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Shaping plasticity to enhance recovery after injury

Numa Dancause^{†,*} and Randolph J. Nudo[‡]

[†]Département de Physiologie, Université de Montréal, Chemin de la Tour Montréal, Québec, Canada

[‡]Landon Center on Aging, Kansas University Medical Center, Kansas City, Kansas, USA

Abstract

The past decade of neuroscience research has provided considerable evidence that the adult brain can undergo substantial reorganization following injury. For example, following an ischemic lesion, such as occurs following a stroke, there is a cascade of molecular, genetic, physiological and anatomical events that allows the remaining structures in the brain to reorganize. Often, these events are associated with recovery, suggesting that they contribute to it. Indeed, the term plasticity in stroke research has had a positive connotation historically. But more recently, efforts have been made to differentiate beneficial from detrimental changes. These notions are timely now that neurorehabilitative research is developing novel treatments to modulate, increase, or inhibit plasticity in targeted brain regions. We will review basic principles of plasticity and some of the new and exciting approaches that are currently being investigated to shape plasticity following injury in the central nervous system.

Keywords

Cortex; Stimulation; Plasticity; Recovery; Rehabilitation; Stroke

Concept of a plastic brain

The adult nervous system is organized in a way that allows for substantial recovery of lost functions after acquired brain injuries. For example, after stroke, the most dramatic recovery in motor function occurs within the first 30 days, though moderate and severe stroke survivors continue to improve for at least 90 days (Duncan et al., 1992). Recovery profiles after focal traumatic brain injury are similar, though diffuse injuries require a longer time (Jang, 2009). The neural bases for such recovery, especially in the absence of specific rehabilitative interventions, have intrigued scientists and clinicians for centuries. It has only been in the past 25 years that modern neurophysiological, neuroanatomical, and neuroimaging tools have been brought to bear on this question, resulting in startling findings regarding the degree of structural and functional plasticity of the central nervous system.

To explain recovery in the absence of interventions—a phenomenon known as spontaneous recovery—three basic theories have been proposed. First, since remote structures connected to the site of injury often go through a temporary period of depressed metabolism and blood flow (diaschisis), it is widely held that at least part of the recovery must be due to the resolution of this process. Second, changes in joint and muscle kinematic patterns are common after cortical injury, and compensatory patterns are often used to accomplish tasks

in either subtle or fundamentally different ways. Third, the nervous system undergoes a process of local, and sometimes distant, rewiring. While it is assumed that this is an adaptive process, it is possible that maladaptive plasticity occurs as well. Studies investigating postinjury adaptive plasticity, in the form of modulation of long-term potentiation, long-term depression, unmasking, synaptogenesis, dendritogenesis, and functional map plasticity, have exploded over the past decade and are arguably the most exciting areas in the field of neuroscience due to their implications for understanding and treating injury-related functional deficits.

Various plasticity mechanisms underlying functional recovery are embodied in the theory of vicariation—the ability of one part of the brain to substitute for the function of another (Slavin et al., 1988). Since modern views of brain organization recognize that the cerebral cortex is arranged in a distributed, hierarchical fashion, vicariation does not necessarily require that a function lost after damage is taken over by a totally unrelated structure, as suggested by some early interpretations but that other related components of the distributed network reorganize to support the recovered function. A number of studies supportive of this theory have demonstrated that the motor cortex of adult mammals changes its activation patterns in response to cortical injuries. Rat and nonhuman primate studies using intracortical microstimulation (ICMS) to derive detailed maps of the functional representations in the motor cortex have suggested that the neural substrates mediating recovery reside within the peri-infarct cortex (Castro-Alamancos and Borrel, 1995; Glees and Cole, 1949; Nudo et al., 1996b), spared motor areas in the injured hemisphere, such as the premotor cortex (Dancause et al., 2006; Frost et al., 2003; Liu and Rouiller, 1999) and the supplementary motor area (Eisner-Janowicz et al., 2008). Physiological reorganization of the neural activity in the sensory cortex of the uninjured hemisphere has also been shown (Rema and Ebner, 2003; Reinecke et al., 2003). Neural reorganization within these spared motor regions of the injured and uninjured hemisphere is thought to be necessary for postinjury recovery of motor function (Biernaskie et al., 2005; Castro-Alamancos et al., 1992; Conner et al., 2005; Kleim et al., 2003a; Liu and Rouiller, 1999; Rouiller et al., 1998).

Plasticity in topographic maps as a functional index

In the 1980s, a fundamental change in our thinking about cortical plasticity occurred, spurred by innovative neurophysiological studies in the somatosensory cortex (Buonomano and Merzenich, 1998). While it had been known for many years that functional plasticity occurs in the cerebral cortex of developing animals, these studies demonstrated that the topographic organization of the representation of skin surfaces in the somatosensory cortex of adult monkeys is modifiable as a result of peripheral nerve injury, disuse or behavioral training. These studies provided credence to the vicariation hypothesis, and impetus for increasing investigation of neurophysiological and neuroanatomical plasticity in the normal and injured cerebral cortex. Subsequently, parallel studies were conducted in other sensory areas of the cerebral cortex, as well as in the motor cortex of experimental animals and in humans. All of these studies have provided strong support for the notion that plasticity of cortical maps is a general trait of cerebral cortex even in mature animals and that rules of temporal coincidence and behavioral context drive emergent properties of cortical modules regardless of their specific cortical location.

Assuming that map plasticity and behavioral abilities are interrelated, as they appear to be, these studies have enormous importance for our understanding of the process of recovery after central and peripheral nervous system injury. Topographic maps can be tracked overtime in individual animals, and thus can be used as biological markers of recovery. Further, by examining cellular and molecular correlates of map change, it may be possible to

more fully understand the neural mechanisms underlying neuroplasticity, and ultimately control these mechanisms for rehabilitative purposes.

Two-stage process of map plasticity

The notion that input and output properties in cortical sensory and motor areas are plastic throughout life is now widely accepted and is generalizable across all cortical regions. With respect to relevance for rehabilitation, most studies have focused on the primary motor cortex (M1), primarily because (a) it is often affected by clinical stroke due to its blood supply by the middle cerebral artery, (b) the clinical effects of stroke in M1 are often devastating (hemiparesis), and (c) the close link between neurons in M1 and motoneurons in the spinal cord via the corticospinal (CS) tract allows the relationship between cortical physiology and motor behavior to be examined at various levels of analysis.

It is likely that at least two processes are involved in the alteration of topographic maps in both somatosensory and motor cortex. First, there is an immediate unmasking phenomenon that cannot be explained on the basis of neuroanatomical sprouting. Instead, there is likely a change in the efficacy of existing synapses allowing subthreshold inputs to be expressed. The expression of inputs from ascending fibers arriving in the cerebral cortex is largely controlled by inhibitory interneurons that utilize γ -amino butyric acid, subtype a (GABA_A) as a neurotransmitter. GABA_A receptor binding in layer IV of adult monkey area 3b is reduced in the deprived cortex within hours of peripheral nerve injury and this reduction persists for at least several weeks, if not permanently (Garrahy et al., 2006; Wellman et al., 2002). This result is consistent with the long-held belief that peripheral nerve transection leads to a disinhibition of tonically suppressed inputs. In the motor cortex of rats, similar mechanisms supporting rapid reorganization of representation borders in the motor cortex have been reported. For example, cortico-cortical connections exist between the vibrissae and the forelimb representations in the rat cortex. Under normal conditions, the projections from the vibrissae to the forelimb representation are inhibited by local GABAergic control. Because of this inhibition, the cortical stimulation results in vibrissae and not forelimb movements. Thus, the local inhibition contributes to the definition of the physiological border between these two representations. If bicuculine, a competitive antagonist of GABA_A receptors, is injected into the forelimb representation, it blocks local inhibition of cortico-cortical projections from the vibrissae. Consequently, some sites where vibrissae movement could be evoked prior to the injection now evoke forelimb movements. Thus, the removal of the local GABAergic inhibition in the forelimb representation results in a rapid expansion of the forelimb area into neighboring vibrissae areas (Jacobs and Donoghue, 1991).

The second phase, lasting at least several weeks, results in the remainder of the deprived cortex gradually becoming responsive to other inputs. In somatosensory cortex, this translates into input from adjacent skin surfaces. It is likely that dendritic sprouting plays a role in this longer-term alteration in reorganizational maps (Hickmott and Steen, 2005). Systematic changes occur in dendritic arborization of layer II/III pyramidal and layer IV spiny stellate cells. There appears to be a progressive expansion of distal but not proximal regions of the dendritic trees of both basal and apical dendrites (Churchill et al., 2004). Blockade of the NMDA receptor at the time of peripheral nerve injury has no effect on the immediate stage of unmasking but prevents long-term reorganization from occurring. Interestingly, NMDA receptor blockade has no apparent effect on the organization of normal area 3b cortex, or on the topography of injury-induced reorganized 3b (Myers et al., 2000). However, by 1 month after injury, GABA_B receptor binding is reduced, and AMPA receptor binding is increased. Comparisons have been made between topographic changes in somatosensory cortex and changes in the hippocampus during LTP (Garrahy et al., 2006).

Map plasticity in motor cortex

Neurophysiological maps can be derived in motor cortex using various stimulation techniques in experimental animals, even under anesthesia. Somatotopic organization of the motor cortex was elegantly shown in the early 1950s in both humans (Penfield and Rasmussen, 1952) and monkeys (Woolsey et al., 1952) using epidural cortical stimulation. In the late 1960s, the development of invasive cortical stimulation techniques, or ICMS, resulted in the capacity to stimulate many more focal sites (Stoney et al., 1968) and thus to create much higher resolution motor maps and precise identification of borders between the representations of different body parts. Using these techniques, it was possible to evaluate the effect of learning on the organization of the M1. The first studies explored cortical plasticity within M1 of normal (uninjured) monkeys and provided a basic description of fundamental properties of cortical plasticity relative to the distal and proximal forelimb representation in M1. In these studies, in order to investigate reorganization associated with motor learning, the M1 representational map of the distal forelimb (digits, wrist, forearm movements) is documented before the animals are trained. After training and improvement of the function on the task, the mapping is redone and compared to the data collected prior to training. Functional reorganization of motor maps was found to be dependent on prior behavioral experience. Reach and retrieval training on the Klüver board results in an increase in the representation of the digits in M1 and a relative decrease in the representation of the wrist and forearm (Fig. 1). If the task is changed to require the monkeys to turn a handle to receive a food pellet, shifting the behavioral demand from digit action to wrist action, wrist representations expand at the expense of digit representations (Nudo et al., 1996a). Further, multijoint movement representations appear after training, reflecting joint combinations and sequences used in the actual task. Multijoint representations thus are driven by temporally correlated activation of two or more movements during training and may reflect the development of muscle and joint synergies in motor cortex. Experiments in rodents using a skilled forelimb-reaching task have provided similar results. Two weeks of training on a single pellet retrieval task induces an expansion of distal forelimb (wrist/digit) movement representations within the sensorimotor cortex and increases the number of synapses per neuron in motor cortex (Kleim et al., 1998, 2004).

Reorganization is not simply due to increased use. Rats trained on tasks that do not specifically necessitate skilled use of the forelimb do not exhibit an expansion of the distal forelimb representation (Kleim et al., 1998, 2002; Remple et al., 2001). These behaviorally driven changes appear to be skill- or learning-dependent, as training animals on a task requiring no additional learning or skill acquisition (e.g., monkeys retrieving pellets from a large well), results in no changes in either motor maps or synaptic density. Similarly in monkeys, cortical maps remain stable from one mapping session to the next unless the monkeys are required to learn a new motor skill (Plautz et al., 2000).

Early studies using cortical surface stimulation techniques suggested that the hand representation in M1 of adult primates undergoes substantial remodeling following small lesions, and the cortical remodeling is correlated with functional recovery (Glees and Cole, 1950). Using more modern ICMS techniques, Nudo and Milliken (1996) found that movements represented in the infarcted zone did not reappear in the cortical sector surrounding the infarct. Instead, relatively small, subtotal lesions in representations of hand movements resulted in widespread reduction in the spared hand representations adjacent to the lesion, and apparent increases in adjacent proximal representations (see Fig. 2c).

It was reasonable to hypothesize that training techniques used in uninjured monkeys to demonstrate skill-dependent changes could have an adaptive influence on motor representations after cortical injury. In another experiment, small ischemic lesions were

made in the M1 hand area, sparing a large portion of this area. Deficits in motor skill were apparent in the pellet retrieval task. Within about 5 days, the monkeys were able to participate in the task again. Here, instead of letting the animal spontaneously recover, repetitive training was introduced using a protocol similar to the one used to induce motor learning in control animals (Nudo et al., 1996a). As monkeys regained proficiency at retrieval from large food wells, they advanced to progressively smaller wells. For most monkeys, pellet retrieval proficiency returned within about 2 weeks. At that point, the M1 hand area was explored with ICMS techniques once again. In monkeys receiving training, the spared M1 hand area was not statistically different from their baseline maps. That is, instead of a reduction in M1 hand area as seen in spontaneously recovered monkeys, the hand area was retained. In some cases, the hand area clearly expanded into former proximal representations (Nudo et al., 1996b). Due to the similarities of the training regimen to constraint-induced movement therapy (CIMT), this study has been cited as one of the first detailed demonstrations of the neurophysiological basis for poststroke physiotherapy.

Widespread effects in motor cortex networks after focal lesions

Focal lesions in a small portion of M1 have very different effects on remote hand representations in premotor cortex. Because of reciprocal connectivity of these areas with M1, if M1 is injured, there are inevitable effects in secondary motor areas. Using the ventral premotor cortex (PMv) as a model for these remote effects, as early as a few days after M1 injury, neurons in PMv undergo substantial changes in expression of proteins thought to be involved in neuroprotection and angiogenesis (Stowe et al., 2008).

In the chronic stage after M1 injury, there is a linear relationship between the size of the M1 infarct and enlargement of the hand representation in PMv. After lesions in M1 that destroy less than 30% of the hand area, the PMv hand representation actually shrinks slightly. However, after progressively larger M1 injuries, the PMv representation expands in proportion to the M1 loss (Dancause et al., 2006; Frost et al., 2003). These remote effects of M1 lesions have now been extended to the hand representation in the supplementary motor area (SMA), again relating remote map expansion with M1 lesion size (Eisner-Janowicz et al., 2008).

Due to a rich network of reciprocal intra-cortical connections, after focal injury to M1, remote areas are triggered to reorganize their axonal projection pathways. In rats, after cortical injury, the cerebral cortex in the intact hemisphere sprouts crossed axonal projections to the striatum of the injured side of the brain (Napieralski et al., 1996). There is also evidence that plasticity of intrinsic intracortical pathways can occur. Recently, using a squirrel monkey model of M1 infarct, we discovered that several months after an M1 infarct, PMv intracortical axons developed an aberrant trajectory (Dancause et al., 2005). Axons projecting toward the site of the lesion made sharp turns and avoided the lesion zone. A substantial number of axons then turned more caudally, heading lateral to circumvent the central sulcus, and finally terminated in a parietal area within the somatosensory cortex, area 1 (possibly both areas 1 and 2). This *de novo* cortical connection represented axonal growth of more than 1 cm, a very long distance in the small squirrel monkey brain (Fig. 3). Moreover, it was also shown that CS projections can reorganize. Following a lesion in M1 and Brodmann area 6, the ipsilesional SMA increases its projections to the contralateral spinal cord in laminae VII and IX (McNeal et al., 2010). The increase of projections is correlated with the recovery and a secondary lesion of SMA reinstated the motor deficits. Thus, the intriguing possibility exists that areas remote from cortical injury adaptively reorganize to compensate for the loss of M1 CS output by sending larger numbers of CS axons to terminate on the denervated motor neurons.

All of these studies provide strong support for the presence of major anatomical rewiring following injury in the mature brain, such as occurs as a consequence of stroke. This impressive anatomical reorganization could be supported by sequential waves of neuronal growth-promoting genes following the injury (Carmichael et al., 2005). Understanding the functional significance of injury-induced sprouting is an important topic for future research.

Postlesion map changes: adaptive, maladaptive or epiphenomenal?

Though remote areas expand following an M1 lesion, the functional significance of this change is still unclear. SMA may be an excellent model for understanding these effects, since it receives its blood supply from the anterior cerebral artery and is often spared after MCA strokes. The SMA of the two hemispheres are heavily interconnected and share dense reciprocal projections with M1 (Rouiller et al., 1994). It has also been estimated that 23% of SMA CS neurons project to the ipsilateral cord (Dum and Strick, 1996). But a recent study in SMA after extensive ischemic lesions that extended across the M1, the dorsal premotor cortex (PMd), and PMv hand areas questions a direct functional relationship of map reorganization to recovery (Eisner-Janowicz et al., 2008). In this study, behavioral recovery was limited to the first 3 weeks postinjury. Behavioral performance remained relatively constant and suboptimal throughout the next 10 weeks. However, maps of the hand area in SMA actually contracted in the first 3 postinfarct weeks. They subsequently expanded over the next 10 weeks. This temporal mismatch is not easily explained by a simple relationship of remote reorganization in a single area to behavioral recovery.

Also, SMA has greater influence on motor neuron pools controlling proximal, rather than distal muscles (Boudrias et al., 2006). In the Eisner-Janowicz study, the changes that were seen in the SMA hand representation after injury were attributed to wrist and forearm movement representations, not more distal, finger and thumb representations. In these chronic stages, monkeys were able to reach out and touch the pellet board, but were not able to retrieve pellets from the wells or even insert their fingers into the wells. This is not unlike human stroke survivors who can use proximal musculature to propel the limb forward, but do not have distal control over hand movements. Thus, it is possible that SMA may contribute to the development of compensatory movement patterns that rely in more proximal musculature. Similar results were recently seen in a focal traumatic brain injury model targeting the motor cortex in rats (Nishibe et al., 2010). While changes were seen in the rostral forelimb area after injury to the caudal forelimb area, there was a redistribution of movement representations from distal to proximal. Following a cortical injury, animals adjust the kinematics of forelimb movements to compensate for deficits in the affected musculature, often resulting in both proximal forelimb and postural compensation (Whishaw et al., 2004). Compensatory use of proximal musculature is also commonly observed in humans after stroke (Cirstea and Levin, 2000). Functional outcomes improve overtime, but true recovery may be masked (Whishaw, 2000; Whishaw et al., 1991) or even hindered (Alaverdashvili et al., 2007, 2008) by use of alternative movement strategies (Levin et al., 2009). Thus, if plasticity in remaining motor areas forms the basis for motor recovery (vicariation), and if motor skill acquisition drives the topography of motor maps, plasticity in spared structures likely supports compensatory motor strategies, rather than recovery of the original movement patterns (Fig. 4).

Structural and functional reorganization is not limited to spared regions of the injured hemisphere but may occur in homotopic regions of the intact hemisphere as well (Jones and Schallert, 1992). However, Jones and colleagues have provided substantial evidence that structural changes in both homotopic and heterotopic areas of the intact, contralateral cortex are related to hyperreliance on the intact limb, rather than recovery of the impaired limb (Allred et al., 2008; Bury and Jones, 2002; Chu and Jones, 2000). Human neuroimaging

studies have also repeatedly shown bihemispheric changes in activation patterns after stroke. However, the functional significance of increased activity in the intact hemisphere is still subject to intense debate (Schallert et al., 2003). It is not yet clear whether changes in fMRI patterns represent an adaptive, maladaptive, or ephiphenomenal effect (Dancause, 2006; Nowak et al., 2009).

Treatment strategies currently being developed for stroke patients

There are currently multiple strategies being developed to increase the recovery of patients following a stroke. Approaches used in the hours following the lesion generally try to limit the extent of damage and prevent further cell death. For example, intervention targeting the vascular system, such as tissue plasminogen activator (t-PA) administration, applied in the first few hours following the lesion can decrease lesion size and disability (Lansberg et al., 2009a,b). Similarly, approaches to decrease hyperthermia (Colbourne et al., 2000; Corbett et al., 2000) or the inflammatory response (Patel et al., 1993; Yrjanheikki et al., 1998) initiated within the first few hours following the lesion have shown to increase the neural survival and to decrease the motor deficits in rodent models of stroke.

In the subsequent days, patients go through the acute and subacute phases of recovery. Most of the behavioral improvements occur in this period that is considered to last about 3 months (Duncan, 1998). Rehabilitation, traditionally based on neurofacilitation or functional retraining, usually takes place within these 3 months and aims at increasing adaptive plasticity in the tissue that survived the lesion (Nudo and Dancause, 2007; Shumway-Cook and Woollacot, 2001). The demonstration in animals and humans that cortical maps are malleable as a function of experience in both normal and brain-injured individuals has contributed to the rapid development of new rehabilitative approaches based on experience-dependent plasticity mechanisms.

More recently, the use of CIMT was shown to increase motor function in stroke patients in the chronic phase of recovery (Taub et al., 1999, 2002). CIMT was developed on the basis of pioneering animal studies by Taub and colleagues (Taub, 1980; Taub and Morris, 2001). Due to the extensive amount of research that was conducted to test the efficacy of CIMT, it has arguably become the most mature approach among rehabilitative treatments. CIMT consists of (a) constraint of the less-affected upper extremity, typically with a sling or glove and (b) either shaping or task practice with the impaired upper limb. Shaping includes immediate feedback concerning movements, individualized tasks, prompting and cueing, and progressive increase in the difficulty of the tasks. Task practice consists of repetitive practice of a single individualized task in specified blocks without feedback prompting or cueing. While it is generally thought that the sensory-motor experience with the impaired limb is most important, the differential contributions of constraint and the type of practice (shaping or task practice) are confounded (Uswatte et al., 2006). Interestingly, in the nonhuman primate studies that examined map plasticity in the peri-infarct motor cortex and demonstrated a positive effect of rehabilitative training, the behavioral paradigm was a combination of shaping and task practice principles, since the monkeys repeated a single task (pellet retrieval from small wells) in blocks of trials, but the task was made progressively harder by decreasing well diameter (Nudo et al., 1996b).

A series of experiments to evaluate the presence of cortical representation changes, paralleling the behavioral changes resulting from CIMT therapy, has also been performed in humans (Liepert et al., 1998, 2000a; Taub et al., 2003, Wittenberg et al., 2003). These studies reported increased cortical representations of the affected arm following treatment, an upper limb representational map size that was similar in both affected and less-affected

hemispheres at a 6 months follow-up and shifts of the center of the output map, suggesting recruitment of adjacent brain areas.

Recently, efficacy of CIMT for stroke recovery was tested in a multisite randomized controlled trial in 222 stroke survivors, called EXCITE (extremity constraint-induced therapy evaluation; Wolf et al., 2006). This trial demonstrated improvements in upper extremity functional endpoints compared with control groups up to 2 years after treatment. This is despite the fact that individuals were enrolled in the chronic period after stroke. Several details regarding the optimum protocol still remain. The two most critical factors: duration and intensity of treatment (dosage), and the time of onset for the treatment after stroke are still unresolved. A recent trial in 52 stroke survivors suggested that early treatment (enrollment within 9 days after stroke) with CIMT and at higher doses resulted in less improvement (Dromerick et al., 2009). Whether this clinical trial result is due to early excitotoxic effects of intense use remains to be established (Kozlowski et al., 1996).

In the past few years, several other novel approaches have been explored to increase the adaptive plasticity in the subacute stage of recovery, where much of the neural reorganization supporting the recovery is expected to occur. Often, these approaches are used as adjuncts to conventional rehabilitation. For example, the use of pharmacological manipulation to increase arousal and learning during training (Barbay and Nudo, 2009; Feeney et al., 1982; Gladstone and Black, 2000; Papadopoulos et al., 2009), and the use of pharmacological agents to increase sprouting and anatomical plasticity (Fang et al., 2010; Tsai et al., 2007) are currently being investigated by several groups.

Restoration of function in the peri-infarct area can be aided by pharmacologic treatment. It has long been known that amphetamine paired with training can enhance recovery after lesions (Feeney et al., 1982). In addition, the pairing of amphetamine with training enhances expression of GAP-43 and synaptophysin in both the intact and damaged hemispheres, presumably indicative of synaptogenesis and axonal sprouting (Stroemer et al., 1998). A significant new finding by Carmichael and colleagues (Clarkson et al., 2010) sheds more light on the early events after focal stroke and suggests potential new targets for therapy. These investigators found excessive tonic inhibition in the peri-infarct zone after a stroke-like injury in the cortex of mice. The inhibition is mediated by extrasynaptic GABA_A receptors. The novel approach in this study was to administer a benzodiazepine inverse agonist specific for a subset of the GABA_A receptors at various times after stroke. This treatment resulted in sustained, improved motor function. Further, genetically altering the same subset of GABA_A receptors also improved poststroke recovery. Thus, it may be possible to substantially improve the effect of poststroke rehabilitative interventions by pharmacologically manipulating tonic inhibition in very specific subsets of receptor types.

Another strategy under intensive investigation is the use of cortical stimulation to increase or decrease the activity of targeted brain areas. Recently, the use of both invasive and noninvasive stimulation techniques to favor recovery from stroke has been the focus of extensive research. The use of stimulation has the potential advantages of manipulating the function of specific targeted areas to favor recovery with few, if any, side effects. The following sections will focus on the development of this approach in stroke and review both the literature from animal models as well as the current state of our efforts in humans.

Fundamental rational for the use of stimulation to favor recovery

Electrical stimulation has been attempted or is currently used to treat many neurological conditions. In the early 1970s, there were reports of chronic implants to stimulate the cerebellum and thalamic nuclei for cerebral palsy, spasticity, and epilepsy, and chronic pain (Hosobuchi et al., 1973; Rosenow et al., 2002). However, it is only in the 1990s that

stimulation was shown to be significantly effective to improve tremor, in particular in Parkinson's disease (PD) patients (Benabid et al., 1991; Blond and Siegfried, 1991; Eskandar et al., 2003). Obviously, the body of evidence for the use of stimulation to shape cortical plasticity and favor recovery after stroke is not as extensive as for other conditions such as PD. There are, however, convincing fundamental data providing a strong rationale for its use.

ICMS at high intensity can inhibit neural activity in the vicinity of the stimulating electrode (Asanuma and Ward, 1971). Inversely, it can excite distant neurons via polysynaptic activation (Stoney et al., 1968) likely through cortico-cortical networks. Deoxyglucose, a metabolic marker, is increased in other cortical areas interconnected with the site of stimulation (Sharp and Ryan, 1984) but not in subcortical structures (Sharp et al., 1982). Most importantly, ICMS can be used to generate rapid cortical reorganization of motor representation in rats (Nudo et al., 1990). In these experiments, the cortical representation of the caudal and rostral forelimb areas (CFA and RFA, respectively) and the adjacent representations such as the neck and vibrissa were defined. The border between two specific representations (e.g., forelimb and vibrissa) was precisely identified with interstimulation distances of about 200 μm . Then, a stimulating electrode was placed in one representation and repetitive stimulation was applied for 1–3 h. Following the stimulation, the motor representations were mapped again and the borders between representations redefined. These borders dramatically changed location following the stimulations. The stimulated representation expanded substantially into the unstimulated, neighboring representation, a phenomenon quite similar to the one we previously described in association with motor learning (Kleim et al., 1998, 2002; Plautz et al., 2000; Remple et al., 2001).

Brain stimulation to favor recovery after stroke

It took several years for the use of cortical stimulation to be applied to increase recovery from stroke. In early animal models, electrodes were first placed under the dura and later on, epidurally, as in eventual clinical trials. So far, the general approach has been to combine stimulation of the perilesional cortex with rehabilitative approaches based on movement repetition and the great majority of the studies have been conducted in rodents. Following ischemic lesions, cortical stimulation can increase excitability and the motor responses evoked from the stimulated cortex (Teskey et al., 2003). In addition, stimulation was shown to increase dendritic density in the stimulated cortex (Adkins-Muir and Jones, 2003). Stimulation can also favor the reorganization of representational maps in the stimulated cortex (Kleim et al., 2003b) a result that was also shown in nonhuman primates (Plautz et al., 2003). In the later study, the behavioral training, which consisted of repetitive dextrous finger movements to retrieve food pellets, was combined with stimulation for about an hour each day for several days. The treatment resulted in representational map expansion that was substantially greater than that following spontaneous recovery (Frost et al., 2003). In all of these previous studies, the increased plasticity was associated with an increase of motor recovery.

Whereas very few data are currently available on the parameters of treatment, it appears that both anodal and cathodal stimulations can increase recovery (Adkins et al., 2006; Kleim et al., 2003b) but that cathodal stimulation is more efficient in the early phase following the lesion (Kleim et al., 2003b). In comparison to anodal stimulation, cathodal stimulation may increase survival of vulnerable neurons (Adkins et al., 2006). Another limitation is our understanding of the effects of stimulation frequency. In studies of recovery in rats after stroke, frequencies in the range of 50–100 Hz appear to be effective (Adkins-Muir and Jones, 2003; Adkins et al., 2006, 2008). What is needed to reconcile these issues is a more clear understanding of the mechanisms underlying stimulation-induced plasticity.

Stimulation to favor rewiring after injury

We have previously discussed support for the rewiring capacity of the adult brain following injury. Of course, key questions are whether these anatomical changes are optimal and if they could be molded or directed to increase recovery. If so, can this be done using stimulation? Following a lesion, EEG studies have shown that there is an appearance of delta waves on the ipsilesional side (Gloor et al., 1977; Hirose et al., 1981). In rats, a comparable low-frequency synchronized neuronal activity is observed in perilesional cortex after an ischemic lesion of the cortex (Carmichael and Chesselet, 2002). Synchronous activity is initially observed in the perilesional cortex and on subsequent days appears to spread to other areas of the ipsilesional and contralesional hemispheres. If the perilesional activity is blocked with tetrodotoxine (TTX), an inhibitor of Na channels, distant cortical synchronous neuronal activity is not observed. Furthermore, in the rats with synchronous neural activity, the contralesional cortex formed atypical connections with the ipsilesional striatum. This novel pattern of connections was not present in rats treated with TTX in the perilesional cortex and thus they did not develop the synchronous neural activity. These results suggest that the synchronous neuronal activity initiated in the perilesional cortex and spreading to other distant cortical areas supports major rewiring of the connections of these distant cortical areas.

In a recent set of experiments (Brus-Ramer et al., 2007; Carmel et al., 2010), stimulation has been shown to increase sprouting and recovery following lesion of the CS tract. Epidural stimulation of the CFA of the “normal” hemisphere following a lesion was used to promote recovery following lesions of the CS at the level of the rostral medulla. The stimulation of the contralesional cortex was started on the day after the lesion and the rats received trains of stimulation for 6 h daily, for 10 days. With time after injury, the group with cortical stimulation recovered better than the control group without stimulation. Furthermore, BDA was injected in the stimulated cortex after recovery and anatomical reconstruction showed that there was an increase of ipsilateral projections from the contralesional cortex to the lower cervical segments.

These results suggest that the contralesional hemisphere could, if stimulated, take over some of the lost function from the ipsilesional hemisphere by increasing its ipsilateral control. Does this exploitation of the ipsilateral CS pathway by the contralesional hemisphere require stimulation? Recent studies in humans after stroke have suggested that increased ipsilateral control *may not* be the pathway through which the contralesional hemisphere acts vicariously for the control of the impaired limb. Indeed, single-pulse transcranial magnetic stimulation (TMS) to stimulate the contralesional cortex does not result in an increase of fast CS output to the recovered arm (Alagona et al., 2001), even if the stimulation is specifically applied to the area showing an increased activation in relation to movements of the impaired limb (Gerloff et al., 2006). Moreover, using stimulation of the contralesional hemisphere to increase recovery is diametrically opposite to the ideas of interhemispheric competition and imbalance that are currently dominating the landscape of stimulation protocol development in humans (Nowak et al., 2009; see also section “The role of the contralesional hemisphere in recovery after a stroke”). According to these ideas, the contralesional hemisphere would be detrimental to the impaired limb. It is difficult to reconcile the results from Brus-Ramer et al. (2007) with these hypotheses and, as we will see in the next sections, many studies designed based on the concepts of interhemispheric imbalance have shown to successfully improve performance in stroke patients. These contradictory results may emphasize that our current understanding of interhemispheric interactions and their role in the recovery from stroke are at best incomplete.

The use of brain stimulation to favor recovery from stroke in humans

In humans, the use of stimulation with epidural electrodes comparable to those used previously in animal studies initially gave promising results (Brown and Burns, 2001; Brown et al., 2006; Huang et al., 2008; Levy et al., 2008). However, testing of the efficacy of the stimulation on a larger stroke population in the phase III trial gave less conclusive results (Plow et al., 2009). These data stress that further understanding of the mechanisms supporting the effect of stimulation on recovery after stroke are required for the optimization of these new treatment strategies. Several limitations of our current knowledge of the use of stimulation in stroke have been outlined above and animal models can surely be useful to troubleshoot some of them. But perhaps, most importantly, animal models testing the effects of stimulation have to date used stereotypical lesion locations and sizes. One of the major challenges for the development of treatment strategies for the stroke population is the heterogeneity of lesions and consequently of the source of deficits. It is quite possible that patients with different lesions would benefit from different stimulation treatments, including either different stimulation parameters or alternative locations of stimulation. Supporting these assumptions, in contrast to rats with milder initial impairments following ischemic lesions, animals with severe initial impairments fail to benefit from an identical cortical stimulation treatment (Adkins et al., 2008).

Whereas the results from the latest trial for the use of invasive stimulation in humans after stroke were disappointing, they certainly should not be seen as a sign that invasive stimulation as a treatment should be abandoned. Instead, it may be viewed as a reminder of the complexity of stroke and that more work needs to be done to better define our parameters of treatment. Perhaps in the stroke population, the choices of stimulation type and location need to be adapted to each patient. Whereas the development of patient specific protocols would require considerable work, the diagnostic capacity that could support the development of stimulation treatments in this direction is available. Invasive stimulation does have many advantages such as the degree of precision of the stimulation site, capacity to simultaneously and differentially stimulate at many locations and the almost limitless duration of stimulation treatments. It may also be recalled that the successful use and implantation of invasive stimulation as a viable treatment for PD also required many years of research.

Noninvasive brain stimulation techniques in humans after stroke

In humans, transcranial direct current stimulation (tDCS; Fregni et al., 2005; Lang et al., 2005; Nitsche et al., 2005) or TMS (Hummel and Cohen, 2006; Raux et al., 2010) have been used to promote recovery. Whereas the precision of the stimulation site is lower and duration of stimulation treatment is more limited, these approaches have the great advantage of being noninvasive, lowering the potential for complications. The use of these methods has yielded very exciting results and currently, much effort is being invested to develop protocols that use noninvasive stimulation techniques to favor recovery from stroke.

The use of tDCS in stroke patients is quite new and, while not unanimous (Hesse et al., 2007), many preliminary studies are showing encouraging results. Many more studies are likely to use this approach that has many advantages in comparison to TMS, such as its low cost, the ease of use and the fact that it can be combined with rehabilitative treatments. tDCS delivers weak direct currents to the cortex via two electrodes that polarize the neural tissue. The active electrode, either the anode to increase or the cathode to decrease excitability, is placed on the scalp over the brain area to modulate (Nitsche et al., 2003, 2007). In chronic stroke patients, a single treatment including the activation of the lesioned hemisphere with anodal tDCS can increase the excitability of the ipsilesional M1 and produce transient

improvements in motor performance (Hummel et al., 2005). The application of tDCS over the course of several days prolonged this effect (Boggio et al., 2007). In addition, cathodal tDCS delivered to the contralesional hemisphere can also result in an improvement in motor functions (Fregni et al., 2005; Hummel and Cohen, 2005; see also contralesional hemisphere treatment below). tDCS can also be paired with other approaches. In a recent study, tDCS was combined with peripheral nerve stimulation of the radial and ulnar nerve at the wrist (Celnik et al., 2009). Peripheral nerve stimulation can increase corticomotor excitability (Kaelin-Lang et al., 2002), force (Conforto et al., 2002), and function (Conforto et al., 2007). This pairing of the two stimulation approaches increased the effects of rehabilitative training in stroke patients and was more effective than either type of stimulation alone used with training.

To date, the large majority of human studies using noninvasive stimulation in stroke patients have used TMS. As for tDCS, TMS can increase or decrease activity. Repetitive high-frequency TMS applied directly over the ipsilesional hemisphere increases its excitability and the amplitude of electromyographic (EMG) it can evoke in the impaired limb. These increases are associated with an enhancement of the impaired limb movement accuracy and speed in chronic stroke patients (Kim et al., 2006). Another pattern of stimulation, excitatory theta burst stimulation (Huang et al., 2005), can decrease reaction times of the paretic hand when applied to the ipsilesional M1 (Talelli et al., 2007).

However, for both tDCS and TMS, most studies have used a single treatment session and evaluated the short-term effect on motor performance (Ameli et al., 2009; Kim et al., 2006; Lomarev et al., 2007; Yozbatiran et al., 2009). To our knowledge, only one study investigated the effect of treatment using excitatory TMS stimulation protocol over the ipsilesional M1 in multiple consecutive days. This protocol was applied in patients that sustained the stroke within less than 15 days. The stimulations resulted in an increase of motor performance, even 1 year after the treatment (Khedr et al., 2010). These results suggest that stimulation of the ipsilesional hemisphere may be a viable treatment option to increase recovery. However, they also raise several questions. Why are these results different than the ones obtained with the invasive stimulation? Are both approaches acting through different mechanisms? Are the effects obtained in the study using TMS more beneficial because the stimulation was done early after the lesion instead of in chronic patients? Once again, there is an important need for further investigation to establish parameters of treatments and understand their mechanisms of action.

Other alternative approaches, also using noninvasive stimulation protocols, have been developed to favor recovery after stroke. In these approaches, noninvasive stimulation is used to inhibit the contralesional cortex. The next sections will review our current understanding of the changes in the contralesional hemisphere after stroke and their role in recovery. Then, we will look at what we know about the effects of contralesional inhibition on recovery from stroke.

The role of the contralesional hemisphere in recovery after a stroke

Human fMRI and PET studies have shown that there is an early increase of activity in the contralesional hemisphere following a stroke. This increased contralesional activity is associated with a decrease of excitability and of CS output intensity from the ipsilesional cortex to the impaired hand (Alagona et al., 2001; Carey et al., 2006; Catano et al., 1995, 1996; Di Lazzaro et al., 2008; Heald et al., 1993; Jaillard et al., 2005; Liepert et al., 2000b; Manganotti et al., 2002; Marshall et al., 2000; Rapisarda et al., 1996). In animal studies, an acute increase of somatosensory evoked potentials in the contralesional cortex has also been reported in the hours following lesion (Hossmann et al., 1985; Meyer et al., 1985; Sakatani

et al., 1990). The early increase of activity in the contralesional hemisphere and its negative impact on the impaired limb are generally explained with the concept of interhemispheric competition. In this hypothesis, the loss of neural tissue in the ipsilesional hemisphere results in a decrease of interhemispheric inhibition from the ipsilesional hemisphere (Liepert et al., 2000b), creating an interhemispheric imbalance. The resulting increase of contralesional activity would in turn contribute to the ipsilesional diaschisis through an increase of its callosal inhibition to the ipsilesional cortex. By doing so, the changes of activity in the contralesional hemisphere would be detrimental to the impaired limb. Longitudinal imaging studies in humans generally support this view (Carey et al., 2006; Jaillard et al., 2005; Marshall et al., 2000; Nhan et al., 2004; Ward et al., 2004). Early after the lesion, these studies report atypically high levels of contralesional activity and low ipsilesional activity. With recovery, there is an increase of ipsilesional and decrease of contralesional activity presumably due to a reduction of the interhemispheric imbalance (Cicinelli et al., 1997, 2003; Heald et al., 1993; Liepert et al., 2000b; Turton et al., 1996).

However, the negative role of the contralesional cortex in the recovery is far from being unanimously accepted (Schallert et al., 2003). In the chronic phase of recovery, plasticity in the contralesional hemisphere has been shown to support compensatory behavior and learning with the less-impaired limb in rats (Bury and Jones, 2002; Jones and Schallert, 1992, 1994). Although not related to the recovery of the impaired limb, the plasticity in the contralesional hemisphere could thus make a significant contribution to the overall recovery and maximize the autonomy of stroke survivors. Furthermore, in the chronic phase after stroke the contralesional hemisphere may undergo adaptive plasticity to be more involved in the control of the impaired limb. Some support for this hypothesis is provided in many human functional imaging studies reporting that the increased activation in the contralesional cortex is associated with recovery (Cramer et al., 1997; Riecker et al., 2010; Schaechter and Perdue, 2008; Seitz et al., 1998). It was also shown that inhibition of contralesional areas with atypically high activity in chronic stroke patients can interfere with performance of the impaired hand, whereas inhibition of comparable locations in control subject did not (Lotze et al., 2006). Similarly, the inhibition of the contralesional hemisphere in rats that recovered from large ischemic infarcts generates more behavioral deficits of the impaired forelimb in comparison to control animals (Biernaskie et al., 2005).

Inhibition of the contralesional cortex to improve recovery from stroke

The use of contralesional inhibition to increase recovery is based on the demonstration that suppression of one motor cortex leads to an increased excitability of the contralateral motor cortex (Gilio et al., 2003; Heide et al., 2006; Schambra et al., 2003). In most studies, slow rTMS is used to suppress the contralesional hemisphere excitability (Maeda et al., 2002). In chronic stroke patients, the application of inhibitory stimulation protocols over the contralesional hemisphere increases motor output from the ipsilesional to the paretic limb (Takeuchi et al., 2005). Furthermore, in chronic stroke patients, stimulation protocols to inhibit the contralesional activity have also been shown to produce improvement in motor performance of the hand function (Mansur et al., 2005; Nowak et al., 2008; Takeuchi et al., 2005). In acute patients, one study showed that repetitive theta burst stimulation over the intact hemisphere increase the excitability of the ipsilesional motor cortex (Di Lazzaro et al., 2008). As for the use of ipsilesional stimulation, to date the great majority of studies using contralesional inhibition have looked at the effect of a single session of stimulation on stroke patients and the reported effects were short-lasting.

Only two studies have investigated the effect of multiple sessions of contralesional inhibition to favor recovery of the impaired limb. The first one, in chronic stroke patients, showed that slow rTMS for 5 days in the contralesional hemisphere can significantly

increase CS excitability in the ipsilesional hemisphere and improve motor performance of the impaired limb (Fregni et al., 2006). These effects were still identifiable after 2 weeks. The other study, in acute stroke patients (7–20 days after stroke), showed that 5 consecutive days of treatment to inhibit the contralesional hemisphere increases the ipsilesional output to the paretic upper limb and enhanced recovery (Khedr et al., 2009). The effects were still present 3 months after the treatment. Therefore, it appears that contralesional inhibition could be favorable to recovery.

General conclusions

Relying on a much clearer understanding of plasticity principles, novel treatment protocols following brain lesion are rapidly emerging and evolving. Several research groups are investigating mechanisms and testing the effects of these novel approaches in animal models and in humans. One of these approaches, which is particularly promising, is the use of stimulation. To date, most of the protocols are designed with the assumption that following a lesion, the ipsilesional cortex is hypoactive and should be activated and that the contralesional cortex is hyperactive and should be inhibited. Accordingly, stimulation in humans has been used to either increase the activity in the ipsilesional hemisphere or to inhibit the contralesional cortex. However, some studies have provided results that are contradictory to these hypotheses (Biernaskie et al., 2005; Brus-Ramer et al., 2009; Carmel et al., 2010; Pomeroy et al., 2007), and stress that our current hypotheses may not be entirely accurate. These dominating views were largely extrapolated from evidence collected in control subject. It is quite possible that ipsilesional function and rules of interhemispheric interactions are changed following stroke. Nonetheless, several of the novel studies on the use of stimulation after stroke have provided encouraging results and support the notion that stimulation could become a valuable addition to traditional rehabilitative approaches. While much work still needs to be done, it is possible that one day we will be able to use these techniques to increase favorable and decrease detrimental plasticity to maximize recovery. It is likely that to maximize benefit this shaping of plasticity will have to be adapted to the patient's remaining intact structures.

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Fig. 1.

Representation of finger extension, finger flexion, and wrist abduction movements in M1 derived from pre- and post-training mapping procedures in squirrel monkeys. Finger extension movements are shown in black, finger flexion movements in dark gray, wrist abduction movements in light gray, and other distal forelimb movements in stippling. Relative area devoted to both finger extension and finger flexion movements increased after pellet retrieval training. Figures are reproduced from Nudo et al. (1996a) with permissions.

Fig. 2.

Cartoon depicting the reorganization of the distal forelimb representation in M1 following an ischemic lesion. In these studies, the motor map in M1 is derived prior to the lesion (a). Then, a focal ischemic lesion is made in the distal forelimb area ((b); lesion location superimposed on prelesion map). If no intervention is performed and the animal spontaneously recovers, when the motor map is derived again there is a further loss of the distal forelimb representation that occurred after the initial lesion ((c); map status after spontaneous recovery). In a separate group of animals, if therapy based on movement repetition, motor learning, and restraint of the less-impaired forelimb is performed, then the loss of distal forelimb representation is prevented ((d); map status after recovery with therapy). In some cases, there is an increase of distal forelimb representation in the perilesional tissue.

Fig. 3.

Cartoon summary of the reorganization that occurs in PMv following M1 lesion. (a) Prior to the lesion, PMv distal forelimb representation is interconnected with M1 and with secondary somatosensory areas in the posterior operculum. (b) Following a large M1 infarct that destroys most of the distal forelimb representation in M1, the cortical area devoted to this representation in PMv expands (red arrows). These physiological changes are associated with abrupt changes of axon orientation and the border of M1 and novel projections to the primary somatosensory cortex. CS, central sulcus; PO/IP, posterior operculum/inferior parietal cortex. Modified with permission from Dancause, *Reviews in the Neurosciences* 2006. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this chapter.)

Fig. 4. Changes in motor representations in the rostral forelimb area of rats after a controlled cortical impact in the caudal forelimb area. In this study, while the total (combined) rostral forelimb area did not change, distal representations were reduced in area, while proximal representations were enlarged. Several examples using microstimulation techniques in animals suggest that remote reorganization supports learning of compensatory movement patterns rather than recovery of the lost movement patterns. Modified from Nishibe et al. (2010) and reproduced with permission.