Retuning the misfiring brain

Randolph J. Nudo*

Center on Aging and Department of Molecular and Integrative Physiology, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160

The past 20 years have witnessed enormous advances in our understanding of the structure and function of the cerebral cortex. Paramount among these advances is the realization that the detailed structural and functional organization of the cerebral cortex is maintained dynamically throughout life, shaped continually by experience and acutely by central or peripheral injury (1, 2). For example, the primary somatosensory cortex, located in the postcentral gyrus, contains an orderly "map" of the cutaneous receptor distribution. The various skin surfaces are represented in the cortex in a topographic fashion, with the surfaces of the feet located medially, and the hands and face more laterally. Several studies have now shown that this orderly topographic map is altered by repetitive tactile stimulation, such as takes place during the learning of a new sensorimotor skill (e.g., learning a new arpeggio on a guitar) (3–6). Cortical representations of the skin surfaces used in a skilled sensorimotor task become enlarged with practice, and cortical receptive fields become smaller. Only the representations of the most highly stimulated and trained digits are enlarged. Because somatosensory map enlargement has consistently been associated with improved behavioral performance, this dynamic process is considered adaptive. The network, cellular, and synaptic events that underlie cortical map plasticity are now beginning to be understood, as investigators in related fields, such as developmental biology, membrane biophysics, and genetic analysis, begin to address more mechanistic questions.

Although it is now well accepted that training-dependent enlargements of cortical representations occur, it has also been demonstrated that unusual sensorimotor experiences can result in unusual patterns of cortical organization. For example, in a study in nonhuman primates, Clark and colleagues (7, 8) surgically connected the skin surfaces of two adjacent fingers in a so-called digital syndactly preparation. Several months later, the normal somatotopic boundary between the two digits was blurred. Instead of responding to stimulation of one or the other finger, neurons within a wide swath of the somatosensory hand area responded to stimulation of either digit. That is, the receptive fields crossed the suture line and extended across both digits, a highly unusual arrangement (7, 8). This study and others helped strengthen a temporal correlation hypothesis of cortical dynamic processing. According to this hypothesis, which emerged from the Hebbian plasticity literature, as temporal correlation of inputs from various skin surfaces is increased, as in digital syndactly, new features of cortical map topography emerge (2).

As basic and clinical research in cortical plasticity has matured, the field has spawned a growing number of investigators interested in the application of neuroscientific principles of cortical dynamics to clinical problems. An important step in this direction was taken in 1996 with the publication of a proposed nonhuman primate model of focal hand dystonia by Byl and colleagues (9–11). Dystonias are disorders characterized by sustained involuntary muscle contractions resulting in abnormal movements or postures. Dystonic movements are associated with abnormal patterns of electromyographic activity with cocontraction of antagonist muscles and overflow into extraneous muscles (12). Focal dystonias, such as blepharospasm (eyelids), torticollis (neck), and writer's cramp (hand), affect a limited subset of muscles. Other types of focal dystonias include typist's cramp, pianist's cramp, and musician's cramp (13, 14). Such occupational dystonias tend to be quite task-specific, and are only evident during certain postures and/or joint movement combinations. In the case of the primate model developed by Byl and colleagues, monkeys engaged in a repetitive motor task (digital grasp) while weak vibratory stimuli were delivered to the hand that engaged widespread digital surfaces. After several weeks of repetitive practice, their motor performance deteriorated. The monkeys began to have difficulty in making complete contact with or removing their hand from the handpiece. Examination of the somatosensory cortex of these monkeys revealed that the representations of the fingers were substantially altered. The boundaries between individual finger representations were degraded, representing a seemingly maladaptive form of cortical plasticity (9).

The cerebral cortex is shaped continually by experience and by central or peripheral injury.

Similar findings have been found in neuroimaging studies of somatosensory cortex in human subjects with focal hand dystonia (15, 16). For example, in dystonic musicians, magnetic source imaging reveals a similar degrading of the boundaries between the finger representations (17). Thus, a putative hypothesis to explain the neural basis for at least certain types of focal hand dystonia emerged: heavy hand use, especially in highly attended, skilled activities, is accompanied by synchronous inputs from multiple skin surfaces at unusually high rates, resulting in degradation of the normal somatosensory cortex topography (ref. 18; Fig. 1). The abnormal somatosensory processing would, in turn, lead to development of sensorimotor abnormalities. Consistent with this hypothesis, recent studies have revealed that spatial and temporal tactile discrimination also is impaired in focal hand dystonia (19).

Curiously, similar somatosensory map distortions have been observed in the cortex opposite the nondystonic hand (20). However, other models have been developed that suggest that dystonias are the result of deficient inhibition of motor pathways (12). Deficient inhibition, similar to that seen in basal ganglia disease, might lead to excessive motor outputs and overflow into inappropriate muscles. Thus, focal hand dystonias may be the result of an abnormal reduction in inhibition. This idea gained support from transcranial magnetic imaging studies of patients with dystonia demonstrating increased excitability in motor cortex (21). Because it is thought that inhibitory mechanisms within the cere-

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*E-mail: rnudo@kumc.edu.

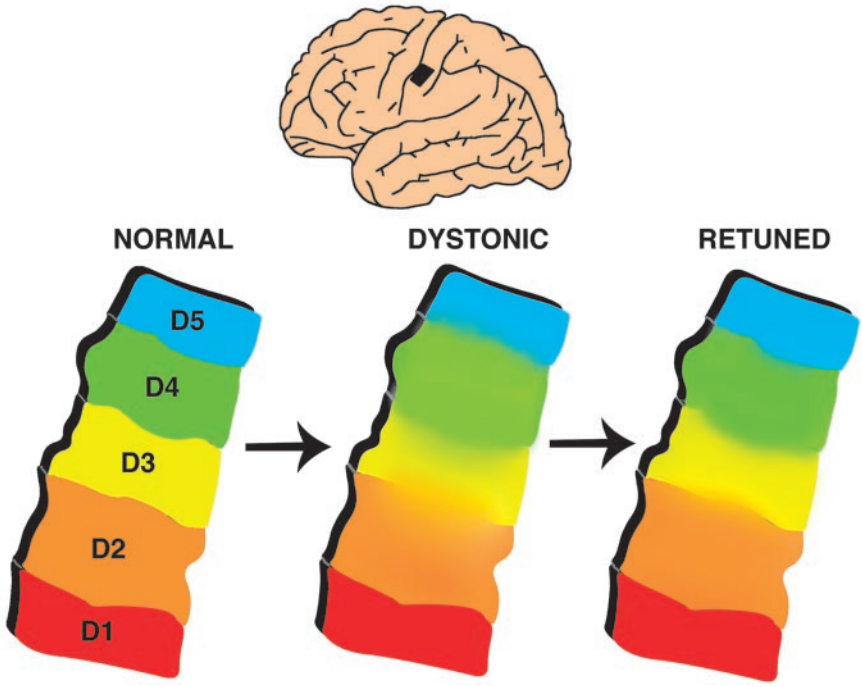

Fig. 1. Cartoon depicting hypothetical alterations in the topography of the hand representation in somatosensory cortex (see black box in *Upper* for location in the human brain. The normal arrangement is characterized by an orderly sequence from D5 (little finger) laterally to D1 (thumb). Boundaries between finger representations are sharp. In focal hand dystonia, the boundaries between finger representations are degraded, resulting in cortical regions that represent large skin surfaces crossing multiple digits. In the article by Candia *et al.* (26), sensory motor retuning was used to reduce dystonic symptoms. After the therapy, ''retuned'' maps appeared normalized.

bral cortex shape somatosensory receptive field properties (22), it is also possible that reduced inhibition may play a role in the production of degraded somatosensory maps.

Although patients with focal hand dystonia display a blurred somatosensory map, the clinical significance of the practice-induced map distortions had yet to be tested directly. Efficacy of pharmacologic treatments for dystonia have been mixed. Although some success with intramuscular botulinum toxin has been found in patients with certain types of dystonia (23), few effective treatments have been found for focal hand dystonia. Standard treatment often focuses on occupational therapy, such as adapting the environment or altering posture (e.g., adjusting sitting posture for writer's cramp). A recent study focusing on sensory discrimination training holds promise (24, 25).

In this issue of PNAS, Candia *et al.* (26) describe an orthotic-aided behavioral treatment for focal hand dystonia that apparently reverses the somatosensory map distortions associated with this motor disorder. Somatosensory map normalization is accompanied by a reduction in dystonic symptoms. In a group of 10 professional musicians with unilateral focal hand dystonia, Candia *et al.* examined the topography of the somatosensory cortex hand representation by using magnetic source imaging. Although these state-of-the-art neuroimaging tools do not provide the fine spatial resolution of the neurophysiologic studies conducted in monkeys (9), they are noninvasive and provide sufficient detail to examine the basic topography of somatosensory maps.

The treatment, called sensory motor retuning, involves immobilization of one or more fingers by using an individualized splint (27, 28). Any of the fingers other than the dystonic finger may be immobilized. The behavioral therapy consists of sequential movements of nonimmobilized fingers. The duration of therapy was gradually increased to ≈2 h per day over a period of 8 days. After therapy, movements of the dystonic finger were substantially more controlled. Supporting the map degredation hypothesis as a neural basis for focal hand dystonia, imaging results demonstrated a reduction in the mean Euclidean distances between individual finger representations, suggesting a normalization of functional topography associated with the therapy (Fig. 1).

This study has several implications for the neurorehabilitation of movement disorders. It provides evidence that behavioral approaches can be effective in reducing abnormal movements in at least some forms of focal hand dystonia. The fact that dystonic movements are treatable via behavioral therapy further implies a central, rather than peripheral mechanism. It has been established that focal hand dystonia is associated with a distorted hand map in the somatosensory cortex. The normalization of this map through behavioral therapy suggests that the integrity of the somatosensory hand map may be necessary for normal sensorimotor control.

Finally, this study and others like it suggest a broader implication for the treatment of neurological disorders. Our understanding of the mechanisms underlying neural plasticity are maturing. We know that use-dependent alterations of cortical representations can be adaptive, as in the case of the learning of new sensorimotor skills. Furthermore, after peripheral or central injury, the cerebral cortex can respond by engaging compensatory mechanisms to enable limited recovery of lost sensorimotor functions. However, alterations of cortical function are not always adaptive. Under certain conditions, even in an intact nervous system, the particular task demands may engage plasticity mechanisms in maladaptive ways. Neurorehabilitation scientists are now in a position to design novel therapeutic interventions for movement disorders that use newfound knowledge of the neuroscientific principles underlying structural and functional plasticity. This emerging perspective in neurorehabilitation will enable future therapists to shape malformed central networks into more adaptive modes.

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