# Guest Editorial

Neuroplasticity and rehabilitation

Neuroplasticity is the ability of the central nervous system to remodel itself. In the last few decades, we have learned that neuroplasticity is not only possible but that it is also constantly occurring; the brain is always changing. Neuroplasticity is how we adapt to changing conditions, learn new facts, and develop new skills. If the brain is injured, it tries to repair itself with these normal mechanisms. If all goes well, spontaneous recovery can be excellent. Of course, the natural scope of these plastic processes is limited, and sometimes the end point of the remodeling is problematic itself. The job for those of us interested in rehabilitation is to promote plasticity in the right direction and, sometimes, to correct it if it has taken a wrong turn. We must, therefore, understand neuroplasticity and learn to control it. Fortunately, this is an active area for current research.
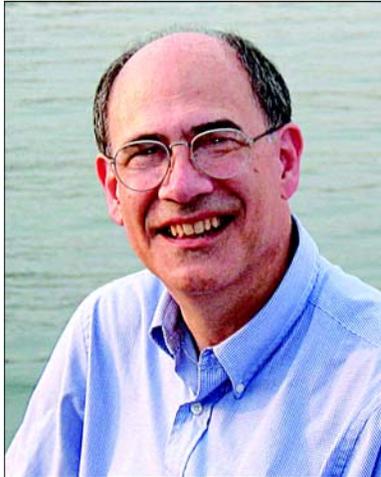
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MECHANISMS OF NEUROPLASTICITY

Neuroplasticity can be understood at several levels. The first level is that of the individual neuron and the events responsible for remodeling that occur within the cell. The second level is that of groups of neurons and their functions that can change to alter behavior. At the cellular level, multiple processes can occur both in parallel and serially. Generally speaking, some processes are quick, but transient, and can allow for rapid adaptations. Others take longer, but are then more permanent. One principle appears to be that the more persistent an early change is, the more likely it is that it will be permanent.

The fastest type of change is a simple modulation of neuronal traffic that leads to a change in the amount of excitation and inhibition. Apparently, many neural networks are chronically and largely inactive because of tonic inhibition. Release of this inhibition will allow the networks to function; a process sometimes called "unmasking." Unmasking can be demonstrated in animal models with local delivery of gamma-amino-butyric acid antagonists, which immediately opens new functional networks [1].

Another relatively rapid change involves alteration of the strength of specific synapses. The magnitude of the response of the synapses changes as a function of the pattern of activity that they experience, both at the individual synapse and at the temporal conjunction of two or more synapses on the same cell. The most well-known of these processes are long-term potentiation (LTP), which is an increase in synaptic strength, and long-term depression (LTD), which is a decrease in synaptic strength [2]. After only minutes of synaptic activity, there can be changes that last hours or are relatively permanent. The molecular and cellular biologies of LTP and LTD are being intensively studied, and a fascinating set of cellular processes have been discovered, which are triggered and regulated by the influx of calcium at the active synapses. It is important to recognize as well that a decrease in inhibition will facilitate changes in synaptic strength, and this links unmasking to LTP and LTD.

Another type of cellular change is anatomical and involves remodeling the dendritic spines of neurons and their resultant connectivity [3]. Some spines appear to come and go relatively quickly. Of course, when there are more long-lasting anatomical changes, a plastic process is more secure.

Basic processes of neuroplasticity can be studied noninvasively in humans, but the correlations between the cellular mechanisms and the results from human

studies are uncertain [4]. One method for studying unmasking is acute deafferentation, which can be induced by peripheral ischemia. When employing this method, we commonly use a blood pressure cuff inflated over a subject's elbow; within minutes, nerve traffic begins to lessen, and it disappears completely within 20 to 30 min. This deafferentation appears to cause a decrease in inhibition in the local region of the motor cortex, where the neurons are located that innervate the deafferented part of the body and its adjacent parts. We can readily study this response by observing the rapid increase in excitability of the cortical motor representations[*] that control adjacent body parts with the application of transcranial magnetic stimulation (TMS). Using microneurography, we demonstrated that the deafferented area itself shows an increase in excitability [5]. When there is peripheral deafferentation for longer periods, as is seen with amputation or spinal cord injury, other mechanisms are triggered that cause more permanent changes. However, these more permanent changes can go awry, as seen by the phenomenon of phantom pain [6].

A number of human models are being used for the study of longer-term neuroplastic changes, which may be the result of changes in synaptic strength or synaptic remodeling. Motor learning can be modeled (or "studied") with the use of a variety of motor tasks from simple pinching to moving the thumb in one direction to more complex skills such as movement sequences. The early events focus on the motor cortex, where increases in metabolic activity are measured with neuroimaging and changes in muscle excitability with TMS [7]. Motor learning can have some permanence, and some aspects of it are similar to LTP and LTD.

Another set of models for longer-term changes are those that artificially modulate neuronal traffic to regions such as the motor cortex. Repetitive TMS

at rates of ≥ 5 Hz lead to increases in excitability, while rates of ≤ 1 Hz can lead to loss of inhibition. Use of the theta burst stimulation technique to pattern the stimuli may be even more effective [8]. The application of direct current to the brain with a technique called direct current transcranial stimulation can also lead to increases and decreases in excitability, depending on whether the anode or cathode is placed over the motor cortex [9]. Additionally, paired stimuli at the motor cortex, such as a median nerve stimulus combined with TMS (a technique called paired afferent stimulation), can lead to excitation or inhibition, depending on the interval between the stimuli [10].

PRINCIPLES OF REHABILITATION

Understanding neuroplastic mechanisms allows us to recognize how the brain tries to repair itself. Several important principles emerge:

1. Body parts can compete for representation in the brain and use of a body part can enhance its representation.

Representation areas increase or decrease depending on use. A good example is Braille readers who use their fingers many hours a day in the skilled task of interpreting Braille characters [11]. In this situation, the first dorsal interosseus (FDI) is used for reading, while the adductor digiti minimi (ADM) is largely passive. Using TMS mapping, we did not find significant differences between the motor representations of right and left FDI and ADM in control subjects. However, in proficient Braille readers, the representation of the FDI in the reading hand was significantly larger than that in the nonreading hand, or in either hand of the control subjects. Conversely, the representation of the ADM in the reading hand was significantly smaller than that in the nonreading hand, or in either hand of the control subjects. These results suggest that the cortical representation of the reading finger in proficient Braille readers is enlarged at the expense of the representation of other fingers. Conversely, if

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[*] A body part is represented in various areas of the brain, both motor and sensory. The sensory representations are those that are active when sensory stimulation of that body part occurs. The motor representations are those whose activity produces movement of that body part. Representations can be determined with many techniques, including TMS and neuroimaging.

a body part is not used, its representation area shrinks. For example, the representation area of the tibialis anterior is smaller after the ankle is immobilized in a cast for several weeks [12].

In case of a stroke that damages a body part representation in the primary motor cortex, plasticity permits some reorganization that will restore a representation [13]. This process must be competitive with all the body parts.

2. The premotor cortex can substitute for the motor cortex to control motion.

While the primary motor cortex has the largest and most powerful contribution to the function of the corticospinal tract, the premotor cortex also contributes. We know, from both anatomical and physiological studies, that there are contributions of the premotor cortex to the function of the corticospinal tract, but stimulation thresholds of the premotor cortex are higher than that of the primary motor cortex. So, while the main output of the premotor cortex is ordinarily to the primary motor cortex, the premotor cortex can also be the source of supraspinal control signals [14].

3. The contralesional hemisphere can take over motor control if all else fails.

Although rather weak in humans, there are ipsilateral, corticospinal neural pathways. Although these pathways innervate many more proximal than distal muscles, they can be documented in normal humans, even in distal muscles, with the use of TMS [15]. Such pathways are necessarily involved in recovery of patients with hemispherectomy. Although controversial, these pathways may possibly be relevant in stroke recovery [16]. Another possible role of the undamaged hemisphere could be its interactions with the damaged hemisphere; there are transcallosal connections that are not completely characterized. Some of these transcallosal connections are inhibitory, and improvement might occur if these connections were themselves inhibited. Functional magnetic resonance imaging studies show that the damaged hemisphere has increased blood flow when bilateral movements are made;

these data are consistent with the idea that activity of the undamaged hemisphere might support the damaged hemisphere [17]. Another possibility is that the ipsilateral hemisphere helps with activity of the premotor cortex rather than the motor cortex itself [18].

4. Neuroplastic mechanisms can be facilitated and this is a good basis for intervention.

Intensive, focused physical therapy should help restore motor function, and evidence shows that the earlier and more intensive the therapy, the better the outcome. This concept has been most fully demonstrated by the multiple successes of constraint-induced (CI) movement therapy. This method forces patients to use the hemiplegic limb by constraining the good limb [19]. In a number of clinical trials, patients have shown behavioral improvement with the use of CI, even those with chronic and apparently stable deficits. TMS maps of the weakened muscles increase in size in these circumstances, which shows that the expected cortical changes appear to be occurring [20]. Other techniques, such as neuromuscular electrical stimulation [21], robot-enhanced training [22], and virtual reality training [23] likely use the same principle.

Bilateral symmetrical arm movement training appears helpful; this might be due to facilitation of the contralesional hemisphere. One example is repetitive bilateral arm training with rhythmic auditory cueing [24]; patients showed significant improvements that were largely sustained at 8 weeks after this training concluded.

A prolonged period of peripheral nerve stimulation will increase the excitability of related TMS muscle representations in the motor cortex [25], and this suggests that sensory stimulation could be a useful rehabilitation tool. Sensory stimulation can be applied in a number of ways from passive movement to cutaneous stimulation with transcutaneous electrical nerve stimulation and even to acupuncture. Stimulation of the pharynx may improve swallowing function [26].

Another method for improving rehabilitation is the combined use of drug therapy and physical

therapy. In general, studies indicate that the combination is important; drugs by themselves seem not to be efficacious. The most fully documented improvements are with amphetamine and related noradrenergic agents. Drug therapy was first demonstrated to be valuable in a rat model; now several clinical trials show that amphetamine, together with physical therapy, is better than physical therapy alone [27]. The mechanism for this drug action is not completely clear. While it is possible that it works by relieving diaschisis, amphetamine also enhances plastic changes in motor learning in both animals and humans [28]. Evidence has also been found for enhanced neural sprouting and synaptogenesis [29]. Now other agents, such as fluoxetine, methylphenidate, and levodopa, have been shown to be of use.

CONCLUSION

For the future, a variety of innovative methods may well emerge that take advantage of plastic processes. An example is a technique that we have been exploring that uses exercise together with local anesthesia. After hemiplegic stroke, significant function is often lost in the hand, while strength is retained in the proximal arm muscles. Since competition exists between body parts for representation in the motor cortex, it is possible that use of the proximal muscles makes it difficult for hand muscles to increase their representation. We know that peripheral deafferentation increases the excitability of proximal muscles, and recently we have demonstrated that this increase is magnified by exercise of the proximal muscles during the peripheral block [30]. We reasoned that anesthesia of proximal muscles and exercise of the hand might increase cortical representation of the hand and concomitantly improve hand function. Preliminary results suggest that this may indeed occur [31]. Other techniques may utilize brain stimulation methods to improve rehabilitation [32].

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