Neuroplasticity
Implications of neuroplasticity for neurosurgeons
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Abstract
The brain exhibits neuroplasticity, the capacity to be modifiable by experience. Over the last decade there has been an explosion of knowledge in the field of neuroplasticity. New brain stimulation techniques are being designed to enhance neuroplasticity and several neuromodulatory trials are underway to enhance behavioral gains from rehabilitation. An understanding of neuroplasticity is essential for the practicing neurosurgeon since a lot of the drugs neurosurgeons prescribe affect neuroplasticity and a lot of neurosurgical diseases will be treated by therapies which modulate plasticity. In this article we review fundamental concepts of neuroplasticity for the practicing neurosurgeon.

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1. Introduction

Until very recently, the adult brain was considered immutable, and the notion of neurogenesis in the adult brain was regarded as far-fetched. In the last 2 decades, it is clear that the central nervous is plastic, that is, it changes as a result of experience, and that neurogenesis occurs in the adult brain at discrete locales, the subventricular zone of the lateral ventricles, and the subgranular zone of the dentate gyrus [48]. These paradigm shifts have fueled the notion that brain function can be modulated to improve neurologic recovery.

Neuroplasticity is the future of science in neurosurgery [31]. A Medline search using the term neuroplasticity revealed 1319 articles in 2000 and 2432 articles in 2007, almost a doubling in peer-reviewed articles on neuroplasticity over the last 7 years. Neuromodulation will play an increasing role in the future of neurosurgical practice. Already, there are ongoing clinical trials of neuromodulatory therapies for stroke, depression, and pain. In this review, I present a brief overview of some of the concepts in neuromodulation and neuroplasticity for the practicing neurosurgeon.

2. Fundamentals of neuroplasticity-Hebb and associative long-term potentiation

In 1949, Donald Hebb wrote: “the persistence or repetition of a reverberatory activity (or “trace”) tends to induce lasting cellular changes that add to its stability. When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A’s efficiency, as one of the cells firing B, is increased” [29]. An understanding of Hebbian theory, effectively summarized by the popular paraphrase, “neurons that fire together, wire together,” is essential to the understanding of neuroplasticity.

Hebbian mechanisms explain most of the observed neuroplasticity after central nervous system injury [9]. The discovery of hippocampal long-term potentiation (LTP) [6] provided in vivo confirmation of Hebb’s theories [62]. In LTP, a high-frequency stimulus applied to a presynaptic neuron can cause a long-lasting increase in the size of the excitatory postsynaptic potentials (EPSPs) fired by the postsynaptic neuron. For example, in the hippocampus, a single stimulus to the perforant pathway caused an EPSP in
the dentate gyrus. However, when conditioned by a high-frequency train of stimuli, subsequent stimuli can generate a larger and longer-lasting increase in the EPSP [6]. Long-term potentiation is Hebbian [9] if it depends on concomitant and synchronous activation of another input to the same cell or concomitant and synchronous postsynaptic depolarization. Hebbian LTP is rampant in nervous systems and a leading cellular substrate for learning and memory [5,9]. The N-methyl-D-aspartic acid NMDA receptor makes it possible for Hebbian LTP to occur in neurons. In the presence of glutamate and membrane depolarization, the receptor allows calcium influx that causes a simultaneous detection of the postsynaptic and presynaptic activity [9].

3. Measures of plasticity

Transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) are among the best noninvasive tools for measuring cortical plasticity. Transcranial magnetic stimulation, developed in 1985 [4], induces a time-varying current that in turn elicits an electric current that excites corticospinal axons and synapses. This generates a descending corticospinal volley that contains a D wave (direct wave) followed by several I waves (indirect waves). Direct waves are thought to be produced by direct axonal stimulation, whereas I waves are thought to arise from transynaptic stimulation. Transcranial magnetic stimulation effects are recorded as motor evoked potentials (MEPs) using surface electrodes on the muscle of interest. Common indices of plasticity that can be measured with single pulse TMS are the stimulation intensity that elicits MEPs (MEP threshold), amplitude and latency of MEPs, and the slope of plots of amplitude against intensity (input output or recruitment curve). These indices provide information about the state of cortical excitability after injury or intervention. The input output curves are typically sigmoidal. The slope of the steep portion of the sigmoidal curve increases with increasing cortical plasticity.

Other aspects of cortical excitability can be examined using paired pulse TMS studies. In paired pulse TMS studies, a conditioning subthreshold or suprathreshold stimulus is followed by a second test pulse to assess the effect of the conditioning pulse on the size of MEP response generated by the test pulse alone. Subthreshold conditioning pulses inhibit suprathreshold test pulses at interstimulus intervals (ISIs) between 1 and 5 milliseconds. This is referred to as short-interval intracortical inhibition (SICI). The MEP responses to suprathreshold test stimuli are facilitated at ISIs between 10 and 25 milliseconds. This is referred to as intracortical facilitation (ICF). Suprathreshold conditioning pulses paired with suprathreshold test pulses at interstimulus intervals of 50 to 200 milliseconds cause long-interval intracortical inhibition. Short-interval intracortical inhibition appears to be mediated through intracortical inhibitory mechanisms because I waves are also inhibited and spinal H reflexes are unchanged during SICI [36]. Unlike SICI, evidence for ICF is less clear but also seems to support intracortical mechanisms [13]. Conditioning median nerve stimulation inhibit test MEP responses at ISIs between 20 and 30 milliseconds or at ISIs between 100 and 200 milliseconds. These are referred to as short-latency afferent inhibition and long-latency afferent inhibition (LAI), respectively. Short-latency afferent inhibition and LAI are thought to be mediated by different mechanisms [13]. Indices of plasticity such as short-latency afferent inhibition, LAI, SICI, and long-interval intracortical inhibition and ICF are altered in various disorders [13].

In addition to single and paired pulse TMS studies, plasticity can also be measured using fMRI. Functional magnetic resonance imaging parameters of plasticity include size or number pixels activated in regions of interest, displacement in coordinates of peak or center of mass of activations, and creation of new areas of activation. The laterality index calculated by the ratio $C = I/C + I$ where $C$ = activation volume in contralateral sensorimotor cortex and $I$ = activation volume in ipsilateral sensorimotor cortex is a measure of the latency of fMRI activation. The laterality index ranges from $-1$ (100% ipsilateral activation) to $+1$ (100% contralateral activation).

4. Plasticity of cortical maps

Penfield and Boldrey [54] published the sensorimotor cortical maps of the human body in 1937. Cortical maps can change as a result of injury such as peripheral deafferentation [45], stroke [69], amputation [46], and experiences such as meditation [7,18,40], training [68], pharmacology [64], and noninvasive brain stimulation [26]. Hebbian mechanisms underlie creation of cortical maps—cortical map plasticity and synaptic plasticity are linked by Hebbian mechanisms [9]. Neurons that fire together are more likely to be somatotopical neighbors.

5. Cortical plasticity after stroke

Stroke causes significant reorganization changes in the brain. Early after stroke, there is task-related recruitment of bilateral new areas of activation in the sensorimotor networks involving primary motor cortex, premotor cortex, cingulated motor areas, parietal cortex, insula, supplemental motor area SMA, and cerebellum [14,16,70,71]. Over time, there appears to be focusing of these patterns with a return toward more normal activation patterns in recoverers [11,12,21,42]. Chronic stroke patients with significant impairment tend to show persistent recruitment of ipsilateral primary and secondary motor areas with a reduction of laterality index compared to normal and good recoverers [11].

6. Cortical plasticity after spinal cord injury

Cortical plasticity also occurs after spinal cord injury. Transcranial magnetic stimulation studies show an enlargement
of the cortical representation of muscles immediately proximal to the injured spinal segment [66]. Somatotopic changes generally involve displacement of cortical representations of rostral muscles into areas previously occupied by the deafferented areas. Examples of altered somatotopy include activation of the leg area by hand movements [8] or superior and medial shift of activation foci for tongue movements into the hand area [47]. In a recent study of 6 patients with chronic spinal cord injury SCI, Lotze et al [38] demonstrated a displacement of 11.9 mm of biceps brachii cortical maps into the thoracic deafferented area. A second consistent finding, demonstrated in several studies, is a posterior shift in motor cortical activity in patients with spinal cord injury SCI compared to controls [15,28,67].

A recent longitudinal study by Jürkiewicz [35] shows findings reminiscent of the evolution of cortical maps in stroke patients. In the subacute period after spinal injury, there was minimal task-related activation in the primary motor cortex (M1) but greater activation in associated cortical sensorimotor cortical areas compared to controls. Recovery was associated with progressive enlargement of M1 activation volumes and decreased activation in association areas. Recoverers with little or no impairment had a pattern of activation similar to that observed in controls.

7. Noninvasive brain stimulation techniques for modulating plasticity

Repetitive TMS (rTMS), paired associative stimulation, and transcranial direct current stimulation (tDCS) are the 3 main noninvasive brain stimulation techniques for altering cortical plasticity.

During rTMS, a single TMS pulse is applied in a repetitive fashion causing changes in cortical physiology well beyond the duration of stimulation [41]. Depending on the threshold and frequency of stimulation, rTMS may be excitatory or inhibitory. High-frequency rTMS greater than 1 Hz is generally excitatory, whereas low frequency (≤1 Hz) is generally inhibitory. There are currently several ongoing trials of rTMS in the treatment of depression, pain, and stroke.

Transcranial direct current stimulation can achieve the same modulatory effects as rTMS [49,50]. During tDCS, large electrodes are placed overlying the motor cortex and contralateral forehead, and a weak direct current (1-2 mA) is passed between the anode and cathode. Anodal stimulation (anode overlying motor cortex) increases cortical excitability and cathodal stimulation decreases cortical excitability. Application of tDCS for about 10 to 15 minutes can create changes in cortical excitability lasting for 90 minutes [49]. Transcranial direct current stimulation has significant advantages over rTMS. It has greater safety profile (less risk of seizures) and is cheaper than rTMS. Transcranial direct current stimulation is also being investigated for treatment in a variety of central nervous system (CNS) disorders.

Paired associative stimulation involves pairing of a peripheral nerve stimulus timed to arrive at the motor cortex at the same time as a TMS stimulus in a Hebbian fashion [63]. At interstimulus intervals of approximately 25 milliseconds, enhancement of cortical excitability occurs. Inhibitory effects occur at paired associative stimulation at ISIs around 10 milliseconds [75]. Using these 3 brain stimulation techniques, cortical excitability and appropriate parameters, cortical excitability can be up-regulated or down-regulated depending on stimulation parameters.

8. Repetitive training and cortical plasticity

Motor practice, skill acquisition, motor learning, and repetitive training are examples of use dependent plasticity. They are accompanied by corresponding increases in corticomotor excitability and enlargement of cortical maps [52,68]. Study of highly accomplished musicians show steeper recruitment curves or heightened cortical excitability compared to healthy individuals [58]. Studies of braille readers show an expansion of the sensorimotor cortical representation of the reading finger [51,53]. There is some evidence that motor learning occurs through LTP-like mechanisms [55-57]. This association between skill and plasticity has motivated neurorehabilitation scientists to try to enhance motor recovery using activity dependent therapies.

9. Activity-based therapies for spinal cord injury and stroke

Activity-based therapies are based on the premise that recovery can be mediated by physical retraining using the physiological properties of spinal and supraspinal circuits. Plasticity of spinal circuits appears to be activity dependent, and repetitive practice using task specific sensory input can engage spinal locomotor networks and improve recovery [2]. Activity-based therapies use repetitive practice of the lost task with the goal of recovering the task via reorganization of the spinal and supraspinal circuits. Musicians and athletes are examples of how repetitive practice can improve motor function. Acquisition of the simplest behaviors is associated with changes in spinal and supraspinal circuits [74].

Locomotor training represents the most common activity-dependent therapy. Great interest in human locomotor studies followed the observation that cats with complete transections of the spinal cord recovered locomotor stepping response after intense treadmill training involving partial body weight support and optimization of assistance during stance cycle [3,60]. Recovery appears to be dependent on specific principles of training that are distinct from spontaneous recovery [19]. Specific tasks and specific sensory input are essential for recovery just as putting cats on treadmill does not achieve the same level of recovery as training them to walk on the treadmill with appropriate weight support [2,3,39,61]. Multiple human studies have reported benefits of body weight supported treadmill training in improving locomotion in patients with chronic spinal cord injury [22,30,32,65,72,73]. Use of body weight support allows an injured individual the opportunities to approximate normal stepping patterns. Robotic
training methods such as Lokomat are also available to assist with automated stepping limb pattern. Alternatively trained therapists can provide manual assistance including assist with truncal support, lower limb movements, appropriate pelvic rotation, and weight transfer to loading in stance phase. At the present time, these therapies have not proven to be efficacious in large randomized controlled multicenter studies. A recent Cochrane review concluded that there was insufficient evidence to establish efficacy of robotic or manual treadmill trainings in improving walking outcomes after spinal cord injury [44].

10. Pharmacology of cortical plasticity

N-methyl-D-aspartic acid NMDA or Gamma-aminobutyric acid GABA receptor agonists and antagonists modify cortical plasticity [76]. There is also evidence from small-scale studies that drugs such as amphetamine and dopamine [10,17,20,23,27,31,43,59] significantly influence neurologic recovery process. These drugs modify some of the rM1 and TMS indices of plasticity discussed above. In one study, methylphenidate, a norepinephrine agonist, increased the slope of the MEPs intensity curve in a hand muscle and reduced SICI [34]. In another study, methylphenidate increased activation in the ipsilesional primary sensorimotor cortex and decreased activation of the ipsilesional anterior cingulum [64].

11. Plasticity and recovery

As described above, changes in indices of plasticity frequently accompany recovery and motor training. At the present time, there is no definitive evidence from large-scale randomized trials that shows that specific topographic maps or physiological signatures can be induced to improve recovery [37]. It has not been possible to consistently predict behavioral correlates of specific cortical maps. The behavioral correlates of cortical map changes from TMS modulatory interventions are still being worked out. The unproven hypothesis is that correction of the abnormal cortical map or abnormally physiology will result in a corresponding improvement in the deficient or abnormal behavior and that specific physiological states can be induced to improve behavioral outcomes. However, this hypothesis is supported by recent single-institution studies. For example, in stroke, several studies have shown that reducing cortical inhibition in the unaffected hemisphere may be beneficial for motor recovery after injury [1]. Other studies have shown that recovery can be improved by enhancing activity in the affected hemisphere [33]. Fregni et al [25] showed that anodal (excitatory) tDCS of the primary motor cortex in Parkinson disease to be associated with significant improvement of motor function compared to sham stimulation. In another sham-controlled phase II trial of tDCS, Fregni et al [24] reported significant pain improvement after anodal stimulation of the motor cortex injury in patients with central pain after traumatic spinal cord injury. Although these are small-scale studies, they provide some face validity to efficacy of noninvasive brain stimulation in neurorehabilitation, and larger studies are warranted.

12. Implications for neurosurgeons

The implications of a thorough understanding of CNS plasticity for neurosurgeons are clear. Many diseases we treat and other complications in our patients will be successfully treated with neuromodulatory therapies, most of which work by altering CNS plasticity. It is also important to realize that many of the medications we prescribe work through glutaminergic and gabaergic mechanisms with the potential to adversely alter plasticity. Although neuromodulating therapies are not a cure all for most of the diseases we treat, a thorough understanding of the fundamentals of neural plasticity is essential for the practicing neurosurgeon.

References


