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Consensus paper: Use of transcranial magnetic stimulation to probe motor cortex plasticity in dystonia and levodopa-induced dyskinesia

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Plasticity includes the ability of the nervous system to optimize neuronal activity at a cellular and system level according to the needs imposed by the environment. Neuroplasticity phenomena within sensorimotor cortex are crucial to enhance function to increase skillfulness. Such plasticity may be termed "adaptive" to indicate its ecologically beneficial role. In professional musicians, enhanced adaptive plasticity is associated with one of the highest level of motor skill a human being can achieve and the amount of these changes is even dependent on the age at which instrumental playing was started. In addition, adaptive neuroplastic changes occur when nervous system try to repair itself thus compensating dysfunctions. However, when these adaptive phenomena are pushed to an extreme, they can produce a maladaptive sensorimotor reorganization that interferes with motor performance rather than improving it. The model we discuss here is focal hand dystonia I which an intrinsic abnormality of neural plasticity, in some predisposed individuals, may lead to abnormal sensorimotor integration and to the appearance of a characteristic movement disorder. Deficient homeostatic control might be an important mechanism triggering this maladaptive reorganization, and future behavioral studies are needed to confirm this hypothesis.

In the second part of this consensus paper, we will critically discuss as a second model, the hypothesis that levodopa-induced dyskinesia correlate with an aberrant form of plasticity in the human primary motor cortex, possibly because of abnormal oscillations within the basal ganglia loop. Disorders of cortical plasticity have not in the past been considered as possible causes of human clinical states. The recognition that this can occur, together with a speculative mechanism, generates an important and provocative hypothesis for future research at the clinical-scientific interface.

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The acquisition of new motor skills relies on the ability of synapses, within motor areas, to undergo changes in synaptic efficiency,[1-3] which are driven by efferent demand and afferent input. For instance, several studies wth string players[4] and piano learners[5] have shown that skillful playing of music require extensive procedural and motor learning that results in plastic reorganization of the human brain. However, a system capable of such flexible reorganization harbors the risk of unwanted changes. The question we would like to address in this consensus paper is whether it is possible to envisage that plasticity phenomena could be affected in diseases and give rise to identifiable clinical states. The model we propose here is focal hand dystonia (FHD), in which patients have involuntary muscle contractions at rest or during the performance of highly skilled fine motor tasks, resulting in impaired motor performance. We argue that normal mechanisms of neural plasticity that are recruited after injury or during practice are abnormal in some individuals. This leads to inappropriate associations between sensory input and motor output and the appearance of a characteristic movement disorder. In the second part of this paper, we will show how patients with Parkinson's disease (PD) and with levodopa-induced dyskinesia (LID) may exhibit a very different type of plasticity alterations within sensorimotor cortex, compared with dystonia, which may be secondary to an altered pattern of oscillations within the basal ganglia loop.

Enhanced gain of plasticity in focal dystonia

Dystonia is a motor disorder characterized by sustained involuntary muscular contractions resulting from cocontraction of antagonistic muscles and overflow into extraneous muscles.[6] One fascinating and intriguing feature of dystonia is the task specificity. For instance, in simple writer's cramp, the mere act of handwriting induces the classic dystonic posture, whereas the same patient can use the hand normally in other motor tasks.[7] Indeed the occurrence of dystonia in these high-skilled stereotypical movements suggests a breakdown within motor memories that may result from abnormal plasticity. In some circumstances, dystonic movements can be the consequence of periods of intensive training of a particular movement.[8] This is the case of musician's dystonia in which patients spend many hours per day with their attention focused on instrumental practice. It has been proposed that synchronous and convergent afferent input arising from repetitive motor tasks may play an important role in driving the abnormal cortical plasticity seen in FHD (discussed later in the text). This hypothesis arises from work conducted in both animal and human subjects. In an animal model of dystonia, Byl et al[9] demonstrated that primates who were trained to make a particular highly specific hand movement (while receiving a synchronous vibration of the whole hand) can develop a clinical condition very similar to FHD. What it is interesting to note is that the finger map within somatosensory cortex was distorted with larger receptive fields and overlapping representations of the individual digits.[9] Therefore, in keeping with these studies, it can be postulated that if motor training is pushed to an extreme, it can produce a maladaptive sensorimotor reorganization that interferes with task performance rather than improving it.[10] In addition, it has been demonstrated that surgical joining of the skin of adjacent digits, which increases synchronous afferent inputs, produces changes similar to over-training.[11] Likewise, in healthy humans, Hebbian-like pairing of tactile stimuli to digits induce a distortion of somatosensory maps.[12] Finally, synchronous stimulation of peripheral muscles induces organizational changes in motor representations, characterized by an increase in map size of stimulated muscles and a reduction in map separation, as assessed b using transcranial magnetic stimulation (TMS).[13] Even if none of these subjects had an overt dystonia develop, motor map disorganization was similar to that observed in both motor[14] and sensory representation[15] in FHD. Although the results of these studies are very obvious, on the other hand, they only show that some types of repetitive activity can lead to an abnormal reorganization of the sensorimotor cortex and dystonia but does not give any clues as to why only in humans, some subjects do have dystonia develop after excessive training, whereas others are completely healthy.

It could be hypothesized that subtle abnormalities of plasticity may render some individuals susceptible to dystonia if plastic changes are driven to their extreme by frequent repetition. Given the low penetrance of dystonia in familial cases,[16] identification of genetic mutations or polymorphisms determining increased susceptibility is challenging. Indeed, there is now evidence suggesting that mechanisms of neural plasticity that are recruited after injury or during practice may be subtly abnormal in dystonic patients.[17-20] A number of noninvasive neurophysiologic methods have recently been developed to study plasticity at a system level in the human brain looking at long-term potentation (LTP) and long-term depression (LTD)-like phenomena. The paired associative-stimulation (PAS) protocol consists of repetitive TMS (rTMS) over the motor cortex with each magnetic stimulus paired with contralateral peripheral nerve stimulation.[21] This protocol resembles experimental procedures producing Hebbian LTP/LTD- plasticity in animal experimentation. By using PAS, it was demonstrated that the LTP-like facilitatory