concentration and activation of protein phosphatases

tor channel's permeability to Na^+ ions. Secondly, it promotes the AMPA-receptors trafficking (Figure 2B, left). Before the induction of LTP only a small number of AMPA receptors are associated with the postsynaptic membrane, whereas the majority remain stored in the cyto. Under the effect of CaMKII, the stored AMPA receptors migrate to the dendritic spines, where they are incorporated into the postsynaptic membrane. A greater number of active AMPA receptors in the postsynaptic membrane account for the increased efficacy of the synapse connecting the two neurons.

Low-frequency stimulation of the presynaptic axon, used in step 2 to induce LTD, leads to far less accumulation of Ca^{2+} ions and CaM in the postsynaptic neuron. Low CaM level, which is inadequate to activate CaMKII, activates protein phosphatases instead (Figure 2B, right). Note that protein phosphatases, which dephosphorylate and inactivate proteins, act inversely to protein kinases, which phosphorylate and activate proteins. Thus, the prevalence of protein phosphatases in the cell results in a lower glutamate binding by AMPA receptors, and impairs the trafficking of AMPA receptors from the cytoplasmic store to so the postsynaptic membrane. In consequence the synapse becomes less sensitive to glutamate, and is less efficient in transmitting the excitation, which is just the essence of LTD

LTP was also elicited in the motor cortex, and the same involvement of glutamate transmission was observed similarly as in the hippocampus (Buonomano and Merzenich 1998). The electric pulses were delivered to the underlying white matter with the purpose to excite afferent presynaptic fibers innervating pyramidal neurons in layer V, and recordings of EPSP were made from this layer . However, the studies with cortical motor neurons often brought less success than did those with hippocampal neurons. In order to elicit LTP, it was necessary to reduce the neuronal inhibition with GABA-ergic antagonists, or to facilitate the influx of Ca^{2+} ions by decreasing the magnesium blockade of NMDA receptors. This was presumably because the pyramidal neurons of the motor cortex are tonically inhibited by neurons in adjacent or remote cortical areas.

An LTP-like increase in synaptic efficacy was found in the primary motor cortex of rats, which has learned the performance of a motor task with the contralateral forepaw (Rioult-Pedotti et al.1998). Neuronal LTD-like processes are thought to play a role in the reorganization of horizontal connections in the primary motor cortex (Hess and Donogue 1996). This can lead to the elimination of inactive inputs to the pyramidal neurons, thereby facilitating the expansion of active cortical areas.

Representational plasticity

The representational plasticity of the sensorimotor cortex was evidenced in numerous experimental and clinical studies. Some frequently cited examples are reported below.

String playing musicians have larger sensory representation of fingers of the left hand in comparison both with fingers of the right hands and with the fingers of the left hand of control subjects (Elbert et al. 1995).

The blind proficient in Braille reading, revealed larger cortical representation for the right index finger (used for reading), as compared with the left index finger (not used for reading) in the same person, or with the representation of the right index finger in unexperienced control subjects (Pascual-Leone and Torres 1993).

People with congenital syndactyly have a common cortical representation for the fused fingers. These fingers after surgical separation developed separate representations in the somatosensory cortex (Mogilner et al 1993).

Maguire et al. (2000) described a profound reorganization of the hippocampus in London taxi drivers, who need a larger neuronal network to store the spatial memory of the city topography.

Cortical motor areas

The region of the cerebral cortex controlling motor and sensory activities is termed the sensorimotor cortex. The sensorimotor cortex consists of motor and somatosensory areas. The motor areas are located in the frontal lobe, whereas the somatosensory areas are located in the parietal lobe.

The motor areas comprise the primary motor area, and secondary (association) areas: premotor (dorsal and ventral), supplementary motor area (SMA) and pre-supplementary motor area (pre-SMA)

The somatosensory areas comprise the primary somatosensory area (S1), the secondary somatosensory area (S2) and association somatosensory areas. The primary somatosensory area (S1) is located in the postcentral gyrus of the parietal lobe. It comprises four Brodmann's areas - 3a, 3b, 1, and 2. S1 is the target of sensory information from the skin, joints and muscles. The secondary somatosensory area (S2) is located posteriorly to the lateral part of S1. The superior parietal lobulus, separated from the postcentral gyrus by the postcentral sulcus, contains two sensory association areas - BA5 and BA7b. Corticospinal neurons are also present in the somatosensory areas S1 and S2. Therefore, these areas, apart of their role in the somatic sensation, are also involved in the control of motor functions.

Classically, the somatotopic organization of the two primary areas of the sensorimotor cortex, that is, the primary motor and the somatosensory area S1, has been conceptualized under the form of the homunculus cartoon, with nonoverlapping point-to-point representations of particular muscles and sensory skin areas (Penfield and Rasmussen 1957). Nowadays, however, it became evident that this model, instead of having a general value, is applicable only to major anatomical divisions of the body, such as the head, trunk, arms and legs. Distal components of these bodily regions, as fingers, lips or feet, are represented in functionally organized subregions, which are not stable, but can expand or shrink depending on actual physiological or behavioral demands (Sanes and Donoghue 2000).

Neuronal structure of the sensorimotor cortex

The sensorimotor cortex has a six-layer structure. The successive layers are as follows: I - molecular, II - external granular, III, external pyramidal, IV - internal granular, V - internal pyramidal and VI - multiform layer. The somatosensory input information reaches the cortex through thalamocortical fibers arising in the ventrobasal thalamic nuclei. Most of the thalamocortical fibers terminate in layer IV, which is particularly developed in the S1 area. From layer IV there is a robust vertical flow of information, targeting layers II, III and V. Output from the sensorimotor cortex occurs through pyramidal cells.

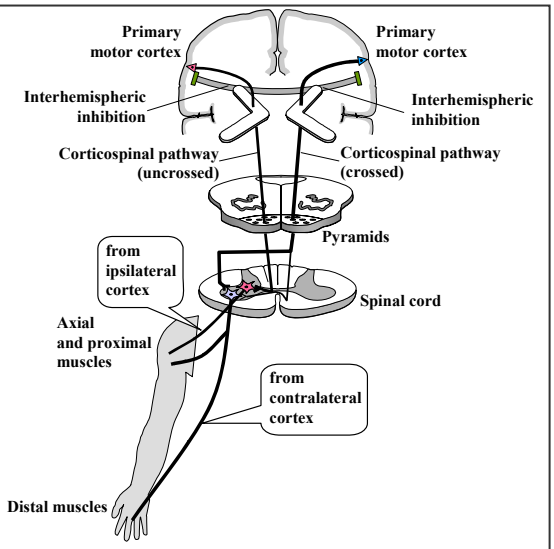

Figure 3

Contralateral and ipsilateral innervation of the upper limb muscles by the motor cortex

The primary motor cortex, located in the precentral gyrus (BA [Brodmann's area] 4 of the frontal lobe, contains a particularly large layer V. Layer IV is scarse, so that layers II, III and V contain an array of pyramidal neurons increasing in size, from the smallest ones present in layers II and III, to the largest neurons in layer V. The axons of these large pyramidal cells (also termed corticospinal neurons) give rise to the corticospinal tracts. Small pyramidal neurons project to other cortical regions of the same and the opposite hemisphere. Apart from the motor function, the primary motor cortex also receives sensory information from the motor organs, and so is involved in somatic sensation.

Corticospinal connections

The corticospinal tracts descend through the internal capsule and medullary pyramids to the spinal cord. After leaving the medullary pyramids, about 90% of the corticospinal fibers cross the midline, run in the lateral funiculus, and innervate motor centers on the contralateral side of the spinal cord. The remaining 10% descend in the ventral funiculus, and cross the midline

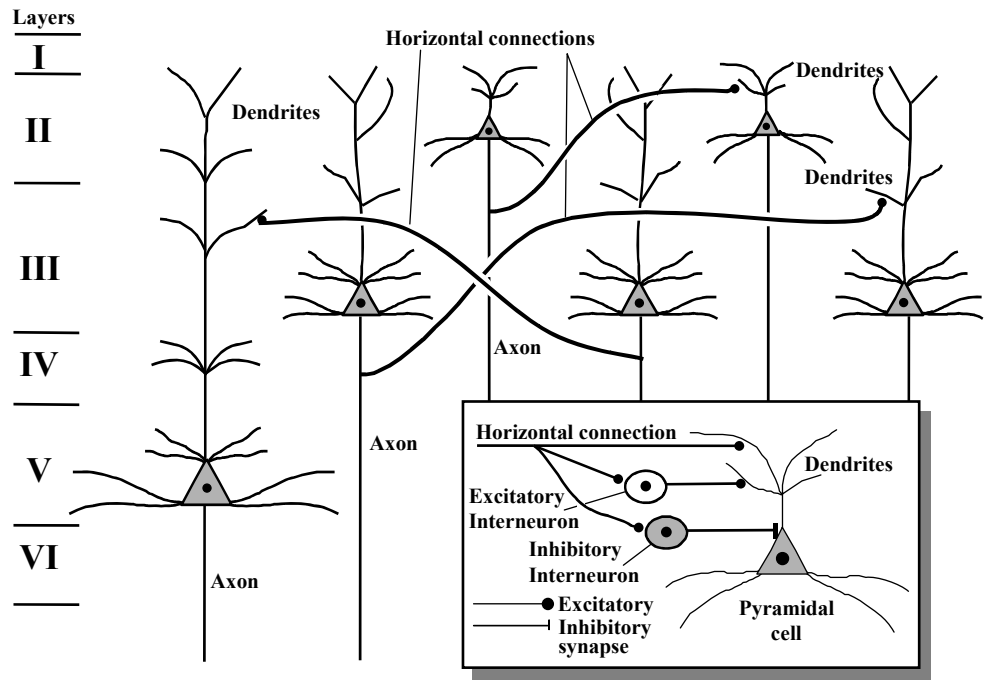

Figure 4

Distribution of large (layer V) and small (layers II and III) pyramidal cells in the motor cortex. Horizontal connections, made by collaterals emerging from axons of small pyramidal cells, are shown. The insert illustrates a direct excitatory action of the collaterals on nearby pyramidal cells, and an indirect action, exerted through excitatory and inhibitory interneurons

just before entering the spinal motor center. Due to this organization, the muscles of each side of the body are controlled by the opposite (contralateral) cerebral hemisphere. A minority of corticospinal fibers remain uncrossed, and innervate spinal motor centers on the same (ipsilateral) side of the body. However, only axial muscles stabilizing the body posture, and proximal muscles of the limbs are targets of this ipsilateral innervation, whereas distal muscles of the upper limbs, performing fine manipulatory movements, are controlled almost exclusively by the contralateral hemisphere (Figure 6).

The dynamic features of the primary motor cortex activity depend on particular neuronal organization of this area. Studies with functional magnetic resonance imaging (fMRI) in humans found labile overlapping activations in the primary motor cortex, as subjects performed distinctive movements of the fingers, wrist, and elbow. Complementary electrophysiological studies in animals revealed that a single cortical neuron can send commands to multiple muscles, and vice versa, a single muscle can receive commands from multiple cortical neurons . Importantly, this divergence/convergence scheme is continuously modified to conform to the requirements of each actually executed motor activity (Schieber and Baker 2003).

Horizontal connections in the primary motor cortex

Apart from the downstream corticospinal and corticocortical outputs, the primary motor cortex contains horizontal intracortical connections between adjacent cortical areas. The horizontal fibers arise mainly from small pyramidal cells in layers II and III (Figure 3). Axons of these pyramidal neurons do not contribute to the corticospinal tracts, but project to remote cortical regions of the same and the opposite hemisphere, thus forming intercortical connections. These axons on their way give off collaterals, passing horizontally through layers II and III, which excite, by means of glutamatergic synapses, pyramidal neurons, as well as excitatory and inhibitory interneurons in adjacent cortical zones. The inhibitory interneurons on their turn inhibit, by means of GABA-ergic synapses, the pyramidal neurons (see insert in fig-

ure 3). Thus, a pyramidal neuron, through horizontal connections, can directly excite adjacent or remote pyramidal neurons, and can also modulate their excitation through excitatory and inhibitory interneurons (Buonomano and Merzenich 1998).

Importantly, the synapses between the horizontal fibers and pyramidal neurons undergo plastic changes induced by activity and training, and can encode memory traces of fine manual movements. Also, the horizontal connections are not stable, but can be strengthened or weakened depending on behavioral demands. Therefore, the primary motor cortex is the main target of post-stroke rehabilitation, aming to facilitate the recovery of the lost neuronal connectivity.

Non-invasive examination of the motor cortex

The motor areas of the brain and the cerebellum can be examined non-invasively with neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), SPECT (single photon emission computerized tomography) and PET. FMRI uses differential magnetic properties of hemoglobin and deoxyhemoglobin, which modify the radio frequency (RF) signaling elicited from the brain in a strong magnetic field, depending on oxygen extraction from the blood by the brain area under study. DTI designed to track myelinated fiber connections, based on the Brown's motion of water molecules. Whereas fMRI mainly reflects the metabolic activity of cell bodies, DTI enables to examine the integrity of corticospinal axons. This is particularly important for the assessment of the consequences of subcortical lesions, but also enables to follow the progress of development of vicarious connections in the course of post-stroke recovery. SPECT and PAT measure the intensity of radiation produced by radioactive isotopes, accumulated in the brain after being introduced into the human organism.

Two procedures - transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) allow non-invasive stimulation of the cerebral cortex.

Transcranial Magnetic Stimulation (TMS)

TMS uses a rapidly changing magnetic field to elicit, via electromagnetic induction, electric currents flowing in the cerebral cortex parallel to its surface. To achieve this, a wire coil is held over the scalp to make the magnetic field reach the area of interest through the overlying skin and skull bone. The electric currents induced by the magnetic field excite directly horizontal connections between pyramidal neurons, and indirectly the pyramidal neurons innervated by these horizontal pathways (Figure 5).

In order to study cortical motor functions under normal and pathological condition, the magnetic coil is held over the primary motor cortex. The electrodes for electromyographic (EMG) recording are placed on the skin over the muscle of interest. The position of the coil on the scalp is adjusted, so that each TMS pulse would elicit in the muscle a clear-cut EMG response, termed a motor evoked potential (MEP).

Depending on the stimulus parameters, TMS can elicit in cortical networks excitatory or inhibitory phenomena, Therefore, to meet specific

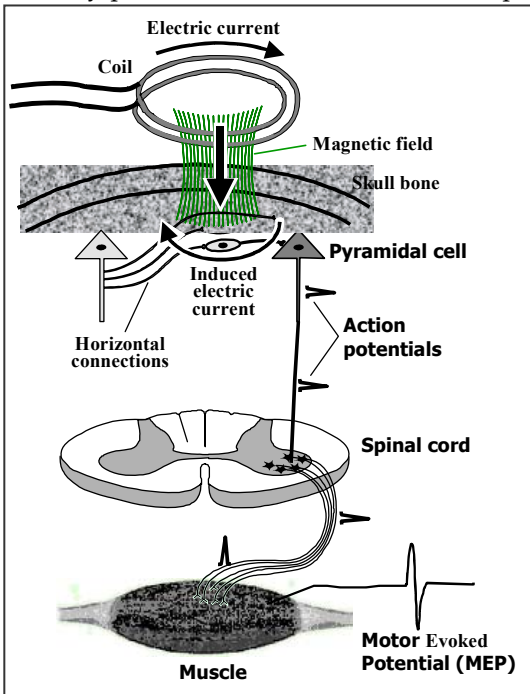

Figure 5

Transcranial magnetic stimulation (TMS) of the motor cortex. TMS induces electric currents in the horizontal connections, which can excite or inhibit the target pyramidal cells. The stimulus intensity is set so as to elicit muscle evoked potentials (MEP) in the muscle of interest

requirements of diagnosis or therapy, the magnetic stimuli are delivered as single, paired, or repetitive pulses.

TMS with single pulses

In the domain of the cortical motor control, single magnetic pulses are mainly used to check the excitability of corticospinal neurons. To accomplish this, the following variables are measured.

- The amplitude and latency of MEP;
- The motor threshold, that is, the lowest TMS intensity eliciting visible MEP (usually of 50 μV amplitude);
- The extent of scalp area over which MEP can be elicited;
- The recruitment curve, that is, the plot of MEP amplitude against increasing TMS intensity (the steeper the curve, the higher the cortical excitability).

Single magnetic pulses can also suppress tonic muscle activity, which effect is termed a "silent period" and depends on activation of inhibitory interneurons. Single TMS can even interfere with the ongoing performance of a motor task. In this case the stimulus-produced inhibition develops within the same cortical circuitry, which is actually excited during execution of the task. Therefore, single TMS, synchronous with voluntary motor actions, is suited to identify the cortical areas involved in the performance of motor activities.

TMS with paired pulses

In a paired-pulse paradigm, two TMS pulses are delivered in a nonoverlapping sequence. Depending on the length of the gap (the interstimulus interval) separating the two stimuli, the first stimulus, itself being ineffective, can either augment or suppress the magnitude of MEP to the second stimulus. The augmentation of MEP is due to a facilitatory process termed intracortical facilitation (ICF), whereas the suppression of MEP can occur either in the form of short-latency intracortical inhibition (SICI) or as long-latency intracortical inhibition (LICI).

In order to induce ICF or SICI, the first stimulus is set at subthreshold level, and the second stimulus is of suprathreshold intensity. At short interstimulus intervals (1-4 ms), the paired-pulse TMS stimulation produces SICI; that is, the MEP magnitude to the second pulse is lower than when the second pulse is given alone. At longer interstimulus intervals (8-10 ms), the paired-pulse stimulation produces ICF.

Distinct to the intracortical inhibition is the intercortical inhibition. The latter is often seen in the muscle ipsilateral to the stimulated cortex, while the contralateral muscle manifests a clear-cut MEP.

Repetitive TMS

Repetitive TMS (rTMS) is used to modulate the excitability of neurons in the cerebral cortex, rather than to stimulate or inhibit them directly. Usually the cortical modulation produced by rTMS outlasts the time of the stimulation. The modulatory effect of rTMS depends on the frequency, intensity, and duration of the stimulating pulses. Repetitive TMS with low-frequency pulses (1Hz) decreases cortical excitability, whereas at higher frequencies (5Hz), rTMS increases cortical excitability. Repetitive TMS applied at 5 Hz frequency during motor training can enhance practice-dependent plasticity. This finding makes rTMS a promising tool to improve the motor cortex functions after brain lesions, particularly in patients after ischemic stroke. Low-frequency rTMS applied to the nonlesioned hemisphere to alleviate its overexcitation, and high-frequency rTMS applied to the affected hemisphere to augment its excitation might facilitate the performance of motor tasks with the paretic hand.

Transcranial direct current stimulation

The purpose of transcranial direct current stimulation (tDCS) is to make the cerebral corex more or less sensitive to other stimuli of various origins. TDCS consists of passing direct current through the skull by means of two wet gel-sponge electrodes. The active electrode is positioned on the scalp to polarize electrically the underlyimg motor cortex, and the reference electrode is attached to the skin of the contralateral supraorbital region (Figure 6).

Activity-driven plasticity

In response to practice and experience, the neuronal organization of the cerebral cortex undergoes functional and structural modifications, termed activity-driven (or activity-dependent)

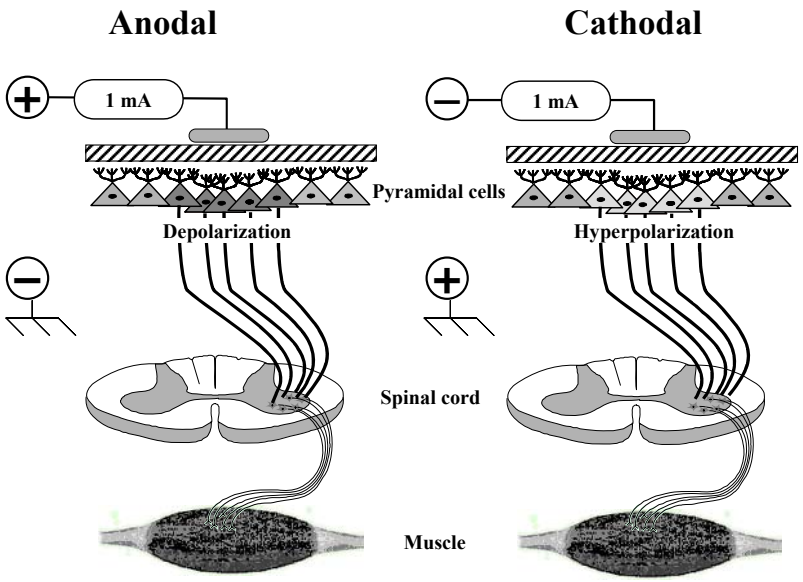

Figure 6

Transcranial direct currrent stimulation. Depolarization and hyperpolarization of the pyramidal cells elicited by passing, respectively, anodal or cathodal current through the motor cortex

changes. These plastic processes have been studied in volunteers given a variety of tasks engaging cognition processes or motor skills. The two task categories – cognitive and motor – produced a different pattern of cortical activity, as evidenced with neuroimaging techniques. Performing cognitive tests for working memory or visuomotor learning was accompanied by a decrease in activity in relevant brain regions. The decrease in activation is thought to reflect a more efficient functioning of neural networks, engaging only limited number of neurons in the execution of a learned cognition-based procedure. On the opposite, the improvement in motor skills led to an increase in activity in the relevant motor areas. The increase in activity was seen in the form of enhanced fMRI or PET signaling from a given region (thereby reflecting a neuronal plasticity process) or appeared as an expansion of a relevant area, thus reflecting the representational variant of plasticity (Kelly et al. 2006).

Karni et al.(1998) proposed that motor learning proceeds in several phases: a fast initial phase corresponds to the acquisition of a task-relevant knowledge. It involves attentional and cognitive processes, and leads to encoding of an explicit motor memory trace. This phase is followed by a consolidation period lasting several hours, during which the conscious (explicit) memory of the task improves, even if the task itself is not exercised. The final phase is a slow learning process extending over weeks of practice, during which the performance gradually increases. The slow learning, thought to occur implicitly, leads to increase in activation in specific topographical areas of the primary motor cortex, or to expansions of brain representations of the exercising muscles (reviewed by Kelly and Garavan 2005). The mechanism, through which these expansions occur, relies on extensions of horizontal connections between pyramidal neurons in adjacent cortical zones. The horizontal connectivity in the primary motor cortex can expand as a result of increased synaptic efficacy through a plasticity process similar to long-term potentiation. Another mechanism can involve a removal of intracortical inhibition and uncovering of silent horizontal connections (Buonomano and Merzenich 1998). Since the strengthening of horizontal connections proceeds with practice, the slow learning is considered to rely on an activity-dependent plastic process.

Activity-driven plasticity in the motor cortex enables implicit learning of motor skills and is beneficial for the recovery from stroke, there the cognitive knowledge of the tasks is preserved, but the execution is impaired. One should bear in mind, however, that brain plasticity processes stimulated by activity training may sometimes have a maladaptive value, as the focal

hand dystonia in musicians in response to repetitive movements and extensive practice (Pujol et al. 2000), or the phantom limb syndrome.

Brain plasticity and the recovery from ischemic brain stroke

Brain stroke in the medial cerebral artery vascularization area is the cause of long-term disability due to persistent upper limb paresis, which impairs the activities of patient's normal life, as dressing, eating, self-care and personal hygiene. The severity of the disability and the success of post-stroke recovery depend much on the size of the lesion and its location.

In cases of subtotal ischemic injury, neurons in the adjacent, intact tissue (so-called penubra, peri-infarct or peri-lesional zone) within the motor hand area survive. However, early after the stroke this zone, upon brain imaging, often appears reduced in size. The reduction in size is attributed to diaschisis, caused by a loss of connections from the central area, which are necessary to support the function of its surroundings (Mountz 2007). This shrinked zone, however, can expand due to appropriate rehabilitation training.

The reduction in size of the spared peri-lesional portion was observed in monkeys with experimentally produced ischemic focus in the sensorimotor cortex (Nudo 2007). However, when monkeys were given rehabilitative training, the spared area was preserved, or even expanded toward adjacent representation of the proximal part of the limb. This result shows that when the injury is small, the spared area may contain sufficient neuronal circuitry to take over the role of the lesioned brain tissue. Then, the involvement of other motor regions, as the premotor cortex, in the recovery process may be not necessary. Pertinent to this issue is the finding of upregulation of NMDA receptors, and downregulation of $GABA_A$ receptors in the spared area, which makes it prone for the induction of plastic changes and for the recruitment of additional corticospinal neurons to substitute functionally the destroyed ones. This observation allows to infer that a similar recovery process may be triggered by rehabilitaton in human patients with small ischemic lesions.

Liepert et al. (2000b) used paired-pulse TMS to examine short-latency intracortical inhibition (SICI) and intracortical facilitation (ICF) in patients who had undergone acute cerebral infarction, and manifested a mild to moderate hemiparesis. In comparison to pronounced SICI on the unaffected side, SICI in the affected hemisphere was significantly reduced. ICF did not differ between the hemispheres. The reduction of SICI is thought to reflect a disinhibitory process in the spared portion of the lesioned tissue, which relies on a reduced activity of GABA-ergic inhibitory interneurons. This disinhibition is regarded as a compensatory mechanism which, by increasing cortical excitability, promotes post-stroke cortical reorganization and favors the recovery.

The cortical disinhibition, assessed by paired-pulse TMS, does not exclude the existence of other inhibitory processes in the cortical circuitry, based on different neuronal mechanisms. In the same study, Liepert et al. (2000b) evoked prolonged 'silent periods' (that is, suppression of existing muscle tension) by administering single TMS pulses to the lesioned cortex, in contrast to shorter 'silent periods', which were seen as the intact cortex was stimulated. It is also important to point to the enhanced intercortical (transcallosal) inhibition, which the intact hemisphere exerts on the lesioned cortex (see below).

With larger injuries, when there are no available residuals in the lesioned primary motor cortex, other motor areas in the affected and/or the intact hemisphere take over the role of the lesioned primary motor cortex and participate in the recovery. This process is termed vicariation.

Putative role of the intact primary motor cortex

Some evidence suggests that the motor cortex in the nonlesioned (healthy) hemisphere can take over the functions of the lesioned cortex. This notion is supported by studies demonstrating that functionaly efficient ipsilateral corticospinal connections exist in healthy persons, and are potentially capable to take over the control over the paretic arm afer ischemic stroke.

Chen et al. (1997) administered TMS stimulation to the right or the left primary motor area of healthy subjects with the purpose to compare the disruption of a simple or a complex finger-tapping sequence, performed with the ipsilateral hand (right or left, respectively) on an electronic piano. The stimulation on either side worsened the accuracy of timing the ipsilateral finger movements both in simple and in more complex sequences. With the complex sequences, however, the stimulation of the left motor cortex induced more timing errors, when the left hand was used, than did the stimulation of the right motor cortex. Contralateral stimulation severely disrupted the performance irrespective of its complexity. The left hemisphere appeared then superior compared to the right hemisphere in timing complex motor sequences in the ipsilateral arm, and can be more involved in the processing of skill performance. In view of this property, the primary motor cortex of the intact, particularly the left hemisphere comes to possess enough capability to take over the function of the injured motor area on the lesioned side.

Ziemann et al. (1999) succeeded to activate selectively ipsi- or contralateral muscles by gently adjusting the position and direction of the TMS coil over the subject's skull. Motor evoked potentials were obtained in th ipsilateral side in the finger and wrist extensors and in the biceps, but only if the muscle of interest was voluntarily contracted. The authors suggest that ipsilateral muscles are activated by uncrossed slow-conducting corticoreticulospinal and corticopropriospinal pathways. This route is distinct to the crossed fast-conducting corticospinal pathways, activating contralateral muscles.

Normally, the two hemispheres remain in a relatively stable balance due to reciprocal inhibitory interactions; that is, the primary motor area in each hemisphere suppresses, to some extent the symmetric area in the opposite hemisphere. In stroke patients, however, the inhibitory action of the lesioned hemisphere on the healty hemisphere is markedly reduced. As a result, the intact hemisphere becomes permanently overactive (Harris-Love and Cohen 2006). One could expect several consequences of this overactivity, which might be beneficial for the recovery process.

First, the overactive intact sensorimotor cortex could be prone to send motor commands to the ipsilateral paretic limb through uncrossed pyramidal pathways. Although the uncrossed fibers target those spinal motoneurons which innervate proximal, and not distal limb muscles, even crude movements of the paretic arm might be beneficial for patient's recovery from stroke.

Secondly, the overactive intact primary motor cortex recruits remote motor areas, such as the premotor area in the same intact hemisphere, the supplementary motor area in the either hemisphere, and the cerebellum contralaterally to the intact hemisphere. The activated association motor areas might take over the function of the lesioned sensorimotor cortex (Rossini et al. 2007).

In accordance with these premises, Cramer et al. (1997) found increased activation in the intact sensorimotor cortex during performance of a finger-tapping task, executed with the paretic hand by patients with good recovery from stroke. The patients also showed increased activation in the premotor area of the same hemisphere, and in the either supplementary motor area.

However, the contribution of the intact motor cortex to the recovery process is not universally recognized. Truly, some evidence shows that the improvement of performance is sometimes associated with overactivity of the nonlesioned sensorimotor cortex, as for example, during bilateral training (see below). But other data show that the overactive intact hemisphere may rather exert a deleterious effect on the recovery. By overinhibiting the injured hemisphere, it opposes the formation of beneficial plastic changes in the lesioned hand area, or even disturbs the training of movements with the paretic arm. Whereas in healthy people the inhibition of the primary motor cortex by the opposite hemishere subsides just before the execution of the movement, this does not come to occur in stoke patients; in consequence, the persistent intercortical inhibition impairs the motility of the paretic limb (Harris-Love and Cohen 2006).

Overactivity of the intact motor area is scored with the laterality index, computed from the formula (L-I)/(L+I). The characters denote the magnitudes of neuroimaging signals, taken

from the lesioned (L) and the intact (I) hemisphere during performance of motor tasks with the paretic and the intact hand. The laterality index can range from +1 (only the lesioned hemisphere is active) to –1 (only the intact hemisphere is active). Stroke patients manifesting a low laterality index long after the stroke usually show poor recovery, whereas good recovery is in most cases accompanied by a prompt increase of the index score (Rossini et al. 2007).

The role of non-primary cortical areas

With greater injuries, the premotor area, particularly its dorsal part, substitutes the lesioned motor cortex in the control of movements; this process is termed vicariation. But as the primary motor cortex, also the premotor area in the lesioned, rather than in the intact hemisphere, appears important for the proces of recovery. The premotor cortex, as well as SMA, normally do not issue motor commands directly, but only "instruct" the primary motor cortex how to execute a given movement. However, after injury of the primary motor area, the premotor cortex can indirectly stimulate spinal motoneurons through pyramidal cells, whose axons descend to the brain stem and activate reticulospinal pathways and propriospinal circuits.

Fridman et al. (2004) stimulated with single TMS pulses the dorsal premotor cortex of the lesioned hemisphere in satisfactorily recovered chronic stroke patients, having focal lesions located in the internal capsule. This region contains pyramidal pathways originating in the primary motor cortex. The stimulation interfered with the ongoing performance of the motor task, executed by the paretic hand. No such disruption of performance was seen when the premotor cortex in the intact hemisphere was stimulated, and the task was executed with the intact hand. This experiment argues that the premotor area in the lesioned, but not in the intact hemisphere possesses functionally efficient vicarious connections to the spinal cord.

Johansen-Berg et al. (2002) used single TMS to stimulate ipsilateral motor areas while healthy subjects and post-stroke patients performed a simple or a complex motor task. The task started with a visual cue, and the reaction time (or latency) from the cue to the onset of performance was measured. The simple task involved the movement of the index finger only, whereas the complex task consisted of a random movement of 4 fingers. In healthy subjects, the TMS pulse ad ministered to the ipsilateral dorsal premotor area 100 ms after the visual cue prolonged the reaction time of the complex task, but had no effect on the simple task. In post-stroke patients, TMS stimulation of the dorsal premotor area in the intact hemisphere prolonged the reaction time of the simple task performed with the paretic hand (the complex task was too difficult for them). Importantly, the reaction time was more prolonged in patients in a worse clinical condition. This result supports a notion that the vicarious role of the dorsal premotor area in the intact hemisphere in the recovery from stroke is apparent in poorly recovered patients, rather than in patients with good recovery.

The differential involvement of the lesioned and the intact hemisphere in the process of post-stroke recovery depending on patients' disability was also compared with electroencephalographic (EEG) recordings. Serrien et al. (2004) analyzed EEG records during the performance of a submaximal isometric grip task. In unrecovered stroke patients executing the grip with the affected hand, the task-relevant flow of information between the either sensorimotor cortex came from the ipsilateral (undamaged) hemisphere. In recovered patients and in healthy controls, the cortical EEG activity came from the contralateral cortex.

Possible vicarious connections to the spinal cord, involved in the recovery from stroke, are shown in figure 7.

Brain plasticity and rehabilitation training

Shortly after injury, plastic changes occur in the cerebral cortex to compensate for the loss of function of the affected region. Although in some cases these changes can lead to substantial spontaneous recovery, better results are obtained with therapeutic interventions, expected to focus the brain plasticity processes in a beneficial direction. An important way to induce plastic changes in the brain is practice. The activity-dependent changes are indispensable for

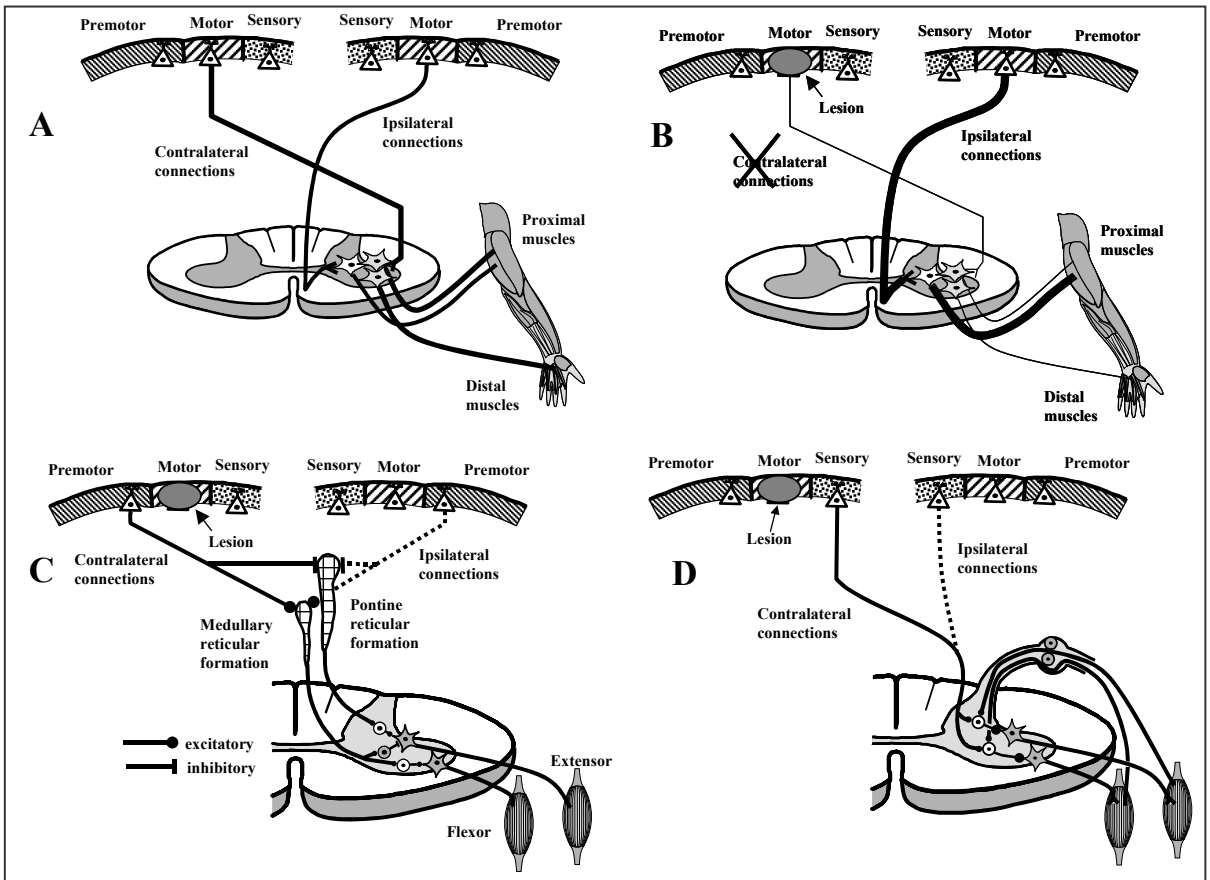

Figure 7

Vicarious connections innervating the paretic arm in the case of ischemic lesion of the primary motor cortex. A – contralateral amd ipsilateral innervation in health conditions. B – the intact primary motor cortex takes over the function of the lesioned hemisphere and excites the limb muscles through uncrossed fibers in the pyramidal pathways. C – connections from the contralateral and ipsilateral premotor area. C – connections from the contralateral and the ipsilateral somatosensory area

the acquisition of skills. Accordingly, rehabilitation procedures that involve active training of the paretic hand aim to prompt plastic reorganization of the affected sensorimotor cortical region.

The importance of rehabilitation strategy for the development of plastic changes in the motor cortex was studied most extensively in patient given constraint-induced motor therapy or bilateral training.

Constraint-induced motor therapy

Constraint-induced motor therapy (CIMT) is a method of training the paretic arm, while the intact arm remains restrained during 90% of the waking time, in order to limit its use in most daily activities. In the meantime, the patients receive, several hours per day excluding weekends, extensive training of the paretic arm in a variety of tasks. The forced behavioral therapy, adopted in the variants of CIMT, intends to overcome the 'learned nonuse' of the paretic arm, and to promote a plastic reorganization of the motor cortex in a beneficial direction for the recovery. The effectiveness of the training is evaluated, additionally to routine laboratory tests, with the motor activity log (MAL), an interview tracking patient's 20 real-world activities of daily living, such as feeding, dressing the upper and the lower extremity, bathing and grooming, performed outside the laboratory.

From the neurobiological point of view, the prolonged nonuse of the paretic arm, together with the concomitant overuse of the intact arm, should lead to an expansion of motor representations in the intact hemisphere, at the cost of shrinkage of motor representations in the lesioned hemisphere. Theoretically then, the intense CIMT procedures would do the reverse; that is, they should promote the activity-driven plasticity in the lesioned hemisphere to nor-

malize the cortical maps in the two hemispheres. In reality, however, this assumption was confirmed by some investigators, whereas mixed results were reported by others (reviewed by Mark et al 2006).

Promising results supporting the superiority of CIMT over conventional therapies were obtained by Liepert et al. (2000a, 2001, 2006). Patients with chronic stroke were given 6-hours daily CIMT training up to 12 days. This relatively short therapy resulted in large improvements in paretic hand dexterity, confirmed by an increase in the MAL scores. The recovered limb functionality persisted undiminished up to 6 months post-training testing.

The clinical improvement was paralleled by the data of TMS mapping. The stimulation of the lesioned hemisphere revealed a large expansion of the abductor pollicis brevis musclerepresentation, with a shift of the center of gravity (CoG). The mechanism of this massive cortical reorganization probably reflected an increase in neuronal connectivity in the lesioned hemisphere. A likely mechanism is an enhancement of the synaptic strength and/or reduction in activity of local inhibitory interneurons. Finally, the translocation of CoG may indicate an increase in activity of spared neurons in the periphery of the lesioned locus.

The behavioral improvement after CIMT was accompanied by an increase in MEP amplitudes, together with a decrease in MEP thesholds, which argues for an increase in cortical excitability in the affected hemisphere.

Other authors, using neuroimaging techniques, also reported changes in activity in the primary motor and secondary motor areas after CIMT. The results, however, were not consistent with respect to the hemisphere where these activations prevailed. Thus, of the five patients studied by Kim et al. (2004), three responded to CIMT with activation in the primary motor, the premotor and the supplementary motor areas of the lesioned hemisphere. On the opposite, one patient manifested similar activations, but on the intact side, and one displayed decrease in activation in the primary motor cortex of the lesioned hemisphere. Szaflarski et al. (2006) studied the effectiveness of CIMT therapy in 4 patients. One patient, who exhibited only minor improvement of the paretic limb function, also manifested no change in post-treatment fMRI data. In others, the conspicuous motor improvement was accompanied by robust modifications of cortical and subcortical activity, however in one patient only was the post-treatment increase in activity confined to the lesioned hemisphere.

The effectiveness of CIMT in modulating brain plasticity during post-stroke recovery was recenty reevaluated by Gauthier et al. (2008). The authors supplemented the conventional training procedures with behavioral techniques, which they termed the transfer package. The purpose of this additional therapy was to make use of therapeutic gains, achieved in the laboratory, in patient's real-world activities with the use of the paretic arm.

The CIMT therapy group exhibited increased gray matter content in sensory and motor areas, contralateral and ipsilateral to the affected arm. No such changes were seen in the control comparison group, given conventional training. The authors emphasize that the training to induce structural changes in the motor and sensory areas, must be behaviorally relevant. They speculate that the growth of gray matter in these brain regions might be due to dendritic arborization and increase in synaptic density. It is also conceivable that the special rehabilitation procedure used in this study, might stimulate the process of neurogenesis in the infarcted locus.

Bilateral arm training

Bilateral arm training therapy, that is, performing the same motor task with the either arm, uses the phenomenon of interlimb coupling, in which the movements of one arm tend to follow the movements of the opposite arm.

Paired-pulse TMS administered to healthy volunteers executing a motor task with one arm, revealed increased intracortical facilitation and decreased intracortical inhibition in the contralateral motor cortex, and increased intracortical inhibition in the cortex on the same side as the trained arm. When subjects performed the task with the either arm, increased intracortical facilitation and decreased intracortical inhibition occurred in both hemispheres. These results show that bilateral arm training modulates activity in the motor cortex of both hemispheres

(McCombe Waller and Whitall 2004). Since interlimb coupling, particularly during arm reaching movements, persists after brain stroke, it is conceivable that the paretic arm might benefit from performing similar training movements as the intact arm.

In the study of Goldberg and Hanley (2004), participants pushed and pulled bilaterally, in synchrony or alternation, two handles. The training was paced by auditory stimuli delivered at 1 Hz or lower rate. The superiority of rhythmic over nonrhythmic therapies relies on a better spatiotemporal congruence of the trained movements, when they are imposed by a pace (Whitall et al. 2000). Controls were qualified to standard therapeutic procedures, matching in time the bilateral training, such as thoracic spine mobilization, scapular mobilization, weight bearing with the paretic arm, and opening a closed fist. Some patients given bilateral training, but none of the control group, displayed increased activity in the precentral and the postcentral gyrus of the intact cerebral hemisphere, and in the contralateral (with respect to the intact hemisphere) cerebellum. In these patients, but not in others, an improvement of the paretic arm function was noted.

An important outcome of the bimanual training is the activation in the intact hemisphere (Luft et al. 2004). It is to remind that activation in the intact hemisphere commonly occurs early after stroke. This is interpreted by a strengthening of uncrossed corticospinal projections, which are little active in health. Thereafter, along with the progress of recovery, this activation declines, whereas its persistence is regarded as a sign of unfavorable prognosis.

The beneficial effect of contralateral hemisphere activation in bilateral training is based on complex mechanisms. It can be attributed to a lessening of interhemispheric (intact to lesioned) inhibition, in favor of enhanced interhemispheric facilitation. This might lead to cortical disinhibition in the lesioned hemisphere and thus facilitate the involvement of the spared area in the control of movements. Another mechanism could rely on increased coupling between the hemispheres: When bilateral symmeric movements are performed, the motor command, sent to the intact hemisphere to activate the intact arm, can be dispatched as a mirror image, using ipsilateral connections, to the homologous muscles of the paretic arm (Cauraugh ans Summers 2005). Thus, the activation of the intact hemisphere in the course of bilateral training might facilitate the recovery process in the lesioned motor cortex, which is forced to induce coupled movements of the paretic arm.

Therapeutic benefits from non-invasive cortical stimulation

Repetitive TMS was used in stroke patients to upregulate the activity in the lesioned hemisphere. This procedure improved paretic arm motor performance in some patients (Khedr et al. 2005). Attempts were also made to downregulate the overactivity in the intact hemisphere in order to suppress its inhibitory action on the lesioned motor cortex (Ward and Cohen 2004; Mansur et al. 2005).

Promising results were obtained by raising the excitability of the motor cortex with transcranial direct current stimulation (tDCS). In the study of Hummel et al. (2005), the active electrode (anode) was positioned on the patient's scalp just over the hand area of the affected primary motor cortex. Direct 1 mA current was passed through the skull during 20 min. Trials with brief current duration (30 s), termed sham stimulations, were included as controls; they elicited identical transient tingling sensation on the scalp, as did the true tDCS at their onset, but were too short-lasting to modify the cortical excitability.

First, the patients practiced the Jebsen-Taylor Hand Function Test. The test consists of a series of tasks taken from daily motor activity, such as turning over cards, picking up small objects and placing them in a can, picking up small objects with a teaspoon and placing them in a can (mimicking a feeding function), stacking chequers, moving large light cans, and moving heavy cans. The time needed to complete the performance was a measure of motor efficiency. Then the patients were asked to perform the tasks in the course of tDCS, or sham stimulations. At the end of the session, the performance was examined several times without cortical stimulation to estimate the duration of the tDSC effect.

The beneficial effect of tDCS on patients' performance behavior was found to correlate with an increase in excitability of the lesioned primary motor area, assessed with diagnostic TMS stimulation. The behavioral improvement was accompanied by (1) steeper increase in MEP amplitude upon raising TMS magnitude, and (2) reduced short-latency intracortical inhibition (SICI).

Although non-invasive stimulation of the motor cortex in the affected hemisphere can improve the function of the paretic hand within sessions, little is known whether this effect might contribute to a long-term recovery. One can expect better results from administering the cortical stimulation not alone, but following consecutive routine rehabilitation training sessions.

Perspectives

Future research in the field of rehabilitation-dependent brain plasticity is going to be focused on better understanding the neurobiological consequences of brain stroke, with the involvement of growth factors, cytokines and hormones. One can expect that more attention will be given to behaviorally relevant training procedures.

The plastic processes will be studied in more detail with particular attention given to the formation of new neurons in the ischemic area. Promising results were reported in animal (Magavi et al. 2000; Chen et al. 2004) and human studies (Jin et al. 2006). The possibility to stimulate neurogenesis in the lesioned tissue might substantially increase the effectivemenss of post-stroke therapy.

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Corresponding author

Bogdan Sadowski
Professor Emeritus from the Polish Academy of Sciences
Schroegera 72 m 18
01-822 Warszawa
Phone: +48 22 8340603
Fax: not available
e-mail sadbogd@yahoo.com