

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Harnessing Plasticity to Reset Dysfunctional Neurons

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For a long time, it was thought that the adult mammalian brain was hard-wired and that once circuits were laid down and their functions assigned, little change was possible. This notion is no longer tenable. The brain has a lifelong inherent ability to change and adapt: individual neurons and neural circuits can change their “job descriptions” and their allegiance in response to demands. The mechanisms underlying this process are complex, have varying time courses (from milliseconds to months), and are incompletely understood. They include changes in synaptic strength, the pruning and growth of neuronal connections, and even the introduction of new neurons within certain existing circuits. The brain can thus develop attributes and abilities far beyond those that are present at birth. This malleability, termed “plasticity,” allows the nervous system to respond to environmental pressures, physiological changes, and experiences — both good and bad — with changes in function that may persist long after the events that elicited the expression of neural plasticity are no longer present.

Brain plasticity is usually adaptive and beneficial, permitting such useful processes as acquiring a new language or learning to play the piano. Structural and functional imaging studies have shown that new skills are associated with brain reorganization; for example, changes have been observed in the cortical representation of the hand in the pianist or the increased volume of the hippocampus in persons who have become taxi drivers in London.^{1,2} Plasticity is also at play in the recovery of movement or speech that occurs after a stroke or injury, with healthy areas of the brain taking on new responsibilities to compensate and overcome neurologic deficits. In both the acquisition of new skills and the recovery of function after injury, plasticity can be beneficial, leading to enhancement of

the brain’s repertoire and improved function. Plastic changes, however, can also harbor potential danger. The new pattern of neural activation may in itself lead to reorganization and new behaviors that are maladaptive and that not only lack an obvious protective or reparative benefit but, in fact, make matters worse. Examples of this “dark side” of neuroplasticity occur in the amputee who has serious phantom pain in the absence of an ongoing pain stimulus and in the millions of patients with ongoing, bothersome auditory perceptions in the absence of external sounds, as is characteristic in tinnitus^{3,4} disorders that are disabling and challenging to treat.

Engineer and colleagues⁵ recently provided an example of how to recalibrate the activity and reset dysfunctional neurons in a rogue neurologic circuit in which plasticity has gone wrong. The primary auditory cortex is organized tonotopically; individual tones of low-to-high frequencies are represented by clusters of neurons distributed in a continuous band along the cortex. Exposure to high levels of noise causes major plastic changes in the auditory cortex, which can result in disruption of the tonotopic map, exaggeration of responses, defocusing of neurons (responding nonselectively to a wide range of stimuli), and increased cortical oscillatory behavior. These physiological abnormalities putatively underlie tinnitus in humans.

By delivering auditory tones paired with vagus-nerve stimulation (VNS) in normal animals, the investigators found that they could shift the receptive fields of auditory neurons to respond to new tones. This result suggested that “retuning” auditory neurons with VNS–tone pairing might be used to reverse the map distortions and disrupted neural activities observed in a rat model of tinnitus that was induced by exposure to noise. Indeed, the investigators showed that the abnormally responding neurons in the rats that

Table 1. Conditions in Which Maladaptive Neuroplasticity Is Implicated.

Condition	Example
Dystonia	Writer's cramp, musician's dystonia, post-stroke dystonia
Drug-induced dyskinesia	Deficits requiring long-term levodopa treatment in Parkinson's disease
Progressive motor deficits	Worsening of weakness after motor stroke ("learned disuse")
Epilepsy	Kindling (repetitive seizure activity in one area of the brain induces spontaneous seizure activity in another related area)
Drug addiction	Cocaine addiction
Pain and sensory disorders associated with deafferentation	Phantom pain, post-stroke pain, anesthesia dolorosa, tinnitus, the Charles Bonnet syndrome
Psychiatric disorders	Anxiety, bipolar disorder, schizophrenia, attention deficit-hyperactivity disorder

were exposed to noise ceased their maladaptive responses and were reprogrammed to respond to a variety of new tones when these tones were delivered in conjunction with VNS. The resetting of the physiological response was accompanied by a reversal of the abnormal auditory behavior in the rats. The way in which the simultaneous pairing of VNS with the new tones shifts the focus of neurons and resets the altered behavior is not understood and was not investigated by the authors in much detail. However, weakening or disrupting the abnormal existing associations ("depotentialization"), driving the adoption of the new, more physiologically appropriate association (heightening potentiation of the tone-VNS response, which seems to be a more likely mechanism), or both in rats with the coupled tone-VNS stimuli are possible ways in which this resetting is accomplished.

Understanding the molecular and physiological mechanisms that regulate neuroplasticity and developing tools to modulate these phenomena may lead to insights into such diverse processes as memory and learning. These insights may increase the potential to enhance the recovery of function and to reverse maladaptive function in a number of disorders. Drugs and interventions could affect the abnor-

mal set point in a variety of neurologic and psychiatric disorders in which maladaptive plasticity is implicated (Table 1), resulting in treatment of the disease rather than just the symptoms. Techniques such as repetitive transcranial magnetic stimulation and deep-brain stimulation have been used in tens of thousands of persons and have been shown to induce plastic changes in the brain. The study by Engineer et al. shows that VNS — which has been used in the treatment of more than 50,000 patients with epilepsy — is a potentially important addition to the weaponry to rein in misbehaving neurons and combat disorders of brain plasticity.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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